Supporting paper to COMEAP 2010 report:
"The Mortality Effects of Long Term Exposure to Particulate Air Pollution in the United Kingdom"

Working Paper: DEVELOPMENT OF PROPOSALS FOR CESSATION LAG(S) FOR USE IN TOTAL IMPACT CALCULATIONS

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CONTENTS

1 Background

1. The decision regarding choice of lag times is a crucial and difficult part of quantifying the benefits of reducing long-term exposure to fine particles.

2. The 2009 COMEAP report states the following in the Executive Summary:

> *'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.'*

The fuller text is attached at Annex 1. This cites 'a rapid examination' of the Dublin study (Clancy *et al,* 2002) as a source of the above view. A working paper on lags was not produced at the time.

3. To actually proceed with calculations, a quantitative recommendation regarding lags is required. Currently, UK government quantification work uses a range of between a zero and 40 year lag (this is not to suggest that a zero lag or a 40 year lag is especially likely but to indicate the extremes of the range within which the result is likely to lie). The COMEAP statement above is quoted to explain that the result is more likely to be towards the zero lag result than the 40 year lag result. (The range between a zero and a 40 year lag was recommended in the 2001 COMEAP report on long-term exposure to particles. The recommendation was based on the fact that the HEI reanalysis showed no difference in relative risk when stratified by age; this was not compatible with the whole effect requiring a lag of more than 40 or so years.)

4. There are two types of lags (i) an onset lag is the time taken between the onset of exposure and the occurrence of the outcome and (ii) a cessation lag is the time taken between a reduction in exposure and a reduction in mortality risk. These lags do not have to be the same (paragraph 69: Figure 9). For health impact assessment of policies to reduce air pollution, the cessation lag is the most relevant. However, evidence for both types of lags is considered here, as the evidence is limited and as, in combination with mechanistic information, information on onset lags may inform the likely cessation lags.

5. This paper sets out some of the evidence regarding lag times. There are three potential sources of information about onset and cessation lags:

(i) temporal patterns in epidemiological studies of long-term exposure to air pollution and the effect on mortality, of interventions and of distributed lags,
(ii) mechanistic information about the effect of long-term exposure to air pollution on mortality,
(iii) analogy with similar risk factors that may have more information e.g. the smoking cessation literature.

6. These areas are discussed in the paper. The approach taken is to follow certain lines of argument (e.g. analogy with smoking cessation) through to their conclusion despite their uncertainty and then take uncertainty into account by considering the range of possible different conclusions at the end.

2. Temporal patterns in cohort studies and other studies

7. Using epidemiological studies of long-term exposure to air pollution seems the most obvious source for information about lags but this is in fact remarkably difficult. This is because there is no clear cut start and finish of air pollution exposure. Everyone is exposed to some degree all of the time. Even where air pollution declines, it is likely that cities with higher pollution had even higher pollution in the past i.e. recent changes are correlated with past differences in exposure. This makes detecting the delay (or not) to an effect of a change in pollution very difficult. The first section below considers the evidence from cohort studies. This is followed by a discussion of intervention studies and a brief consideration of distributed lag studies.

2.1 Cohort studies

8. Neither Pope *et al* (1995) (American Cancer Society (ACS) study) nor Dockery *et al* (1993) (Six Cities study) was especially informative about either the onset lag or the cessation lag. For Pope *et al* (1995), there was only one measured air pollution time point (the 4 year median for 1979-1983) (although, of course, exposure to air pollution occurred at other times). The Six Cities study did measure air pollution at several time points but, certainly for the initial paper, the numbers of deaths were too small for sophisticated analysis using this information. However, the Health Effects Institute (HEI) Reanalysis (Krewski *et al,* 2000) and later publications using these cohorts performed a number of additional analyses that have provided indirect clues regarding onset and cessation lags. In addition, there is some information in other cohort studies.

9. Cohort study references were collected from a general search on particulate matter, mortality and long-term, chronic or cohort and from searches of authors of key publications. Further references were obtained from references referred to in the publications and in reviews. The references were then read and checked for information on age-dependence or time-dependence. As the main calculations are based on $PM_{2.5}$ and all-cause mortality in studies of the general population, it would make sense for these to be inclusion criteria for information on lags as well. This reduces the uncertainties if trying to translate information on the proportion of the effect due to different lags on a quantitative basis. The following section therefore concentrates on these studies. The studies considered are summarised in Annex 2. Some reference is given to results on other particle metrics, cause-specific mortality and population sub-groups where these appear in the $PM_{2.5}$ and all-cause mortality studies.

2.1.1 Stratification by age

10. An analysis was done whereby the ACS cohort was stratified by age into three roughly equal groups - under 50s, those between 50 and 60 and those over 60 (Krewski *et al,* 2000). Although division of the cohort into smaller numbers led to some loss of statistical significance, the relative risk was raised to a similar degree in all groups and there was no statistically significant difference between age groups (Table 1). A view that an effect only occurred after more than 50 years of exposure is not compatible with this data as the relative risk would not be expected to be raised in the under 50 year old age group. This is what led to the maximum 40 year lag recommended in the 2001 COMEAP report (COMEAP, 2001). (If all of the effect had an onset lag of 40 years, this might allow enough people to be affected between 40 and 50 to give a raised relative risk, if all of the effect had an onset lag of, say, 49 years, then all of the raised relative risk in the under 50s would be allocated to just one year, which seems unlikely). Note that this conclusion only considers that the onset lag is unlikely to be more than 40 years. It does not say that the onset lag needs to be as much as 40 years, particularly not for the whole of the effect.

Table 1 Relative risk (RR) of mortality by age (ACS study). Data from Table 21, p 163, Krewski *et al* (2000))

	Fine particles		**Sulphate**	
Age at enrollment	% of cohort	RR all-cause mortality per 24.5 $\mu g/m^3$	% of cohort	RR all-cause mortality per 19.9 $\mu g/m^3$
< 50	29.3	1.19 (0.91-1.56)	29.3	1.14 (0.91-1.42)
50-60	36.4	1.13 (0.97-1.30)	36.5	1.12 (0.99-1.26)
>60	34.3	1.19 (1.09-1.29)	34.2	1.16 (1.09-1.24)

11. Similar results were found for all-cause mortality when the cohort was stratified by age after longer follow-up (Pope *et al,* 2002). This paper also provided results for cardio-pulmonary and lung cancer mortality. These appear to give different shapes for the relationship of relative risk with age, although there is substantial overlap in the confidence intervals. For cardio-pulmonary mortality, the relative risk is higher in the over seventies, although it is still raised in the under sixties. (Although the latter is not quite statistically significant this may be due to the smaller numbers involved when splitting the cohort). For lung cancer mortality, the relative risk is highest in the 60-70 year age group before falling again in the over seventies. As it is known that it takes time for lung cancer to develop, the relative risk would be expected to be higher in the older age groups. However, all of these age groups are relatively old. There are also other potential explanations such as increased exposure misclassification with age and increases in competing causes of death. Overall, due to the considerable overlap of confidence intervals, it cannot be said that there is a clear relationship with age.

Table 2 Relative risk of mortality by age (ACS study). Pope (personal communication).

Age at enrolment	Fine particles (1979-83)		
	RR all-cause mortality per 10 µg/m^3	RR cardio-pulmonary mortality per 10 µg/m^3	RR lung cancer mortality per 10 µg/m^3
< 60	1.041 (0.999-1.086)	1.052 (0.98-1.129)	1.039 (0.956-1.126)
60-70	1.016 (0.975-1.06)	1.019 (0.965-1.077)	1.14 (1.036-1.254)
>70	1.046 (1.003-1.09)	1.084 (1.034-1.137)	0.989 (0.845-1.158)

12. Neither the study of cardiovascular mortality in the ACS study (Pope *et al,* 2004) nor the extended follow-up (Krewski *et al,* 2009) provided an analysis stratified by age. Jerrett *et al* (2007), in a study on a subset of the ACS cohort, found higher relative risks in younger age groups in an overall analysis but this was not true at all time points or in all sub-groups by education.

13. The Six Cities study differs from the ACS study in that it was designed to provide air pollution measurements every year as follow-up continued. Some information on changing individual characteristics during follow-up was also collected. The ACS study only had air pollution measurements at baseline and, perhaps, one other occasion and individual characteristics were only available at baseline. However, the Six Cities study is smaller. The HEI Reanalysis (Krewski *et al*, 2000) also stratified the Six Cities cohort by age. There was a suggestion of greater relative risks at younger ages (under 40) but the confidence intervals were very wide so this was inconclusive (the interaction with age was not statistically significant).

Table 3 Relative risk of mortality by age (Six Cities study). Data from Table 4, p 139, Krewski *et al* (2000)).

	Fine particles	
Age at enrollment	% of cohort	RR all-cause mortality per 18.6 µg/m^3
< 40	27.4	2.11 (0.88-5.07)
41-55	35.0	1.66 (1.17-2.35)
> 55	37.6	1.17 (0.98-1.40)

14. Villeneuve *et al* (2002) analysed broadly the same data in a different way using Poisson regression rather than the Cox proportional hazards model. It was demonstrated that the overall result was similar using the two methods (RR 1.31 (1.12-1.52) for Poisson regression compared with RR 1.26 (1.08-1.46) in the original paper). The authors argued that Poisson regression was a less 'computationally extensive' approach when there were several time-dependent variables and could be used in these circumstances. When testing for effect modification, the only risk factor showing a statistically significant interaction ($P<0.05$) was age and the results were therefore stratified into ages under 60 and over 60. Perhaps, because the cohort was only divided into two groups, it was more obvious that the relative risk was higher in the lower age group (Table 4). This difference was seen consistently across models using different time-periods of fine particle exposure.

Table 4 Relative risk of mortality by age in the Six Cities Study. (Data from Table 5, Villeneuve *et al* (2002) Ann. Epidemiol. 12(8): 568-576. Copyright (2002), with permission from American College of Epidemiology. http://www.sciencedirect.com/science/journal/10472797).

	Fine particles
Age at enrolment	RR all-cause mortality per 18.6 µg/m^3 (entire follow-up)
All	1.31 (1.12-1.52)
<60	1.89 (1.32-2.69)
> 60	1.21 (1.02-1.43)

15. The extended follow-up of the Six Cities study (Laden *et al,* 2006) did not provide results stratified by age.

16. Stratification by age was also examined in some other cohort studies on long-term exposure to $PM_{2.5}$ and all-cause mortality. Enstrom (2005) performed a sub-group analysis for ages 43-64 and 65-99 years in a study using the California Cancer Prevention Study I. The relative risk was positive and statistically significant only for the youngest age-group. Naess *et al* (2007a) found, in a Norwegian cohort, that relative risks were higher in the 51-70 year old age-group than in the 71-90 year old age group in both men and women, particularly in the highest quartile of exposure (18-22 µg/m^3). Finally, Zeger *et al* (2008) found that relative risks declined from the 65-74 year old age group to the 75-84 year old age group and were no longer statistically significant for ages over 85 years in a replacing Medicare cohort in the Eastern and Central US (overall results were not significant in the Western US and did not show dependence on age).

17. In a critique of a paper by Enstrom (2005), Brunekreef and Hoek (2006) discuss some of the issues relating to smaller effects in the elderly (those born between 1873 and 1909 in the Enstrom study). They note that some studies found important cohort effects for active smoking in a similar time-period. The British Doctors study, for example, found higher relative risks for life-long smoking amongst those born in the 1920s and 1930s than in those born in the 1860s and 1870s (Doll *et al,* 2004). For this and other reasons, it is not straightforward to interpret the information on age-dependence in terms of lags. While it perhaps rules out fine particles only acting via a mechanism that required cumulative exposure over 5 or 6 decades, it does not really provide evidence that helps to distinguish amongst, say, 1, 5 and 20 year onset lags.

2.1.2 Time-dependence

18. The HEI Reanalysis (Krewski *et* al, 2000) used a flexible spline regression model to examine possible time-dependent effects in the ACS study. To reduce the size of the cohort to tractable levels, the cohort was divided into random subsets. Temporal patterns in the hazard ratio varied considerably amongst the random subsets with no one pattern being more frequent than any other.

19. Figure 10 of the HEI reanalysis report (Figure 1 below) gives concentration-response functions described as being plotted against cumulative exposure (the units

are not given but the text suggests that this is in µg/m^3 with no mention of time). It is unclear how this cumulative exposure is derived but it will involve assumptions as the ACS study does not include information on $PM_{2.5}$ concentrations every year. The $PM_{2.5}$ relationship increases and then flattens off above about 15 µg/m^3 'cumulative exposure'. The shape of the sulphate relationship (Figure 11 of the report; Figure 2 below) was different with a shallow increase followed by a steeper one above about 14 µg/m^3 'cumulative exposure'. The text does not comment on the interpretation e.g. does this suggest that a straightforward cumulative exposure relationship does not apply? The Health Review Committee had the following comments '*Interpretation of Figures 10 and 11 in Part II is less clear. These plots were produced as part of the flexible modelling strategy, in which both the baseline hazard function and the concentration-response curve were modelled non-linearly using quadratic spline functions. The switch from LOESS methods to quadratic splines does not explain such a drastic change in the estimated shapes of these curves, or their confidence limits, compared with Figure 5 in Part II.'* (Figure 5 of the report (not shown) is a straightforward plot of effect against concentration and appears approximately linear).

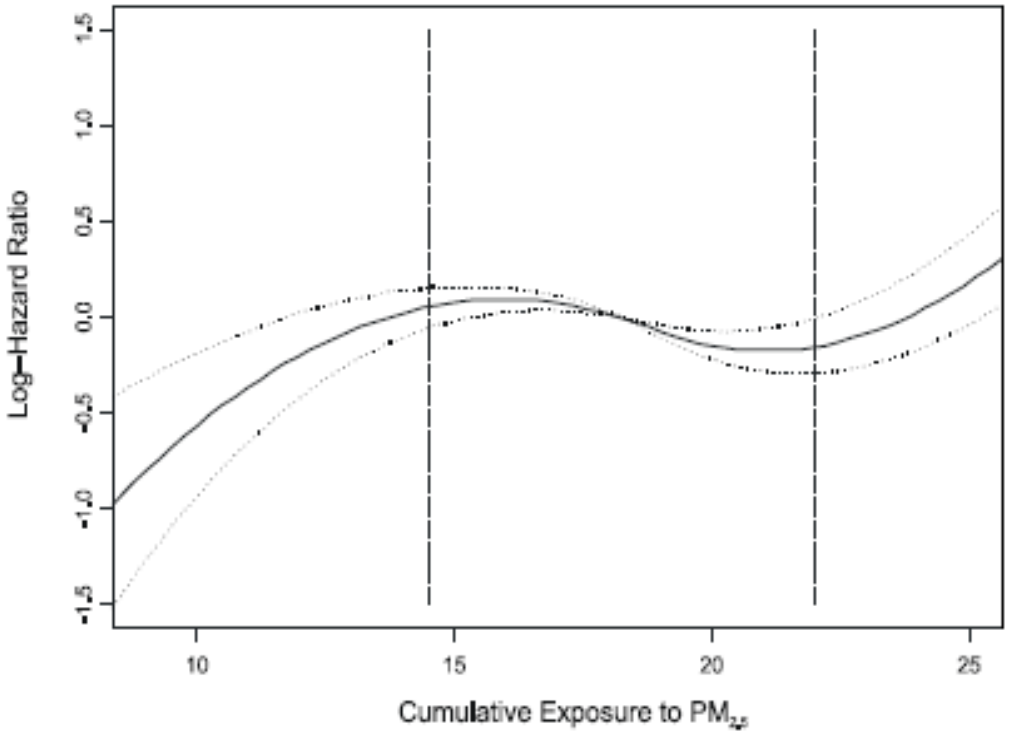


Figure 10. Impact of cumulative exposure to fine particles in the ACS Study. Flexible quadratic spline estimate (3 *df*) of the nonlinear effect of increasing the exposure to fine particles on the log–hazard ratio of mortality in a case-cohort subset of the ACS Study, adjusted for BMI, education level, and pack-years of smoking for current- and former-smokers. The log–hazard ratio was associated with a change in fine particles (24.5 $\mu g/m^3$) equal to the difference in mean concentrations between the most-polluted city and the least-polluted city. Along the horizontal axis, the solid curve represents the point estimate of the log–hazard ratio and the dashed curves the point-wise 95% confidence interval. The left and right dashed vertical lines indicate the first and third quartiles of fine particles in the sample of 2,500 individuals included in the ACS Study.

Figure 1 (Reprinted from Krewski *et al* (2000) with permission from the Health Effects Institute, Boston, MA.)

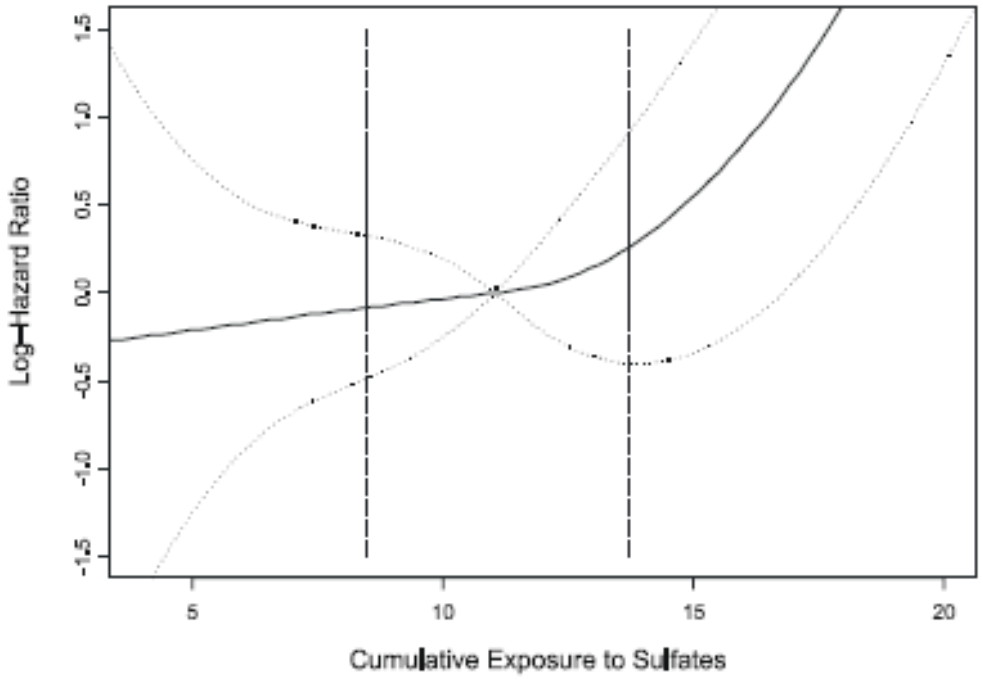


Figure 11. Impact of cumulative exposure to sulfate in the ACS Study. Flexible quadratic spline estimate (3 *df*) of the nonlinear effect of increasing the level of exposure to sulfate on the log–hazard of mortality in a case-cohort subset of the ACS Study. The log–hazard ratio was associated with a change in sulfate (19.9 $\mu g/m^3$) equal to the difference in mean concentrations between the most-polluted city and the least-polluted city. The solid curve represents the point estimate of the log–hazard ratio and the dashed curves represent the point-wise 95% condidence interval.

Figure 2 (Reprinted from Krewski *et al* (2000) with permission from the Health Effects Institute, Boston, MA.)

20. Pope *et al* (2002) examined the effect of two different time-periods of measured fine particle concentrations (1979-1983 and 1999-2000) and of the average between them. There was some suggestion of higher relative risks for the recently measured exposure for all-cause, cardiopulmonary and lung cancer mortality but this was not conclusive as confidence intervals overlapped substantially (Table 5). Also, it is unclear whether this is due to a real effect or to the greater exposure misclassification when using the older measurement data (there were greater numbers of deaths in the more recent time period as the cohort got older). Professor Strachan in Working Paper 5 of COMEAP (2009) showed that using the earlier and later exposure measurements actually gave similar results for all-cause mortality after adjusting for the different ranges in concentrations (wider for earlier measurements). In addition, adjusting for measurement error (derived from the correlation r = 0.78 in Figure 1 of Pope *et al* (2002)) led to the conclusion that the mortality relative risks for 1979-1983 $PM_{2.5}$ and the average were consistent i.e. no strong evidence emerged to prefer the earlier time period over the average.

TABLE 5 Adjusted mortality relative risk (RR) associated with a 10 µg/m^3 change in $PM_{2.5}$ (Reprinted from Table 2 of Pope *et al* (2002) JAMA 287(9): 1132-1141.)

Cause of mortality	**Adjusted RR (95% CI)**		
	1979-1983	**1999-2000**	**Average**
All-cause	1.04 (1.01-1.08)	1.06 (1.02-1.10)	1.06 (1.02-1.11)
Cardio-pulmonary	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)

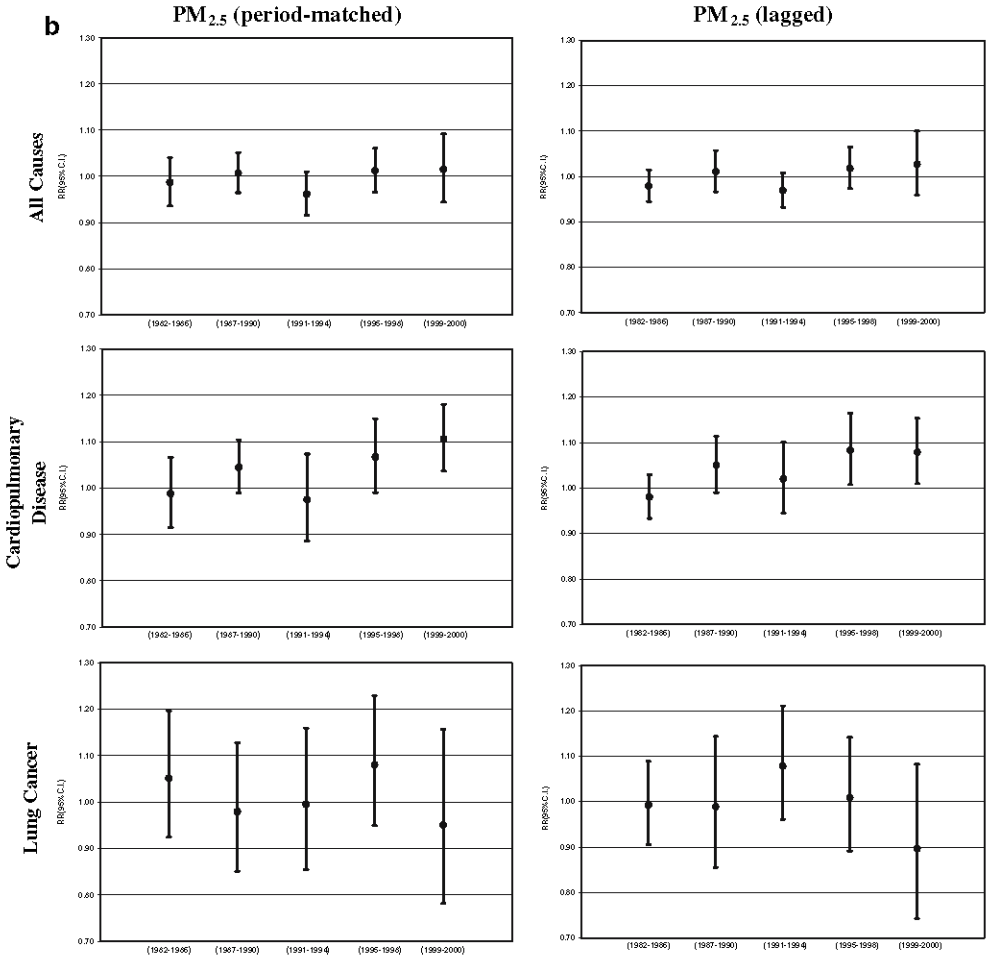
21. Pope *et al* (2004) also provided results by time period of exposure measurement (see the figure on page 79 of the paper). An increased relative risk for the most recent time-period (with overlapping confidence intervals) was found for most of the causes of death showing positive associations.

22. Jerrett *et al* (2007) examined data from 51 cities within the ACS cohort. These 51 cities were included in previous analyses and were suitable for computing new exposure estimates using TSP and PM_{10} to predict levels of $PM_{2.5}$ at times when direct monitoring was not available. The aim was to examine how the relative risks for mortality changed over time. Relative risks were examined for five time-periods (1982-1986; 1987-1990; 1991-1994; 1995-1998 and 1999-2000). $PM_{2.5}$ exposure was defined as concentrations measured in 1999-2000 (for comparison with Pope *et al* (2002)) or imputed concentrations that either matched the time-periods above or were lagged by 5 years.

23. The overall relative risk for all-cause mortality was smaller than for the ACS study and was not significant. (The authors argue that this is due to the exclusion of cities in the Ohio valley which showed higher relative risks in the ACS study). Overall, cardio-

pulmonary mortality relative risks were significant. As shown in Figure 3, all-cause mortality did not change much over the different periods but then it was not significant anyway. Cardiopulmonary relative risks increased in the more recent periods. The pattern with the 5-year lag was almost identical. Lung cancer peaked in the middle period, most clearly with the 5 year lag. (These are cessation lags as the author states that levels of $PM_{2.5}$ were declining.)

Figure 3. Relative risks for all-cause, cardiopulmonary and lung cancer deaths estimated for five time-periods of the follow-up (1982–1986, 1987–1990, 1991–1994, 1995–1998, and 1999–2000) with imputed exposures. (Units of relative risk were not given; y axis states 'RR (95% CI)'). From Figure 3b, Jerrett *et al* (2007) 'Geographies of uncertainty in the health benefits of air quality improvements'. Stochastic Environmental Research and Risk Assessment 21(5):511-522. © Springer-Verlag 2007, with kind permission from Springer Science + Business Media B.V.



24. These patterns are not conclusive as the confidence intervals overlap. Part of the authors' aim in the paper was to discuss the difficulties in interpretation when faced with this type of data. One possible conclusion is that, while $PM_{2.5}$ levels declined, the traffic contribution went up leading to higher cardiopulmonary mortality relative risks.

However, the authors give several other interpretations of changes in relative risks over time:

a) The 'robust survivor' explanation suggests that those with high susceptibility and exposure die in the early part of follow-up. Relative risks would then be lower late in follow-up when the numbers of susceptible people had been depleted. This would lead to declining relative risks over time so does not explain the $PM_{2.5}$ data.

b) The authors investigated mobility over time in a subset of the ACS cohort. They noted that more net in-migration occurred in areas where $PM_{2.5}$ did not decline as much as in other areas of the country. Thus, people allocated a low level of $PM_{2.5}$ for their original city were in fact living somewhere with a higher level of $PM_{2.5}$. This would exaggerate the risk at the lower level of $PM_{2.5}$ (as the death would still be allocated to this level) and this effect would increase over time.

c) Temporal measurement error could have occurred. Although $PM_{2.5}$ was modelled separately for different times, it was calculated on 1999-2000 measurements. This was at the end of follow-up. As the time period got closer to the time of the measured data, measurement error would be reduced and relative risks would go up. (Sulphates were also examined. The measurements were at the beginning of follow-up. In this case, relative risks declined over time.)

Given all these different potential explanations, it is easy to see how distinguishing evidence on lags would be difficult. In addition to these explanations, the lung cancer pattern could be related to changes in pollution many decades before. Exposure estimates did not go back this far in the article.

25. Krewski *et al* (2009) included an aim to address critical exposure time windows in a reanalysis of the extended follow-up of the ACS study (with an additional year of follow-up beyond Pope *et al* (2002)). A subset of the ACS cohort, the Nutrition cohort, had residential histories subsequent to 1982 (but not before) and approximate moving dates. Another cohort (group B) who had died in the same metropolitan area as they had been living at enrolment in 1982 was also studied[1]. People in this group were assumed not to have moved. The analysis was done according to three different time-windows (exposure 1-5 years ago; exposure 6-10 years ago and exposure 11-15 years ago). Akaike's information criterion (AIC) was used to rank which of the models using the different time-windows gave the better fit to the data. The results are shown in Table 6.

[1] The Health Review Committee noted that it is a usual epidemiological principle for cohort studies that a subject's presence in a cohort should not depend on their subsequent death. Group B did not adhere to this principle although it is not clear whether or not bias resulted.

Table 6 Hazard ratios and AIC values by cause of death associated with a 10 μg/m^3 change in $PM_{2.5}$ for three 5 year time-windows. (Adapted from Table 26, Krewski *et al* (2009) with permission from the Health Effects Institute, Boston, MA.)

Exposure Time-Window[a]	$PM_{2.5}$-A Group (*n* = 60,941)	$PM_{2.5}$-B Group (*n* = 81,466)
All Causes		
Years 1-5		
HR	1.01 (0.94-1.08)	1.01 (0.99-1.03)
(Rank) AIC	(3) 81,144.310	(1) 933,094.00
Years 6-10		
HR	0.98 (0.91-1.04)	1.1 (0.99-1.02)
(Rank) AIC	(1) 81,143.776	(2) 933,094.94
Years 11-15		
HR	0.98 (0.92-1.04)	1.1 (0.99-1.02)
(Rank) AIC	(2) 81,143.970	(3) 933,095.03
Lung Cancer		
Years 1-5		
HR	1.12 (0.89-1.40)	1.10 (1.04-1.17)
(Rank) AIC	(2) 7,541.342	(1) 67,541.515
Years 6-10		
HR	1.2 (0.83-1.25)	1.06 (1.01-1.12)
(Rank) AIC	(3) 7,542.180	(2) 67,545.732
Years 11-15		
HR	1.10 (0.91-1.33)	1.05 (1.01-1.10)
(Rank) AIC	(1) 7,541.275	(3) 67,546.285
CPD		
Years 1-5		
HR	1.2 (0.91-1.14)	1.06 (1.03-1.08)
(Rank) AIC	(2) 32,234.695	(3) 462,773.21
Years 6-10		
HR	0.98 (0.89-1.09)	1.05 (1.03-1.07)
(Rank) AIC	(1) 32,234.694	(1) 462,771.08
Years 11-15		
HR	0.99 (0.90-1.09)	1.04 (1.02-1.06)
(Rank) AIC	(3) 32,234.791	(2) 462,772.56

[a] The AIC value is a measure of how well the model fits the available data; the time-window with the lowest AIC value (number 1 in rank) best represents the patterns of mortality.

26. Overall, no clear pattern emerged. No exposure time-window stood out clearly as demonstrating the greatest hazard ratio and/or the lowest AIC except possibly lung

cancer with exposure in years 1-5 in group B. However, it might be expected that lung cancer would be affected more by exposure longer in the past. Generally, the differences in the AIC values were tiny i.e. models with one time-window did not clearly fit better than models with other time-windows. The Health Review Committee commentary notes that results were not presented for 'multi-window' models. (These would attempt to control for the correlation between one exposure time-window and another). The authors of the report were planning to do this but their planned analysis required the direction of the effect in their weighted model to be the same in each exposure window. This was not the case. Correlations between time-windows tended to be high (r ranged from 0.75 to 0.98) which complicates the interpretation of the results in terms of lags. In addition, levels of fine particles were declining over time, so that the longer lags also involved exposure to higher concentrations and the results are relevant to the issue of cessation lags. It was concluded that identification of critical exposure time-windows, even among large national cohorts, remained a challenge.

27. Turning to the Six Cities study, the HEI reanalysis (Krewski *et al,* 2000) took a similar but slightly more obvious approach to examining time-dependence in the Six Cities study compared with the ACS study analysis. Again a flexible spline regression model was used with division of the dataset into more tractable random subsets (4 in this case). The default model with 5 degrees of freedom indicated marginally significant time-dependent effects (p=0.032 for fine particles and p=0.0316 for sulphates). This was robust to various sensitivity analyses but was not detected in less flexible models (3 degrees of freedom or less). These less flexible models also fitted less well.

28. Figure 2 of Krewski *et al* (2000) (Figure 4 below) shows a drop in the log of the hazard ratio over the first 5 years of follow-up followed by a rise to a second peak at about 10-12 years of follow-up. This does not necessarily relate directly to lags as pollution levels are changing through follow-up as well as hazard ratios. It was noted, for example, that there was a sharp increase in fine particle levels in Steubenville after about 11 years of follow-up. If this was the explanation, this would suggest a reasonable proportion of the effect had a short lag as the change in Steubenville contributed to a change in hazard ratio at about the same time. Although fine particles were not measured in the first 5 years of follow-up, TSP was, and this showed a decrease in the first 5 years (Dockery *et al,* 1993), again suggesting an explanation for the shape of the curve. The shape for sulphates (Figure 3 of Krewski *et al* (2000) and Figure 5 below) was similar.

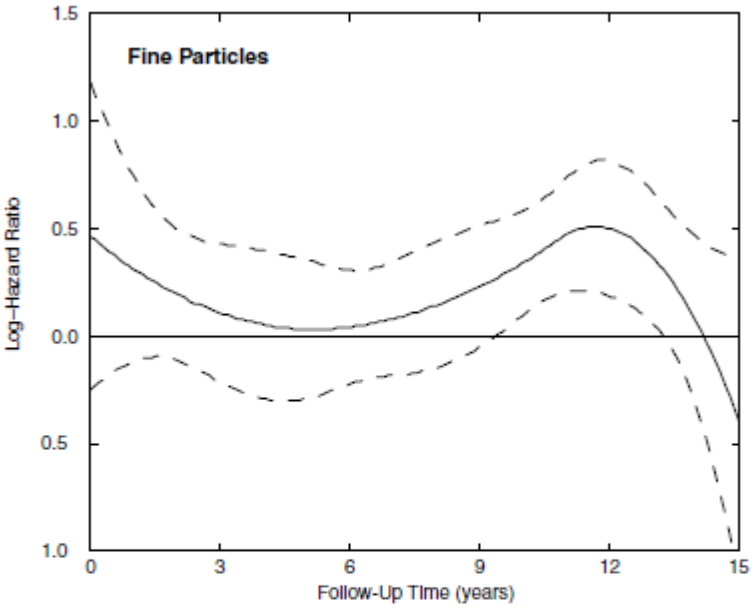


Figure 2. Change in the impact of fine particles over time in the Six Cities Study. Flexible quadratic spline estimate (5 *df*) of the time-dependent effect of fine particles on the log–hazard ratio of mortality in a subset of the Six Cities Study (n = 2,856 of which 1,430 were deaths). The log–hazard ratio was associated with a change in fine particles (18.6 $\mu g/m^3$) equal to the difference in mean concentrations between the most-polluted city and the least-polluted city. The solid curve represents the point estimate of the log–hazard ratio and the dashed curves represent the point-wise 95% confidence interval.

Figure 4 (Reprinted from Krewski *et al* (2000) with permission from the Health Effects Institute, Boston, MA.)

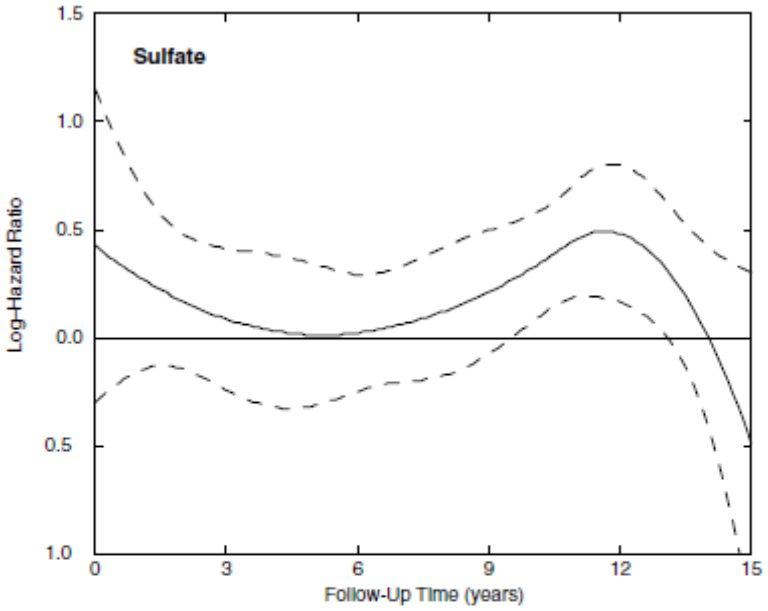


Figure 3. Change in the impact of sulfate over time in the Six Cities Study. Flexible quadratic spline estimate (5 *df*) of the time-dependent effect of sulfate on the log–hazard ratio of mortality in a subset of the Six Cities Study (n = 2,856 of which 1,430 were deaths). The log–hazard ratio was associated with a change in sulfate (8.0 μg/m^3) equal to the difference in mean concentrations between the most-polluted city and the least-polluted city. The solid curve represents the point estimate of the log–hazard ratio and the dashed curves represent the point-wise 95% confidence interval.

Figure 5 (Reprinted from Krewski *et al* (2000) with permission from the Health Effects Institute, Boston, MA.)

29. This analysis was extended further to look in more detail at the impact of variations in concentrations of fine particles over time. The original study had used the mean level of fine particles in each city and assumed that this was constant over time. Although this extended analysis was included in the HEI reanalysis, it is covered in more detail in a subsequent publication by Villeneuve *et al* (2002). As described in paragraph 14, Poisson regression analysis was used. As shown in Table 7, use of time-dependent estimates of levels of fine particles attenuated the relative risks and provided poorer goodness of fit (higher value) than using a fixed mean level over the follow-up period. Similar results (not shown here) were found when the cohort was split between over and under 60s.

30. Taken at face value, these results can be taken as being consistent with the hypothesis that cumulative or life-long exposure to $PM_{2.5}$ is an important predictor of mortality. However, the authors note that the small size of the cohort, the wide year to year variations in mortality in each city and the correlation between time-periods may have dampened the ability to detect any difference in the effect of $PM_{2.5}$ on mortality between any specific time-periods.

Table 7 The relative risk of all-cause mortality for selected indices of fine particles (per 18.6 µg/m^3) based on multivariate Poisson regression analysis and log-likelihood goodness of fit for models using the different indices. (Adapted from Tables 5 and 6 of Villeneuve *et al* (2002) Ann. Epidemiol. 12(8): 568-576. Copyright (2002), with permission from the American College of Epidemiology. http://www.sciencedirect.com/science/journal/10472797).

Model	$PM_{2.5}$ exposure city-specific index	Relative risk (all ages)	Log-likelihood goodness of fit
1	Fixed exposure over entire follow-up (mean level)	1.31 (1.12-1.52)	9964.6
2	13 calendar periods (no smoothing)	1.19 (1.04-1.36)	9970.3
3	13 calendar periods (smoothing)[a]	1.16 (1.02-1.32)	9971.5
4	Time-dependent (last 2 years)	1.16 (1.02-1.31)	9971.5
5	Time-dependent (3-5 years before current year)	1.14 (1.04-1.27)	9971.2
6	Time-dependent (> 5 years before current year)	1.14 (1.05-1.23)	9967.3
7	No index of air pollution	n/a	9976.7

[a] Log-linear regression on annual mean $PM_{2.5}$ levels. The calendar periods were 1970-1978, 1979, 1980, 1981….1989 and 1990+. (Note that direct measurement of $PM_{2.5}$ was not available prior to 1979, levels were assumed to be the same as the first annual mean measurement available after that time).

31. Laden *et al* (2006) also examined the effect of different $PM_{2.5}$ concentrations at different times in the Six Cities study but the results were based on longer follow-up through to 1998. Where direct measurement of $PM_{2.5}$ was absent, levels were inferred from visibility data or PM_{10} data (r=0.93 for inferred data and measured data where both were available). Annual mean $PM_{2.5}$ concentrations decreased during the time of the study in all cities but most dramatically in the dirtiest cities. Cox proportional-hazards modelling was used.

32. The relative risk for all-cause mortality for a 10 µg/m^3 increase in $PM_{2.5}$ (based on city-specific means over the whole period) was 1.16 (1.07-1.26). Using city-specific means over period 1 (1974-1989 represented by measurements in 1980-1985) instead gave a relative risk of 1.18 (1.09-1.27). The relative risk for the decrease from period 1 to period 2 (1990-1998), controlled for period 1 was 0.73 (0.57-0.95)[2]. This suggests that the effect is at least partially reversible over a decade or so. This was not the case for lung cancer mortality which is known to take longer to occur and longer to reverse.

33. An analysis was also done in which mortality was related to $PM_{2.5}$ in the year before death. This gave a relative risk of 1.14 (1.06-1.22) – very similar to that for the entire period. The authors state that this also suggests that the mortality effects may be

[2] The relative risks in this paragraph probably used deaths over the whole follow-up period as only one value is given for total cases in Table 3 of the paper (see Table 8 below).

partially reversible, possibly over time-periods as short as a year. It was also noted that there appears to be a second independent effect that could be described as the development of chronic disease. However, it was noted that the study's ability to assess the appropriate time-scale was limited because, although $PM_{2.5}$ levels declined, the ranking of cities did not change substantially over most of the study period. Direct measurement of $PM_{2.5}$ was not available for the whole of period 2. Finally, although there was follow-up information on individual risk factors (e.g. smoking) available for the first period, this information was not used which could have led to misclassification of confounders. (The authors argue that this was examined in the HEI reanalysis and did not substantially change the conclusions). However, there was no follow-up information on individual risk factors in period 2 and period 2 was not examined in the HEI reanalysis.

Table 8 Adjusted proportional hazard mortality rate ratios and 95% confidence intervals for a 10 μg/m^3 increase in average $PM_{2.5}$ from the entire period and specific time-periods. Adapted from Table 3 of Laden *et al* (2006) 'Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study.' American Journal of Respiratory and Critical Care Medicine 173(6): 667-672. Official Journal of the American Thoracic Society, Diane Gern, Publisher. Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society.

	Model 1		Model 2	
	Cases	RR for entire follow-up average $PM_{2.5}$	RR for period 1 average $PM_{2.5}$	RR for decrease in average $PM_{2.5}$ from Period 1 to Period 2
Total mortality	2,732	1.16 (1.07-1.26)	1.18 (1.09 – 1.27)	0.73 (0.57-0.95)
Cardiovascular	1,196	1.28 (1.13–1.44)	1.28 (1.14-1.43)	0.69 (0.57-0.95)
Respiratory	195	1.08 (0.79-1.49)	1.21 (0.89-1.66)	0.43 (0.16-1.13)
Lung cancer	226	1.27 (0.96-1.69)	1.20 (0.91-1.58)	1.06 (0.43-2.62)
Other	1,115	1.02 (0.90-1.17)	1.05 (0.93-1.19)	0.85 (0.56-1.27)

34. Schwartz *et al* (2008) also examined the Six Cities study for evidence of time-dependence. A series of distributed lag models were set up considering only the same year's exposure, the same year's exposure plus the previous year's exposure and so on up to exposure 5 years before death giving a total of 11 models. The reason for excluding models considering exposure more than 5 years before death is not given. The models were then each assigned a posterior probability given the fit to the data and the models averaged using the posterior probability as a weighting. The results are shown in Figure 6. It was concluded that the effect was almost entirely due to exposure within the last 2 years. For lung cancer, the coefficients were higher and the effect was accounted for by exposure within the previous 3 years. (The latter seems implausible, particularly for an onset lag, unless the impact on lung cancer mortality is unrelated to the genotoxic effects of particles and is related instead to, say, inflammation in the lung worsening lung cancer prognosis. This issue is not discussed in the paper.) Although not mentioned, caveats regarding measurement error and the caveats discussed in paragraph 30 in discussing the paper by Laden *et al* (2006) will still apply as the same dataset is being used.

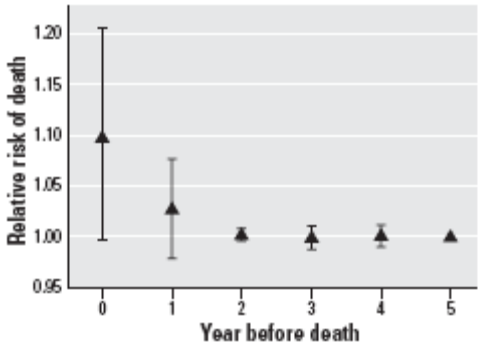


Figure 4. The model-averaged estimated effect of a 10-μg/m^3 increase in $PM_{2.5}$ on all-cause mortality at different lags (in years) between exposure and death. Each lag is estimated independently of the others. Also shown are the pointwise 95% CIs for each lag, based on jacknife estimates.

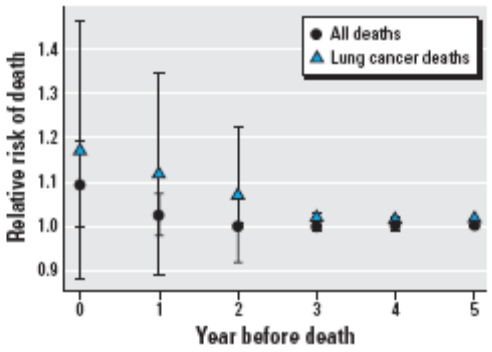


Figure 5. The model-averaged estimated effect of a 10-μg/m^3 increase in $PM_{2.5}$ on all-cause mortality and on lung cancer mortality. The estimated effect for lung cancer remains elevated up to 3 years preceding the death. Also shown are the pointwise 95% CIs for each lag, based on jacknife estimates.

Figure 6 Six Cities study relative risk according to time of exposure before death (from Schwartz *et al,* 2008). Reproduced with permission from Environmental Health Perspectives.

35. The studies described in paragraphs 27-34 come to widely varying conclusions from the same (Six Cities) cohort. This illustrates the uncertainties in coming to views about plausible lags from the evidence currently available. It is a pity that the most recent paper (Schwartz *et al,* 2008) does not discuss these varying conclusions as the authors' views on this would be interesting. There are some differences between the studies. Krewski *et al* (2000) and Villeneuve *et al* (2002) are based on a shorter follow-up (1974-1989 rather than 1974-1998). They included information on confounders from follow-up questionnaires as well as at baseline. Laden *et al* (2006) and Schwartz *et al* (2008) only used information on confounders at baseline. Their argument that this is reasonable, given that the HEI reanalysis (Krewski *et al,* 2000) found that it did not make a significant difference to the results, applies to the 1974-1989 period. It is unknown whether it applies to the 1990-1998 period but there is no updated information on individual confounders from this period anyway. The studies by Laden *et al* (2006) and Schwartz *et al* (2008) will have greater statistical power as there are greater numbers of deaths with longer follow-up. Schwartz *et al* (2008) did not consider exposure more than 5 years before death. Drawing these varying conclusions together will be returned to in the Discussion.

36. Amongst other studies, Puett *et al* (2009) also considered exposure up to 5 years before mortality in women in the Nurses' Health Study. A GIS-spatial smoothing model was used to predict monthly $PM_{2.5}$ concentrations using $PM_{2.5}$ measurements post 1999 and PM_{10} measurements prior to 1999. Unlike some other cohorts, residence history and individual confounders were updated every 6 months. The authors focussed on average exposure in the 12 months prior to the outcome but also considered average exposure in the 1, 3, 24, 36 and 48 months prior to the event. The Cox proportional-hazards models were adjusted for state of residence, year and season. The results are

shown in figure 7. The authors concluded that associations were stronger with times greater than 3 months than with 1 month but were similar for 12-48 months. (There appears to be a trend from 3 to 36 months but this may not be significant given the confidence intervals overlap).

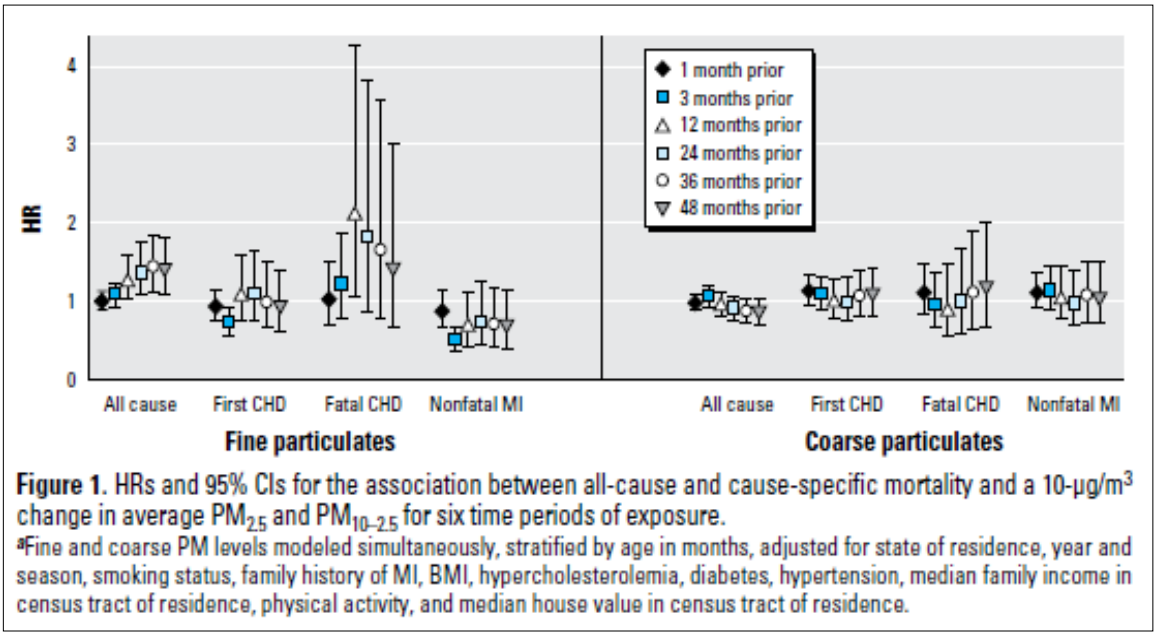


Figure 1. HRs and 95% CIs for the association between all-cause and cause-specific mortality and a 10-μg/m^3 change in average $PM_{2.5}$ and $PM_{10-2.5}$ for six time periods of exposure.
[a]Fine and coarse PM levels modeled simultaneously, stratified by age in months, adjusted for state of residence, year and season, smoking status, family history of MI, BMI, hypercholesterolemia, diabetes, hypertension, median family income in census tract of residence, physical activity, and median house value in census tract of residence.

Figure 7. Hazard ratios from the Nurses' Health Study according to time of exposure before death (from Puett *et al,* 2009). Reproduced with permission from Environmental Health Perspectives.

37. Enstrom (2005) examined the risk of fine particles in the Californian Cancer Prevention study I. In a subgroup analysis, it was found that, while the relative risk for the initial decade (1973-1982) of follow-up (1.016 95% CI 0.996-1.035) was positive and statistically significant, the relative risk for the last two decades of follow-up (0.997 95% CI 0.978-1.016) was neither positive nor statistically significant. It was acknowledged that an effect in the last two decades could not be ruled out as the upper confidence interval exceeded one. One possible explanation for this is that there is a long lag and that those that died in the initial decade had experienced much higher concentrations a long time before. Those that died in the last two decades may not have experienced these concentrations. However, this is not the only possible explanation. For example, there may be cohort effects (see paragraph 17) or differences in sensitivity with age.

38. In a response to the critique by Brunekreef and Hoek (2006), Enstrom (2006) did an analysis comparing the use of the average of 1979-1983 $PM_{2.5}$ (as used in the original Enstrom paper) with the average of 1979-1983 and 1999-2001 $PM_{2.5}$. The relative risks were similar which may suggest it is long-term exposure that matters. Results were not given for 1999-2001 $PM_{2.5}$, perhaps because it would have post-dated most of the deaths. The relative risk was again positive and statistically significant for 1973-1982 follow-up but not for 1983-2002 follow-up when the average of 1979-1983 and 1999-2001 $PM_{2.5}$ rather than just 1979-1983 was used. This suggests that the lack of an

association in the later period of follow-up seen in the first paper was not due to exposure misclassification as a result of having no estimate of $PM_{2.5}$ in the later period.

39. Although not strictly a general population study, the Seventh Day Adventist study may be closer to the general population than, for example, a cohort with pre-existing disease. McDonnell *et al* (2000) examined the effect of $PM_{2.5}$ in a subset of Seventh Day Adventists from the AHSMOG study that lived close enough to airports to use airport visibility data to derive $PM_{2.5}$ concentrations interpolated to home addresses. Only males were examined as results for females were weak or inverse (in contrast to the Nurses' Health Study above which found effects in women). To separately evaluate effects of long-term and more recent exposure, a short-term exposure variable was created by subtracting the mean concentration from 1973 to the date of the death event from the concentration in the 1, 2 or 3 months preceding the event. This gave a short-term deviation from the long-term average. These short-term deviation terms did not have a significant effect on the relationship with all-cause or cardio-respiratory mortality leading the authors to conclude that the effect was a result of long-term exposure. (Deviations from the long-term average of recent exposure in the preceding few years were not examined).

40. Eftim *et al* (2008) evaluated the effect of long-term exposure to $PM_{2.5}$ on mortality in an elderly cohort (65+) derived from Medicare records. It was only possible to control for smoking indirectly using standardised mortality ratios for lung cancer and COPD. This is a dynamic cohort where new enrollees in Medicare can be added over time. In the long-term this may help with understanding the interplay between cohort effects and lag effects but the analysis in this paper only used the 2000-2002 average of $PM_{2.5}$ for the main analysis. Relative risks relating this measure to mortality in 2000, 2001 and 2002 led to similar results but this is not especially informative about lags when exposure is averaged over all these three years. Results were unaffected when $PM_{2.5}$ was averaged over the 1999-2001 period instead but this is still very close in time to the time when deaths occurred.

41. Another study using Medicare data (Janes *et al,* 2007) examined the effect of the previous 12 months exposure to $PM_{2.5}$. The paper concentrated particularly on the risk of confounding bias by analysing the data on both the spatial and temporal scale. They examined associations between temporal changes in $PM_{2.5}$ exposure and mortality at both the national scale and the county scale. They argued that, if the risk estimates are free of confounding, then the estimate should be the same at the national scale as at the county scale. However, it was found that there were large associations at the national scale and no significant associations at the local scale. For example, the percentage change for the national trend was 3.5% (95% CI 2.77 to 4.34) per $\mu g/m^3$ $PM_{2.5}$ in men aged 65-74 but small and insignificant (0.04% (95% CI -0.58 to 0.67) per $\mu g/m^3$ $PM_{2.5}$) for the local trend. The authors consider that confounding is more likely at the national scale than at the local scale. Similar results were found for men and women aged 75-84 and 85 and over, although the percentage changes were lower (2.48% or lower for the national trend; negative or < 0.01 for the local trend.)

42. The authors argue further that the overall results are effectively a weighted average of the results at these two scales and that it is inappropriate to combine such different results. (The overall results were positive and significant, the largest association being 1.48% (95% CI 0.93 to 2.03) for men aged 65-74 but this was an average of a large significant increase for the national trend and a small insignificant increase for the local trend.) A confounded national result plus no significant local scale associations adds up to a lack of evidence for an effect of 12 month exposure to $PM_{2.5}$. The findings were similar when the previous 2 years exposure was considered instead of the previous year. This is clearly an important counter-view to, for example, Schwartz *et al* (2008) which argued that the majority of the effect occurred as a result of exposure in the first 12 months and almost all of it in the first 2 years. However, the Medicare data does not have the same level of information on individual confounders as the Six Cities cohort.

43. Of the other studies examining $PM_{2.5}$ and all-cause mortality in general population cohorts, Beelen *et a*l (2008) concluded that it was too difficult to determine which exposure period was important when exposure in different periods was so closely correlated. Jerrett *et al* (2009) considered that there was insufficient exposure contrast. Naess *et al* (2007a) noted that their study only considered exposure up to 3 years before (1992-1998 mortality was related to an average of $PM_{2.5}$ concentrations from 1992-1995). They were able to show a positive and statistically significant association in the upper quartile of exposure. (There was no control for smoking in this cohort; the authors argue that control for socioeconomic status partly takes smoking into account). Zeger *et al* (2008), Jerrett *et al* (2005), Naess *et al* (2007b) and Ostro *et al* (2010) give no information on time-dependence.

2.2 Intervention studies

44. As can be seen from the discussion above, it can be very difficult to come to a clear conclusion on the question of lags from the cohort studies. Correlation between different exposure periods is a particular challenge. Intervention studies, if they involve a sharp and large change in pollution levels, may therefore provide useful additional information. The studies discussed below are not limited to $PM_{2.5}$ as a particle metric as it less likely that, given the different design of the studies, the results would be used quantitatively to determine the proportion of the cohort effect at different lags. Rather, the studies are being examined for qualitative or semi-quantitative insights.

45. The ban on coal sales in Dublin in 1990 led to a sharp drop in levels of black smoke (35.6 $\mu g/m^3$) (Clancy *et al*, 2002). An immediate drop in standardised death rates that was sustained (with seasonal fluctuations) could be seen in a graph of seasonal death rates against time (see Figure 8a below). However, the values for deaths per 1000 person-years in these plots are unadjusted. The paper notes that there were five flu epidemics in the period of the study. One of these was from December 1989 to January 1990, the winter before the ban on coal sales in September 1990. This may have exaggerated the apparent effect in the first year.

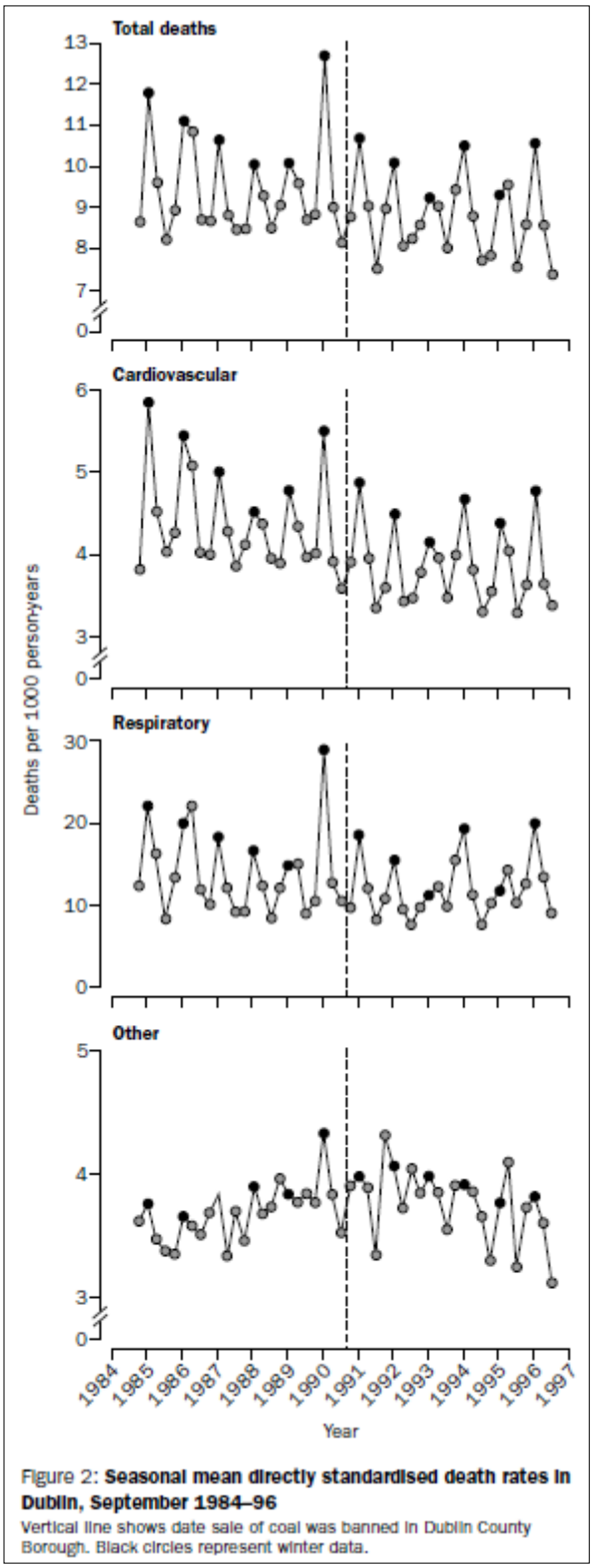


Figure 2: **Seasonal mean directly standardised death rates in Dublin, September 1984–96**
Vertical line shows date sale of coal was banned in Dublin County Borough. Black circles represent winter data.

a)

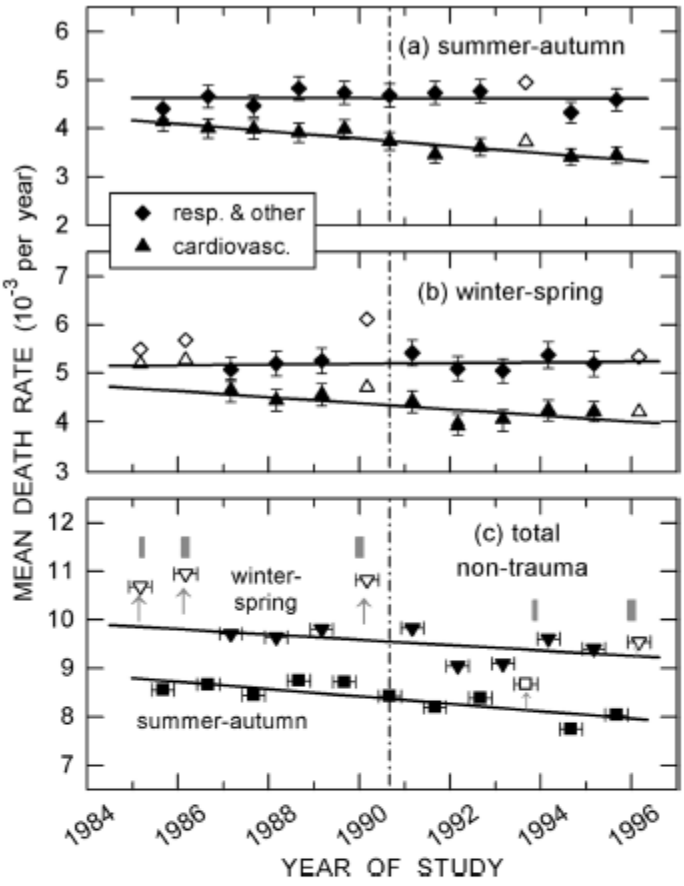


FIG. 3. Time dependence of the mean death rates due to cardiovascular symptoms and the sum of respiratory and other causes for half-year periods, (a) summer and autumn, (b) winter and spring. The error bars indicate the standard deviation derived in determining the mean of the data for respiratory and other causes, ±3.6% for summer–autumn, ±2.6% for winter–spring. (c) Total nontrauma death rates for winter–spring and summer–autumn. The number of data points for the periods before and after the ban is the same (the autumn 1984 and the summer 1996 data could not be included because the summer 1984 and autumn 1996 data are missing). The gray vertical bars denote the duration of epidemics. The straight lines represent the results of linear regression analysis, excluding the data denoted by open symbols, which were sometimes strongly enhanced by the epidemics.

b)

Figure 8 Seasonal mean directly standardised death rates in Dublin, September 1984-96 (unadjusted). Figure 8a reprinted from The Lancet, 360 (9341) Clancy *et al* 'Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study' pp 1210-1214. Copyright (2002) with permission from Elsevier. http://www.sciencedirect.com/science/journal/01406736. Figure 8b reproduced from Wittmaack (2007) with permission from Informa Healthcare.

46. A paper by Wittmaack (2007) discusses the effect of epidemics further and argues that three severe pre-ban winter-spring epidemics and the general decrease in cardiovascular mortality rates over the period could account for the apparent correlation between reduced mortality and reduction in black smoke. In an analysis later in the paper (see below), Clancy *et al* (2002) did control for trends in mortality rates by using trends in the rest of Ireland and for epidemics by the use of indicator variables. Wittmaack (2007) does not comment on this but analyses the data by omitting times influenced by epidemics and looking at whether the time trends in the non-epidemic data within Dublin were affected by the ban on coal sales (Figure 8b). He concludes that there was a gradual decline in total non-trauma deaths (from about 9 (summer) or 10 (winter) deaths per 1000 per year in 1984 to about 8 (summer) or 9 (winter) deaths per 1000 per year in 1996) that was unaffected by the ban in coal sales in 1990.

47. Returning to the paper by Clancy *et al* (2002), fully adjusted results were presented for the 5 years before and the 5 years after the ban. This showed a 5.7% drop in non-trauma mortality rates (Table 9). Wittmaack (2007) did not do an equivalent analysis but looked at the relationship between 6 monthly black smoke concentrations and 6 monthly mortality rates (excluding epidemic periods) in the years before the ban when concentrations were higher. Mortality rates stayed steady or even decreased slightly as black smoke concentrations increased. This was used to argue against the plausibility of even the gradual decline that was shown in general mortality rates in non-epidemic periods being due to black smoke. This is one possible explanation. Another that is not discussed is that the slope may flatten off at higher concentrations (although the range of 30-80 $\mu g/m^3$ black smoke is lower than in some of the classic studies showing flattening off of the relationship at, for example, concentrations greater than 300 $\mu g/m^3$ (Schwartz and Marcus, 1990)). Visual inspection of Figure 4 of Wittmaack (2007) (not shown) suggests that there may be a positive relationship between winter and spring black smoke and mortality rates after the ban, even ignoring epidemic periods. This is less clear for summer and autumn black smoke. However, this is probably better analysed with proper control for temperature as was done by Clancy *et al* (2002).

Table 9 Change in age-standardised total and cause-specific mortality rates for Dublin County Borough 72 months before and after the ban of sale of coal in Dublin (Adapted from The Lancet, 360 (9341) Clancy *et al* 'Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study' pp 1210-1214. Copyright (2002), with permission from Elsevier. http://www.sciencedirect.com/science/journal/01406736)

Mortality Outcome	Adjusted % change (95% CI)	p-value
Total		
Non-trauma	-5.7 (-7.2 to -4.1)	<0.0001
Cause-specific		
Cardiovascular	-10.3 (-12.6 to -8.0)	<0.0001
Respiratory	-15.5 (-19.1 to -11.6)	<0.0001
Other	1.7 (-0.7 to 4.2)	0.17

Adjusted in robust Poisson regression for temperature, relative humidity, day of the week, respiratory epidemics and standardised cause-specific death rates in the rest of Ireland.

48. Bearing these controversies in mind, a 5.7% decline in mortality due to a 35.6 $\mu g/m^3$ decline in black smoke is equivalent to a 1.6% decline in mortality for a 10 $\mu g/m^3$ decrease in black smoke. If it is assumed that other sources of $PM_{2.5}$ (e.g. regional background secondary particles) stay the same, then the change in $PM_{2.5}$ would be about the same. 1.6% is roughly a quarter of the 6% change in mortality per 10 $\mu g/m^3$ change in $PM_{2.5}$ found in the ACS study. Depending on one's view of the criticisms in Wittmaack (2007), this could be viewed as providing some support for the view that a reasonable proportion of the effect picked up in the cohort studies occurs in the first few years. Conversely, it may suggest that respiratory epidemics may need consideration in other studies too, as the distinction between time-series studies and cohort studies becomes more blurred by analysis of time-varying covariates from cohort study data on a time-scale of only a year or two (although across different places and over an extended period).

49. Roosli *et al*, (2005) used the results of the Dublin study to derive a time constant for the speed of the decline in mortality after a sharp reduction in pollution. The change in mortality during a given time-period (% change in mortality times years) was modelled as excess relative risk times time (i.e. assuming the full additional relative risk due to air pollution remained for the entire time) minus the integral of the excess relative risk times e^{-kt}. The latter term assumes an exponential decrease in relative risk (chosen because many biological changes take an exponential form) after time elapses with the speed of the decrease determined by the time-constant k. The derived time constant was calculated as 0.11 for the Dublin study compared with 0.88 for the Utah Valley steel mill study (see paragraph 54). A time-constant of 0.1 gave an estimate of 9.5% of the total effect of a reduction occurring within the first year, 18.1% in the first 2 years and 39.3% in the first 5 years (Table 10).

Table 10 Estimated proportion of effect within different time-periods for different values of time constant k in a dynamic exposure response model. Modified from Roosli *et al* (2005) with permission of the author. Reproduced with the permission of the Oxford University Press.

Time constant k	0.1	0.2	0.5	3	∞[a]
Time-period considered (years)	30	20	10	10	1
Proportion of effect within first year	9.50%	18.10%	39.30%	95.00%	100.00%
Proportion of effect within first 2 years	18.10%	33.00%	63.20%	99.80%	100.00%
Proportion of effect within first 5 years	39.30%	63.20%	82.00%	100.00%	100.00%
[a]Corresponds to steady state model					

50. The paper by Clancy *et al* (2002) does not provide any information about whether there is any effect after a delay of more than 5 years. A subsequent paper by Kabir *et al* (2007) did examine lung cancer but this was not designed in such a way as to give information on longer lags. The approach taken was to use log-linear Poisson regression of annual population-standardised lung cancer death rates, looking at the changes in these rates over time while controlling for black smoke (with a one year lag) and smoking prevalence (annual, lag not mentioned). An interaction term between black smoke and smoking was also included. The one-year lag with black smoke was justified on the basis that (i) it was the best fit (different lag periods were examined but no details are given); (ii) if air pollution acts at a late stage of the carcinogenic process, more recent exposures are likely to be important (iii) lung cancer patients may be susceptible groups for the deaths brought forward and harvesting found in time-series studies and (iv) a drop in lung cancer in the late 1950s following the 1956 Clean Air act.

51. Relative risks were expressed relative to 1990 both before and after the ban (Table 11). Although it was not the author's interpretation, the first interpretation might be that the data does not allow any conclusions regarding differences before and after the ban as the confidence intervals overlap substantially. The whole model was significant (it is unclear what is meant by this but it probably indicates that the variation in the data explained by the model was significant in comparison with the unexplained variation i.e. the model was better than no model). Setting aside the overlapping confidence intervals, there was a reduction in relative risk when black smoke was included in the model comparing mortality before the ban with that in 1990. Inclusion of smoking in the model led to a further reduction in relative risk to below 1. In other words, once the higher levels of black smoke and smoking are taken into account, mortality rates before 1990 are no different from those in 1990. There is not such a marked change in size of

the relative risk when going from the basic model to the model including black smoke after the ban. The authors conclude that there is a temporal association between black smoke and lung cancer death rates. They also conclude (based on the right hand column) that a slightly greater decline in death rates (2%) was achieved in the pre-ban period when black smoke was high but a lower decline in death rates (1%) occurred when black smoke concentrations were low. Overall, the paper is aimed at trying to explain trends in lung cancer over time. It is difficult to conclude much about lags other then that it appears possible to demonstrate a temporal association between black smoke and lung cancer with a one year lag. It is a pity that the other lag periods that were ruled out were not described.

Table 11. Adjusted Rate Ratios of Population-Standardised Lung Cancer Death Rates in Dublin across three Log-Linear Poisson Models between two periods (1981-1990 and 1991-2000). From Kabir *et al* (2007) http://www.imj.ie//ViewArticleDetails.aspx?ArticleID=1816 Reproduced with the permission of the Irish Medical Journal.

	Basic Model (Adjusted for age and gender)	Basic Model +Black Smoke (BS)	Basic Model +BS+ Smoking
	RR (95% CI) *	RR (95% CI)	RR (95% CI)
1981-1990	1.06 (0.93, 1.22)	1.01 (0.86, 1.18)	0.98 (0.83, 1.15)
1990	Reference (RR=1)	Reference (RR=1)	Reference (RR=1)
1991-2000	0.97 (0.85, 1.11)	0.98 (0.86, 1.12)	0.99 (0.87, 1.13)
Whole model:	p=0.01	p=0.01	p=0.01
Deviance:	1.40	1.36	1.35
*RR=Rate Ratio; CI=Confidence Interval			

52. Coal sale bans were also implemented in other cities in Ireland in 1995 and 1998. According to a recent abstract (Dockery *et al*, 2010), mean black smoke levels (but not sulphur dioxide) fell in all centres after the ban. Using similar methods to the 2002 paper, they found significant reductions of 3, 8 and 7% for the 1990, 1995 and 1998 bans. No detailed information on time-scales is given other than a statement that the reductions were immediate and sustained. A full paper on the results is not yet published, although a previous abstract on the 1995 County Cork ban is available (Rich *et al*, 2009).

53. The studies on the ban in coal sales in Dublin have been considered in some detail as the study by Clancy *et al* (2002) has been quite influential. A similar study published in the same year (Hedley *et al*, 2002), looked at changes in death rates after a marked reduction in the sulphur content of fuel oil. A reduction in mortality occurred in the year after the measure was implemented, which returned to the predicted pattern after 5 years. However, there was no change in levels of PM_{10}. Levels of sulphur dioxide were reduced and regional ozone increased. Later work from this group has been examining the composition of PM_{10} over this period and found that levels of nickel and vanadium also changed at the time of the intervention. Description of this work is only available as an abstract (Wong *et al,* 2009). The abstract also indicated that a methodology was developed to apply distributed lag models from time-series methodology to analysis of longer time-windows (windows of up to 4 years were used). The relationship between daily deaths and PM_{10} and SO_2 was statistically significant for windows up to 3.5 years.

54. Another classic 'intervention' study relates to the closure of a steel mill in the Utah valley due to a strike. The original study (Pope, 1989) examined respiratory hospital admissions rather than mortality but a later time-series study of PM_{10} and mortality in the Utah valley included the period of the strike (Pope *et al*, 1992). PM_{10} levels dropped from an average of 50 $\mu g/m^3$ to 35 $\mu g/m^3$ during the 13 month period of the strike. The Poisson regression coefficient derived from the overall time-series study (1.6% per 10 $\mu g/m^3$ 5-day moving average) predicted that daily mortality would average 2.3% higher when the mill was open rather than closed. Actual average deaths per day were 3.2% higher when the mill was open. Although the results were expressed in terms of higher deaths when the mill was open, this does suggest that the 13 months when the steel mill was closed was sufficient time for a decrease in mortality to be shown that was somewhat greater than that explained by day to day changes.

55. Another paper relating to industrial strikes was published more recently (Pope *et al*, 2007). This analysed the effect of a copper smelter strike from mid July 1967 to the beginning of April 1968 in 4 South-western US states. Various models were used to estimate the decrease in mortality during the strike. The estimates varied from about a 1.5% to a 4% decrease in mortality during the strike. The author highlighted, as an example, an estimate of 2.5% (95% CI 1.1 – 4.0%) based on a model that used a strike period indicator for full strike months plus a 1 month lag controlling for time trends, mortality counts in bordering states and nationwide mortality counts for influenza/pneumonia, cardiovascular and other respiratory deaths. This was a somewhat larger estimate than estimates including the first partial month of the strike and excluding a 1-month lag. Lags of more than 1 month were not considered. The results were not directly related to pollutant concentrations but it was noted that there was a regional strike-related reduction in sulphate particles of about 2.5 $\mu g/m^3$. The authors add that using results from the Utah valley study and the Dublin study would have predicted a decline of about 0.8-1.1% in mortality. The ACS study and the Six Cities study would have predicted declines in mortality of 1.5% and up to 4% respectively (presumably assuming no lag). No comparison was made with time-series coefficients but they would be likely to predict smaller declines.

56. Other intervention studies are briefly outlined and the implications of this strand of research discussed in the proceedings of a Health Effects Institute workshop on the subject (Health Effects Institute, 2010). Not all of the intervention studies discussed at the workshop have been discussed above – some only relate to emissions changes, some to only cause-specific mortality, some to outcomes other than mortality and some to more minor changes over longer periods of time.

57. In summary, the intervention studies do provide support for an effect larger than that seen in the time-series studies in the first few years after an intervention. They have the advantage that they clearly relate to cessation lags. None of the studies used $PM_{2.5}$ as a metric. Within the uncertainties of interpretation and the use of different metrics, the results suggest anything from about a tenth (Roosli *et al,* 2005) through to the majority of the effect seen in the cohort studies (Pope *et al,* 2007) occurring within the first year.

2.3 Distributed lag studies

58. As distributed lag studies arose in the context of the interpretation of time-series studies and COMEAP will be considering short-term effects separately, this area of the literature is not covered in detail here. However, a few points will be noted. (This overview does not cover distributed lag studies of only a few days). From 1999-2003, several studies were published suggesting that effect sizes were increased when considering time-scales up to about 40 days rather than just 1 or 2 days (Dominici *et al*, 2003; Schwartz, 2000a; Schwartz, 2000b; Schwartz, 2000c; Zanobetti *et al*, 2002; Zanobetti *et al*, 2003; Zanobetti *et al*, 2000; Zeger *et al*, 1999; Zeger *et al*, 2000) as well as one study which did not support this (Murray and Nelson, 2000). More recently, the conclusions of studies have become more mixed. A series of methodological papers (Fung *et al*, 2005a; Fung *et al*, 2005b; Roberts and Martin, 2007; Roberts and Switzer, 2004; Welty *et al*, 2009) have extended the debate with some papers suggesting that distributed lag models can be misleading with regard to mortality displacement in some circumstances (e.g. Fung *et al*, 2005b; Roberts and Switzer, 2004). Only a few studies used $PM_{2.5}$ as a metric, an example of a paper that did is described here.

59. Schwartz (2000a) examined mortality data from Boston and separated the time-series into long wavelength components (representing time trends and seasonal fluctuations), mid-scale components and very short scale components. The mid-scale components were then examined in more detail as they omit potentially confounding effects of season and the component subject to short-term harvesting. The midscale was divided into windows of 0, 15, 30, 45 and 60 days. The percentage increase in all-cause mortality per 10 $\mu g/m^3$ $PM_{2.5}$ increased steadily from 2.1% (95% CI 1.5-4.3%) to 3.75% (95% CI 3.2-4.3%) across these windows. If the deaths over this medium time-scale were only occurring in people with a few weeks to live, this would not have occurred. The effect would have been cancelled out by a reduction in the number of deaths when those who died earlier would have been expected to have died in the absence of air pollution. The size of these coefficients approaches those found in the cohort studies, providing support for the idea that a reasonable proportion of the long-

term effect is apparent in the first year. This is, however, subject to the methodological debates mentioned above.

2.4 Infant mortality studies

60. Again, this area of the literature will not be considered in detail here. There are reviews available (Glinianaia *et al*, 2004; WHO, 2005). WHO concluded that there was solid evidence for an impact of air pollution on infant mortality, primarily due to respiratory deaths in the post-natal period. COMEAP broadly supported the WHO conclusions in a subsequent statement (COMEAP, 2008). Most of the studies have used TSP or PM_{10} but the effect has been confirmed in a later study using $PM_{2.5}$ (Woodruff *et al*, 2006). The latter study was a matched case-control study in which the $PM_{2.5}$ concentrations were averaged for the period between birth and the post-neonatal death (deaths between 1 month and 1 year). The same time-period was used to calculate the exposure for the matched controls who survived to 1 year. Thus, exposure periods could be between a few days and a year. While infant mortality did not contribute directly to the ACS study results (this only applied to adults over 30), it again demonstrates that effects of fine particles can be detected on time-scales of a year or so.

3. Mechanistic information

61. The section above has illustrated how difficult it is to get information on time-dependence directly from the epidemiological studies. Knowledge of the biological mechanisms involved would allow some predictions about lags. Is there helpful information on this point, either from the epidemiological studies or from other sources?

62. The most obvious information is on cause-specific mortality. There are raised relative risks for cardio-pulmonary mortality and lung cancer mortality (COMEAP, 2009). Within cardiopulmonary mortality, there was some surprise, when the HEI Reanalysis was published, that the main effect seemed to be on cardiovascular mortality (Krewski *et al*, 2000). This has also been supported by later follow-up of the ACS study (Pope *et al,* 2004) and the Six Cities study (Laden *et al,* 2006), although some other studies have found raised and almost significant risks for respiratory mortality (Beelen *et al,* 2008). Several other cohort studies have also shown effects on cardiovascular mortality e.g. Puett *et al* (2009); Miller *et al* (2007). Lung cancer mortality as a cause of death is useful in terms of inferring information on lag times since lung cancer is likely to take a substantial time to develop. It also takes time for risks to fall if exposure to a lung carcinogen ceases. Cardiovascular mortality on the other hand can be the result of both short-acting (e.g. triggers of arrhythmias) and long-acting risk factors (e.g. diet and long-term development of atherosclerotic plaques).

63. Pope *et al* (2004) looked at various different causes of cardiovascular death. The strongest relationship was with ischaemic heart disease (relative risk (RR) 1.18 (95% CI 1.14-1.23) per 10 $\mu g/m^3$ $PM_{2.5}$ compared with 1.12 (1.08-1.15) for all cardiovascular diagnoses) but there was still a relationship with 'dysrhythmias, heart failure and cardiac

arrest' (RR 1.13 (95% CI 1.05-1.21). Thus, none of the multiple mechanisms leading to cardiovascular mortality could be ruled out.

64. COMEAP (2006) discusses the various potential mechanisms for the link between air pollution and cardiovascular disease (short- or long-term exposure). This divided into two major types of mechanisms – neural and inflammatory. The neural mechanisms (whereby air pollution affects, for example, heart rate variability via receptors in the lung) would be expected to be short-acting. The inflammatory mechanisms, on the other hand, could be either short- or long-acting. Inflammation in the lung can affect clotting factors in the blood, leading to occlusion of a coronary artery already narrowed for other reasons. On the other hand, low-grade systemic inflammation over an extended period could lead to the accelerated development of atherosclerotic plaques.

65. An update of an earlier statement on particulate matter and cardiovascular disease from the American Heart Association has recently been published. Brook *et al* (2010) concluded that the overall epidemiological evidence is strong for an effect of particles on ischaemic heart disease; moderate (yet growing) for heart failure and ischaemic stroke; and modest or mixed for peripheral vascular disease and cardiac arrhythmia/arrest. The statement also concluded that the mechanistic evidence was strong for vascular dysfunction or vasoconstriction, moderate for enhanced thrombosis or coagulation potential; elevated arterial blood pressure and enhanced atherosclerosis or plaque vulnerability and that there was some evidence linking particulate matter with arrhythmias. In other words, there is evidence for both acute and chronic mechanisms.

66. If only short-acting mechanisms were operating, it is more likely that people who already had heart disease for other reasons would be affected. This is something that can be checked in an epidemiological context. The HEI Reanalysis (Krewski *et al*, 2000) examined this by looking at whether the relative risk differed in those with and without heart and lung disease at baseline. As shown in Table 12, the relative risk was actually higher (but not significantly so) in those <u>without</u> heart or lung disease at baseline ('other') compared with those with heart and lung disease at baseline. Of course, the absolute risk is higher in those with pre-existing disease. Unfortunately, there is no information other than at baseline so it cannot be ruled out that people with non-symptomatic heart disease at baseline contributed to the risk in those apparently without heart or lung disease. Perhaps it does, nonetheless, suggest that exacerbation of heart disease that is already severe enough to be diagnosed is not the only part of the effect i.e. there may be longer lags involved. Interestingly, the risk of all-cause mortality in those with cancer at baseline was substantially higher (although the CIs still overlapped) than in those without cancer, heart or lung disease at baseline. (This was less clear for sulphate). (The 'other' category is somewhat ambiguous as to whether it refers to the rest of the cohort without cancer, heart or lung disease including those with other diseases or is only those with other diseases. The footnote suggests the latter but the percentage of the cohort seems too high (the percentages add up to more than 100%, presumably because subjects can have more than one disease).)

Table 12 Relative risk of mortality from all causes associated with an increase in fine particles or sulphate by personal disease status at baseline. (Data from Table 21, Krewski *et al* (2000)).

	Fine particles per 24.5 µg/m^3		Sulphate per 19.9 µg/m^3	
Characteristic at baseline	% of cohort	All-cause mortality	% of cohort	All-cause mortality
Heart or lung[a]	37.1	1.15 (1.05-1.26)	37.2	1.15 (1.07-1.23)
Cancer[b]	10.1	1.34 (1.15-1.57)	9.9	1.19 (1.05-1.34)
Other[c]	63.7	1.19 (1.09-1.29)	63.2	1.12 (1.05-1.20)

[a] Defined as doctor-diagnosed high blood pressure, heart disease, stroke, chronic bronchitis, emphysema or asthma.
[b] Defined as any type.
[c] Other disease defined as diabetes, gall stones, chronic indigestion, kidney disease, kidney stones, bladder disease, cirrhosis of the liver, tuberculosis, stomach ulcer, duodenal ulcer, diverticulosis, rectal polyps, colon polyps, thyroid condition, arthritis, prostate trouble or hepatitis.

67. The categories are less ambiguous in a subsequent table showing results subdivided by level of education (see Table 13). In three out of four sub-divisions, the relative risk was higher in those without heart and lung disease, although not significantly so.

Table 13 Relative risk of mortality from all causes associated with an increase in fine particles or sulphate by personal disease status at baseline and level of education. (Data from Table 22, Krewski *et al* (2000)).

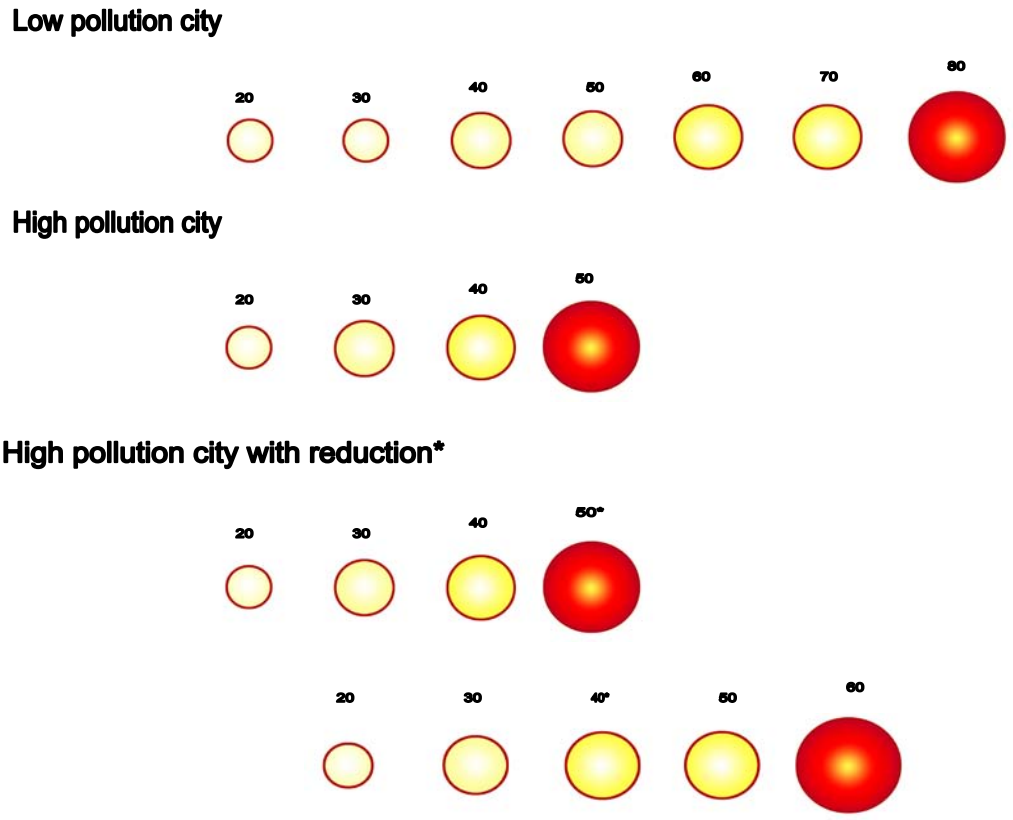
	Fine particles per 24.5 µg/m^3				**Sulphate per 19.9 µg/m^3**			
	High school or less		More than high school		High school or less		More than high school	
Characteristic	n	RR	n	RR	n	RR	n	RR
Heart or lung disease								
Yes	52028	1.26 (1.11-1.42)	61751	1.00 (0.87-1.15)	102663	1.26 (1.15-1.38)	110761	1.00 (0.90-1.29)
No	70911	1.29 (1.09-1.53)	114127	1.14 (0.97-1.35)	141377	1.17 (1.03-1.32)	204248	1.13 (0.99-1.29)

68. Later publications on the ACS study (Pope *et al,* 2002; Pope *et al,* 2004; Krewski *et al,* 2009) did not address this issue, perhaps because as follow-up continues disease at baseline becomes less relevant. The Six Cities study did not have data on disease at baseline. A similar effect has been seen in other studies, for example Miller *et al* (2007) found high relative risks for cardiovascular mortality in a cohort of women without cardiovascular disease at baseline. Puett *et al* (2009) found higher relative risks in those without diabetes or without hypertension at baseline. However, they did find that those with a family history of myocardial infarction or those with hypercholesterolaemia

had higher relative risks. The interaction was significant in the case of family history of myocardial infarction and fatal coronary heart disease.

69. It is worth stressing that disease processes with a long onset lag do not necessarily have to have a long cessation lag, an important point made by Professor Strachan during earlier discussions of the lag issue. A hypothetical example is represented in Figure 9. Development of atherosclerotic plaques happens with age in everyone (numbers above circles represent age). This is proposed to take 60 years to develop in a low pollution city and 30 years in a high pollution city (long onset lags). However, if air pollution is reduced in the high pollution city, it is suggested that the rate of development returns to that of a low pollution city albeit from a worse starting point. Rupture of a plaque at age 50 may not be prevented if people are already there when pollution is reduced. However, for younger cohorts, the rupture that would have developed from age 40 to age 50 is halted. It still happens later after reverting to the low pollution city rate. The cessation lag here is 10 years (occurs at 60 not 50). This demonstrates that cessation lag can be shorter than onset lag.

Figure 9 Hypothetical diagram of air pollution and onset and cessation of effects on development of atherosclerotic plaques



Circles show blood vessels. Yellow of increasing intensity represents growth of atherosclerotic plaques. Red represents rupture of plaques/thrombosis, vessel blockage and death. Calendar time goes from left to right and the numbers above the circles represent the age of the hypothetical subjects. The asterisk denotes the time of the air pollution reduction.

70. Tables earlier in the paper indicate that raised relative risks for lung cancer were found in the ACS study (Pope *et al,* 2002) (significant) and the Six Cities study (Laden *et al,* 2006) (marked but not significant). Raised significant lung cancer risks have been found by Abbey *et al* (1999) (PM_{10}, men only) and raised but non-significant risks have been found by Beelen *et al* (2008) (black smoke); Filleul *et al* (2005) (black smoke, association not found in all analyses) and Naess *et al* (2007a) (PM_{10}, significant in women over 71). Case-control studies results were mixed with one finding an effect (Barbone *et al*, 1995) and another not finding an effect (Vineis *et al*, 2006). An interaction with smoking has been suggested in some studies e.g. (Katsouyanni *et al*, 1991) with greater effects of air pollution in smokers. Many of these studies have been reviewed by Vineis *et al* (2004), Gallus *et al* (2008) and Valavanidis *et al* (2008). Vineis *et al* (2004) noted that the general air pollution cohort studies were not designed to study lung cancer and therefore have rather few cases (i.e. the lack of statistical significance often found may be due to insufficient statistical power rather than a lack of

effect). These studies also often have insufficient details on air pollution exposure decades before. There have been a couple of air pollution studies that used NO_2 as an indicator of traffic pollution (Nafstad *et al*, 2003; Nyberg *et al*, 2000) and found statistically significant raised risks. Both studies examined time-windows and found the strongest relative risks for an average exposure 20 -24 years before the end of follow-up and 21-30 years before follow-up respectively. There is therefore evidence from the air pollution literature for a long onset lag for lung cancer.

71. Particulate matter has been shown to be genotoxic and contains substances known to be genotoxic either directly or indirectly (oxidative damage following oxidative stress). This evidence is reviewed by Valavanidis *et al* (2008). It is entirely plausible that particulate matter acts at the early stage of lung cancer development. It is hard to see how this would be reversed quickly, if at all, since unrepaired mutations could already have become fixed in expanding clones of cancer cells. It is also possible that particulate matter acts at a later stage where further mutations lead to cancer progression. This might be more reversible as it could prevent the final step or one of the final steps before full expression of the cancer. Finally, cell damage due to inflammation could increase the rate of cell repair which can encourage cancer development. This might also be more reversible.

72. In summary, like the section on time-dependence, this section on mechanistic information is not clear cut with some evidence supporting both short-acting and long-acting mechanisms, or, at least not ruling either of them out.

4. Analogy with smoking and smoking cessation

73. Smoking also affects both heart disease and lung cancer but starting and cessation are more obvious than for air pollution and the higher level of risk may also help to distinguish information on onset and cessation lags. An overview of work from the smoking cessation literature is given in the following table.

Table 14 Results from the smoking cessation literature.

Outcome	**Reference and cohort**	**Subjects and sample size**	**Comment on results**
All-cause mortality	Doll and Peto (1976) British Doctors study (20 year follow-up)	34,500 male British doctors	Reduction in risk in first 5 years since quitting, then slow decline up to last follow-up (15-20 years) where risk still slightly raised.
All-cause mortality	Doll *et al* (2004)	34,439 male British doctors	Mortality rates were significantly reduced in former smokers who gave up at any age but the reduction was greater if gave up at a younger age. However, even in the youngest age group (35-44) mortality rates were still a little higher than in non-smokers.

Outcome	Reference and cohort	Subjects and sample size	Comment on results
All-cause mortality	Ben-Shlomo *et al* (1994)	19,000 male civil servants (Whitehall study)	Gradual reduction of risk over 30 years since quitting; risk still raised after 30 years but not statistically significant.
All-cause mortality	Aberg *et al* (1983)	983 men after first MI	Cumulative survival 78% after 5 years in those who quit within 3 months of the MI; 84% after 5 years in those that continued smoking, Mantel test showed significant difference between the survival curves over 8 years of follow-up.
All-cause mortality	Gordon *et al* (1974) (18-year follow-up)	2336 men (Framingham heart study)	Not able to study a detailed time-course of time since cessation. Overall mortality rates of those stating they had given-up at baseline were indistinguishable from those of non-smokers at baseline after 18 years of follow-up. For those who gave up during follow-up, mortality rates were about three-quarters of those of smokers (this reduction was less than that for incidence of CHD). The average length of follow-up after giving up was less than 6 years. NB Those giving up were mainly light smokers at baseline.
All-cause mortality	Omenn *et al* (1990)	21,112 men and women	Prompt decline in mortality risk within the first year of quitting but then a sustained modestly elevated risk for at least 20 years.
All-cause mortality	Burns *et al* (1997)	456,491 males, 594,551 females ACS CPSI	Risks remained elevated up to 15-20 years since quitting when combined across intensity of smoking. Heavy smokers continued to show elevated risks 30-35 years later.
All-cause mortality	Friedman *et al* (1997)	60,838 subjects Kaiser Permanente Medical Care Programme cohort study	Relative risks for all-cause mortality remained elevated until more than 20 years after quitting.
All-cause mortality	Hrubec and McLaughlin (1997)	95,783 never smokers and former smokers (US veterans study)	Relative risks remained elevated 20-29 years since quitting (30-39 years and possibly 40+ years in heavy smokers).
All-cause mortality	Kawachi *et al* (1997) (12 years follow-up)	117,001 women (Nurses' Health Study)	Risks among former smokers approached those of non-smokers 10-14 years after cessation.

Outcome	Reference and cohort	Subjects and sample size	Comment on results
All-cause mortality	Kenfield *et al* (2008) (22 years follow up)	104,519 women (Nurses' Health Study)	13% reduction in risk in first 5 years. Returned to level of non-smoker after 20 years.
All-cause mortality	Enstrom and Heath (1999)	118,094 subjects (California CPSI)	Risk was reduced to some extent in the first 5 years. Risk reduced near to that of non-smokers 20 years after quitting.
All-cause mortality	Ozasa *et al* (2008)	140,026 men, 158,610 women in 2 Japanese cohorts	Quitting at ages younger than 40 and at 40-49 had life-expectancy from 40 similar to non-smokers. This was not the case for quitting at 50-59 or 60-69.
Non-fatal or fatal myocardial infarction or coronary death	Dobson *et al* (1991)	1282 cases with fatal or non-fatal MI or coronary death, 2068 controls (Australian arm of MONICA project)	Risks did drop more than 5 years after quitting but were still about twice the risk of non-smokers. Risk of heart attack or coronary death substantially reduced and no longer statistically significant by 3 years after quitting (although risks remained slightly raised until 12 years after quitting).
Major IHD event (fatal and non-fatal)	Cook *et al* (1986)	7335 men (Regional British Heart Study)	Risk still 60% greater (although not quite statistically significant) more than 20 years after quitting.
Mortality due to ischaemic heart disease or myocardial degeneration	Doll and Peto (1976) British Doctors study (20 year follow-up)	34,500 male British doctors	Substantial reduction of risk in first five years after quitting (by up to about 45% for IHD in men aged 30-54 years, less at older ages). Continuation of slightly raised risk up to longest time since quitting (15-20 years) (Trend significant)
Coronary heart disease mortality	Ockene *et al* (1990)	12,866 men at increased risk of CHD (MRFIT)	Analysis of ex-smokers *vs.* smokers. Risk of CHD death substantially reduced one-year after quitting and further reduced at 3 years.
Coronary heart disease mortality	Burns *et al* (1997)	456,491 males, 594,551 females ACS CPSI	In men, relative risks dropped substantially after the first 5 years and then declined more gradually, remaining elevated until15-20 years after cessation (20-25 years in heavy smokers). Pattern less clear in women as there were fewer former smokers.

Outcome	Reference and cohort	Subjects and sample size	Comment on results
Coronary heart disease mortality	Ben-Shlomo *et al* (1994)	19,000 male civil servants (Whitehall study)	Risk still substantial in category '1-9 years since quitting', much reduced by 10-19 years since quitting but decline slow from then on (risk raised but not significantly after 30 years or more since quitting). (Trend with time not significant, perhaps because risk is lower than for lung cancer or all-cause mortality to start with)
Coronary heart disease mortality	Friedman *et al* (1997)	60,838 subjects Kaiser Permanente Medical Care Programme cohort study	Relative risks for CHD deaths remained elevated until more than 20 years after quitting.
Coronary heart disease mortality	Hrubec and McLaughlin (1997)	95,783 never smokers and former smokers (US veterans study)	Relative risks remained elevated 20-29 years but not 30-39 years since quitting.
Cardio-vascular mortality	Kawachi *et al* (1997) (12 years follow-up)	117,001 women (Nurses' Health Study)	There was a 24% reduction in risk of cardiovascular mortality within 2 years of cessation but risks among former smokers only approached those of non-smokers 10-14 years after cessation.
Coronary heart disease mortality	Kenfield *et al* (2008) (22 years follow up)	104,519 women (Nurses' Health Study)	61% of total CHD benefit of quitting occurred in first 5 years. Risk returned to level of non-smoker after 20 years.
Cardio-vascular mortality/ events	Kramer *et al* (2006)	2400 individuals with familial hypercholesterolaemia	Risk reduced to those of non-smokers within 6-9 years.
Cardio-vascular risk factors	Bakhru and Erlinger (2005)	15,500 subjects (NHANES III) (cross-sectional)	Inflammatory markers and triglycerides did not return to baseline until 5 years or more after ceasing smoking. Other cardiovascular risk factors did not show significant trends with time since cessation of smoking. Authors suggest inflammatory markers most important contributors to risk of smoking since they decline over the same time-scale as cardiovascular mortality.
Lung cancer mortality	Doll and Peto (1976) British Doctors study (20 year follow-up)	34,500 male British doctors	Gradual decline in risk but still substantially raised risk at 15-20 years after quitting (no data above 20 years).

Outcome	Reference and cohort	Subjects and sample size	Comment on results
Lung cancer mortality	Ben-Shlomo *et al* (1994)	19,000 male civil servants (Whitehall study)	Risk still very high 1-9 years after quitting, then drops continuously until back to normal more than 30 years after quitting (but very few deaths left). Trend highly significant. In those who had smoked more than 20 cigarettes per day for more than 20 years, risks only dropped to just under 50% of that in current smokers more than 30 years after cessation (but even smaller numbers of cases).
Lung cancer mortality	Peto *et al* (2000)	Case-control study (667 and 315 male and female lung cancer cases vs. 2108 and 1077 male and female controls)	Risks dropped by about a third compared with current smokers less than ten years after stopping smoking and to about a tenth of the risk in current smokers after 30 years (this was still higher than the risk in non-smokers). Risks fell more in women than men (?due to fewer cigarettes smoked when smoking).
Lung cancer mortality	Ebbert *et al* (2003)	Iowa Women's Health study (41,800 women aged 55-69)	Risks dropped continuously with time since cessation but were still significantly raised up to 30 years after quitting for both lighter and heavier smokers.
Lung cancer mortality	Ockene *et al* (1990)	12,866 men at increased risk of CHD (MRFIT)	Analysis of ex-smokers *vs.* smokers. There was no difference in lung cancer deaths between ex-smokers and smokers either 1 or 3 years after quitting.
Lung cancer mortality	Halpern *et al* (1993)	900,000 people (ACS CPSII)	Those who quit smoking in their 30s had a relative risk only 10% of the risk of smokers at age 75 but still above that of non-smokers (5% that of smokers). Their lung cancer death rate rose with age at a gradual rate higher than that of non-smokers. Quitting reduced risks at any age but to a lesser extent with increasing age.
Lung cancer mortality	Burns *et al* (1997)	456,491 males, 594,551 females ACS CPSI	In men, lung cancer risks remained elevated even 35-40 years after quitting smoking, although numbers were small. In women, the risks remained elevated up to 25-30 years after quitting. There was no information for longer times since quitting.

Outcome	Reference and cohort	Subjects and sample size	Comment on results
Lung cancer mortality	Friedman *et al* (1997)	60,838 subjects Kaiser Permanente Medical Care Programme cohort study	Lung cancer risks remained substantially elevated more than 20 years after quitting.
Lung cancer mortality	Hrubec and McLaughlin (1997)	95,783 never smokers and former smokers (US veterans study)	Relative risks remained elevated more than 40 years since quitting.
All cancers including lung cancer mortality	Kawachi *et al* (1997) (12 years follow-up)	117,001 women (Nurses' Health Study)	There was an increased risk of cancer mortality within 2 years of cessation but risks among former smokers only approached those of non-smokers 10-14 years after cessation. The risk of mortality from all cancers excluding lung cancer was no longer apparent after 2 years.
Lung cancer mortality	Kenfield *et al* (2008) (22 years follow up)	104,519 women (Nurses' Health Study)	21% reduction in risk in first 5 years. Risk had not returned to level of non-smoker after 30 years but was reduced by 93%.
Lung cancer mortality	Doll *et al* (2004)	34,439 male British doctors	Mortality rates were reduced in former smokers who gave up at any age but the reduction was not greater if gave up at a younger age. Mortality rates were still generally higher than in non-smokers, including when gave up at age 35-44.
Lung cancer mortality	Enstrom and Heath (1999)	118,094 subjects (California CPSI)	Risk higher in first year after quitting (ill quitter effect?). Risk reduced with increased duration of quitting but was still higher than that of non-smokers 20 years after quitting.
Lung cancer mortality	Knoke *et al* (2008)	291,940 men CPSI	A sophisticated model was fit taking into account lung-cancer at baseline and other factors. A 2 year lag before assessing the benefits of cessation was the best fit for removing the ill quitter's effect. This resulted in a steeper decline in lung cancer risks which became quite small 25 years after quitting.

(Smoking cessation COPD mortality results are not shown, as using these results for analogy is not necessary when the air pollution evidence for an association with COPD mortality is unclear).

74. As the focus in this paper is air pollution, the above summary does not go into all the possible caveats on a study by study basis. The papers do discuss issues such as the fact that age at quitting smoking may be an important factor of itself even though it is

obviously closely related to time since quitting. For example, the very elderly may have less capacity for repair. Many studies do not have information to distinguish whether people quit because they were ill. The rapid reduction in cardiovascular risks may of itself increase lung cancer deaths as a competing cause of death. There may be cohort effects – for example older cohorts may have started smoking at an older age or conversely be more likely to have smoked unfiltered cigarettes. In some cohorts longer follow-up led to longer estimates of enhanced risks after quitting. Noting these caveats, a fairly consistent picture emerges that cardiovascular mortality drops significantly in the first 5 years but may also have a component that contributes to a more gradual decline over time after 5 years until more than 20 years perhaps 30 years after quitting. Lung cancer mortality declines more continuously over time and risks are still elevated up to 30 years after cessation. Whether the risks return to baseline may be affected by the intensity and duration of smoking before quitting – Ben-Shlomo *et al* (1994), for example, reported elevated risks for both heart disease and lung cancer in heavy smokers smoking for more than 20 years more than 30 years after cessation.

75. While not a smoking cessation paper, a very interesting paper by West (1992) analysed data from the British Doctors Study. The author estimated the cumulative mortality for smoking-related causes by age using life-table methods subject to competing risks of all other causes. This predicted that, after the whole cohort had died, the proportion of total deaths due to lung cancer showed a significant dose-related increase across non-smokers, ex-smokers and light, moderate and heavy smokers (ranging from 0.7% to 10.8% in men). Ischaemic heart disease on the other hand did not show an obvious trend with proportions being 30.6% for non-smokers, 32% for ex-smokers, 32.6% for light smokers but 29.3% and 28.5% for moderate and heavy smokers respectively. The authors emphasised the difference between 'extra' deaths (lung cancer deaths) and 'earlier' deaths (ischaemic heart disease deaths) where there is a worsening of prognosis such that smokers die earlier but the rest of the population catch up and exceed the total numbers of a death from a specific cause over a lifetime. This has interesting implications regarding mechanisms.

5. Discussion

76. It is clear from the review of the evidence so far that there is no cut and dried answer to the question of lags. However, there are hints from the results on time-dependence, mechanisms and analogy with smoking cessation that may help with judgements about appropriate lags to recommend for health impact assessment. It is worth bearing in mind that it is not always clear whether the evidence relates best to onset lags or cessation lags. The intervention studies and the smoking cessation studies clearly involved cessation lags. Laden *et al* (2006) also directly examined a decrease where the relative risk was relative to an earlier period with higher pollution. For many other studies, the relative risk was relative to a lower level of exposure in the same period but these relative risks were then compared across different lags. This was often in the context of declining levels of particles over time. This makes interpretation confusing. While the analysis is in terms of an onset lag (considering whether exposure in various previous periods is linked with the onset of mortality

outcomes as judged by a concentration-response relationship (positive relative risk) within the relevant period), the context is one of cessation lags with absolute risks declining over time. It is assumed that the results are relevant to cessation lags in the following discussion.

77. It is worth starting by posing some questions on the range of lags to set the boundaries:

a) Is there evidence to suggest that an effect of fine-particles on mortality is already apparent within the first year after a change in exposure?

The answer to this is yes. Further, there is evidence that this effect is larger than seen in the time-series studies. In qualitative terms the strength of evidence for this is good with evidence from distributed lag time-series studies (subject to some methodological debate), infant mortality studies, intervention studies and some analyses of the cohort studies.

b) Is there evidence to suggest that the full effect of fine-particles on mortality has occurred 5, 10, 15, 20 or 30 years after a change in exposure?

The answer to this is less clear cut. Some studies suggest the full effect is already apparent within the first 5 years or even 2 years. However, analogy with the smoking cessation literature suggests that while a substantial proportion of the cardiovascular risk reduces within 5 years, slightly raised risks remain up to at least 20 years, perhaps 30 years, after quitting. Lung cancer risks remain substantially elevated for longer than 5 years and again remain for at least 20-30 years. There is some support from the air pollution literature for this with studies finding that exposure over short periods did not fit the data any better than exposure over 15 years or so. Many of the studies did not examine risks beyond 5 years. Some of the literature on air pollution and lung cancer suggests a long onset lag of 30 years. In summary, if covering all possibilities one would have to include 30 years as an outer boundary. However, it does need to be noted that it is probably only a small proportion of the effect that remains at this point.

78. It may be useful to consider what proportion of the all-cause mortality effect might be due to lung cancer and how much due to cardio-pulmonary mortality. This is because the lag patterns may differ for these two outcomes. This has been done very roughly but more sophisticated answers would be possible using life-tables. The rough estimate of the proportions has been done by using the COMEAP recommended coefficients and applying them to 2008 mortality data (it assumes no lag which may not be correct, particularly for lung cancer, unless mortality rates are assumed to be the same in, say, 20 years time). The coefficients need to be applied to mortality rates but have been applied just to number of deaths here since the denominator is the same for each cause (the population of England and Wales). This rough estimate has also ignored the fact that the age-distribution of the deaths will differ somewhat for all-cause, cardio-pulmonary and lung cancer mortality. The estimated air pollution related cardio-

pulmonary deaths and lung cancer deaths can then be expressed as a proportion of all-cause deaths (Table 15).

79. It is noted that the cardiopulmonary deaths and lung cancer deaths do not add up to 100% of the all-cause deaths. This is probably due to the uncertainties in the derivation of the various relative risks. In addition, the COMEAP recommendation for the lung cancer coefficient comes from 1979-1983 exposure measurement not the average of 1979-1983 and 1999-2000 as for the other coefficients. If the missing proportion from the table (about 21%) is added to each cause in roughly the proportion of lung cancer to cardio-pulmonary deaths (0.13), a rough estimate could be proposed that approximately 11% of the effect on all-cause mortality is due to lung cancer mortality and any views about lung cancer lags should be applied to 11% of the effect. The remaining 89% could be allocated to cardio-pulmonary effects (in practice mainly cardiovascular effects).

Table 15 Proportion of deaths due to lung cancer and to cardiopulmonary mortality

Coefficients per 10 µg/m^3			In 2005, anthropogenic air pollution was about 10 µg/m^3
All-cause	1.06		
Cardio-pulmonary	1.09		
Lung cancer	1.08		
2008 deaths			
All-cause	M	243,014	
	F	266,076	
	Total	509,090	
Air pollution-related		30,545	Note population denominator constant (England and Wales population) so not included
I00-I99 (cardiovascular)	M	80,846	
	F	87,392	
	Total	168,238	
J00-J99 (respiratory)	M	32,801	
	F	38,950	
	Total	71,751	
Cardio-pulmonary	Total	239,989	
Air pollution-related		21,599	
% of all-cause?		70.71%	
Neoplasms respiratory and intrathoracic organs	M	17,925	
	F	13,318	
	Total	31,243	
Air pollution-related		2,499	
% of all-cause?		8.18%	

80. It is not straightforward to pull together overall conclusions from this review. This is done in 3 ways – a summary table (Annex 2) listing the findings of each of the studies relating $PM_{2.5}$ to all-cause mortality in cohorts; a table (Table 16) summarising the findings for and against various possible lags and finally a section considering various different lag structures that could be applied to health impact assessment.

Table 16 Summary of evidence on lags

Cessation lag time component	Evidence for and against	Proportion?
Less than 1 year	For Time-series evidence on single and distributed lags. Laden *et al* (2006) found exposure in the year before death was as good a predictor as exposure in the entire follow-up period (although it will be correlated with past exposure). Substantial effects already found in the first year (Schwartz *et al*, 2008; Puett *et al,* 2009). Some mechanisms are compatible with short-term action. If an exponential decay mechanism applies, Roosli *et al* (2005) suggested 10% of the effect in the first year if using a time constant from Clancy *et al* (2002) (Dublin), and more than 40% if using a time constant from Pope *et al* (1992) (Utah valley steel mill). The latter study found a substantial decrease in mortality during a 13 month strike. Pope *et al* (2007) found decreases in mortality of the same order as predicted from the cohort studies during an 8-month strike. Several distributed lag studies show large effects on mortality over a few months approaching the size of effects in the cohort studies over a few months e.g. Schwartz (2000a). Infant mortality studies find an effect within the first year. For and against Krewski *et al* (2009) found using exposure in years 1-5 did not give an obviously better fit than years 6-10 or 11-15. Against Janes *et al* (2007) did not find evidence of effects with the previous 12 months exposure to $PM_{2.5}$. If the association with lung cancer is based on a genotoxic mechanism, it is unlikely that it would all be reversed this soon. Short-term deviations (1, 2 or 3 months) from the long-term average did not have a significant effect (McDonnell *et al,* 2000). Methodological debates suggest distributed lag studies may be misleading (Fung *et al,* 2005b).	Overall from none to the majority of the effect. More papers suggest a substantial proportion of the effect than smaller proportions.

First 5 years	For The Dublin study found effects over the first 5 years (although some debates regarding epidemics) (Clancy *et al,* 2002). Analogy with smoking cessation literature for cardiovascular mortality. Some of the proposed cardiovascular mechanisms are short-acting. Hazard ratios appeared to change with time as pollution levels changed in the Six Cities study (Krewski *et al*, 2000). Schwartz *et al* (2008) suggests the effect occurs within the first two years (although lags beyond 5 years were not considered.) Schwartz *et al* (2008) also found the lung-cancer effect occurred within the first three years (unexpectedly short for a genotoxic mechanism). Puett *et al* (2009) found effects built up and flattened off over different periods up to 48 months before (longer periods were not investigated). For and Against There appears to be a longer-term component in addition (see below). Krewski *et al* (2009) were unable to identify critical time-windows (this may be due to inadequate data or to the presence of short and long-term components); Laden *et al* (2006) also found evidence for both an effect that was reversible in the short-term and a component that was reversible in the longer-term. The causes of death are compatible with both shorter and longer lags. Against Exposure between time-periods is correlated and exposure misclassification probably varies for different time-periods. The ACS study does not have interim exposure measurements and the Six Cities study is small. Apparent higher relative risks for more recent exposure (Pope *et al* (2002)) probably due to measurement error (COMEAP, 2009 Working Paper 5). Janes *et al* (2007) did not find evidence of effects with the previous 2 years exposure to $PM_{2.5}$. Villeneuve *et al* (2002) found risks for the last 2 years and for years 3-5 were attenuated compared with using the entire period.	About a third (all-cause) based on the Dublin study although there are caveats. Schwartz *et al* (2008) would suggest a much greater proportion. The smoking cessation literature suggests a substantial (but not complete) reduction (by a maximum of about 45%) in risk of cardiovascular mortality (perhaps about 90% of the air pollution effect) in the first five years. There may be a tiny reduction in lung cancer risk but most of the reduction in lung cancer risk will take longer (analogy with smoking cessation).

5-30 years	For Krewski *et al* (2000) and Laden *et al* (2006) noted the possibility of a longer-term component. Villeneuve *et al* (2002) found a model using exposure over the entire follow-up period (15 years) fitted the best (although this was not conclusive). Krewski *et al* (2000) did not find higher relative risks in those with heart and lung disease at baseline i.e. not just short-term exacerbation. For and against There is also evidence for a component with shorter lags (see previous rows). Causes of death compatible with both shorter and longer lags. Krewski *et al* (2009) found using exposure in years 6-10 and 11-15 did not give an obviously better fit than years 1-5. Against Exposure between time-periods is correlated and exposure misclassification probably varies for different time-periods. ACS study does not have interim exposure measurements and Six Cities study is small. Some studies showing effects within the first year or two have effect sizes as large as the total effect.	From the smoking cessation literature the remainder (55% or more) of the cardiovascular risk (perhaps 90% of the effect) declines slowly over this period. The majority of the reduction in lung cancer risk (10% of the effect) will be in this time-period.
30-40 years	Limited evidence. The length of follow-up is less than this for the ACS and the Six Cities study. Smoking cessation studies suggest risks may still be raised, particularly for lung cancer in former heavy smokers, even after 30 years. Case numbers are small.	Include a small element of lung cancer risk (itself only 10% of the effect) extending out this long on a precautionary basis? (Air pollution exposure is less than for heavy smokers but air pollution exposure is more extended, including childhood).
More than 40 years	Against Relative risks similar after stratification by age in Krewski *et al* (2000) ruling out very long onset lags and, probably but not definitely, long cessation lags.	None

81. For health impact assessment, we are trying to represent the overall scientific evidence on a particular question in making choices about how health impacts are calculated. Unfortunately, scientific evidence does not always give one obvious answer. Sometimes the evidence is better represented by a series of alternatives that cannot categorically be ruled in or out. Given the difficulty in studying lags, the answers are not conclusive and studies come up with very different results. In addition, combinations of results are possible. The following section therefore takes the approach of setting out a series of alternative options.

Suggested options are:

a) a pattern based on a high proportion of the effect occurring in the first year based on Laden *et al* (2006).

b) a pattern where the effect is phased in over 4 years (approximately representing the results of Puett *et al,* 2009).

c) a more gradual pattern based on studies that were unable to find evidence that short lags fitted the data any better than longer ones (e.g. Krewski *et al,* 2009; Villeneuve *et al,* 2002).

d) a pattern based on an exponential reduction in the size of the effect over time using a time constant from the intervention studies (Roosli *et al,* 2005)

e) a pattern based on the smoking cessation literature. This includes long lags for lung cancer mortality which has some support from the air pollution literature.

Option a

82. While several studies support the idea of a high proportion of the effect occurring in the first year, the paper by Laden *et al* (2006) has the advantage that it provides an overall relative risk for the whole period (1.16 95% CI 1.07-1.26) per 10 μg/m^3 $PM_{2.5}$ as well as for the previous year's exposure (1.14 95% CI 1.06-1.22). Recognising the uncertainty given the overlapping confidence intervals this could be represented as about 85% of the effect occurring in the first year. The paper did not give results for other years individually but did find a significant decrease in effect over an 8 year period when levels of $PM_{2.5}$ were decreasing. This option proposes spreading the remaining 15% of the effect over the remaining 7 years of an 8 year period (about 2.1% a year).

Option b

83. Puett *et al* (2009) found evidence that the effect built up and flattened off for exposure 4 years before. For simplicity this is represented as a linear phasing in over 4 years.

Option c

84. Krewski *et al* (2009) found no difference between relative risks on the basis of exposures in years 1-5, 6-10 and 11-15. This could be regarded as the effect being spread equally over 15 years (6.67% a year). The findings of Villeneuve *et al* (2002) were similar.

Option d

85. Roosli *et al* (2005) proposed an exponential decay function for the reduction in risk after cessation. This needs a time constant for the speed of the decline. The time constant derived from the Dublin study was 0.1 and this is taken as the option here. Other distributions could be calculated for other time constants. Note that the exponential function leads to a very long tail. For convenient presentation in a table, this has been stopped at 98% at 40 years.

Option e

86. The advantage of the smoking cessation literature is that starting and stopping is much clearer although this literature is related to the air pollution literature only by analogy. The smoking cessation literature suggests up to 45% of the cardiovascular risk drops within 5 years with the remainder spread over years 5-30. For the purposes of this option, we will assume that the cardio-pulmonary coefficient used to apportion all-cause mortality across different causes is actually due to cardiovascular mortality as suggested by the ACS study. In that case, 45% of the 89% of the all-cause mortality effect thought to be due to cardio-pulmonary (cardiovascular) mortality, would correspond to 40% of the all-cause mortality risk dropping within 5 years with a remaining 49% (55% of 89%) spread over the next 25 years (1.96% a year). The smoking cessation literature suggests that the lung cancer effects remain substantially elevated for some time and are still slightly raised more than 30 years after quitting. Based on this literature, this option spreads the reduction in risk for the 11% of all-cause mortality apportioned to lung cancer over years 1 to 40 (at 0.275% a year). The lung cancer and cardiovascular mortality elements are then added together to give an overall shape for all-cause mortality.

87. The percentage of the full effect (of a reduction) is given in Table 17 for the different options. Any of these options could be criticised but the group of options gives a flavour of the range of evidence and views on lags in the literature. The percentages allocated to different years are over precise but they are not aimed at being categorical answers. Rather the aim is to generate a family of curves to define an uncertainty envelope within which the answer lies. This is shown in Figure 10. Several points can be noted. Firstly, there is a wide range of possibilities, particularly over the first 20 years but all the options either already have or are close to having a full effect by 30 years. Secondly, the shapes of a series of simpler lags (0, 5, 10, 15, 20 and 30 years) are shown in the background. A range from no lag to a 30 year lag encompasses the envelope of the different options a-e. It is worth noting that the probability of options at the outer edges of the envelope is not necessarily lower than options in the middle.

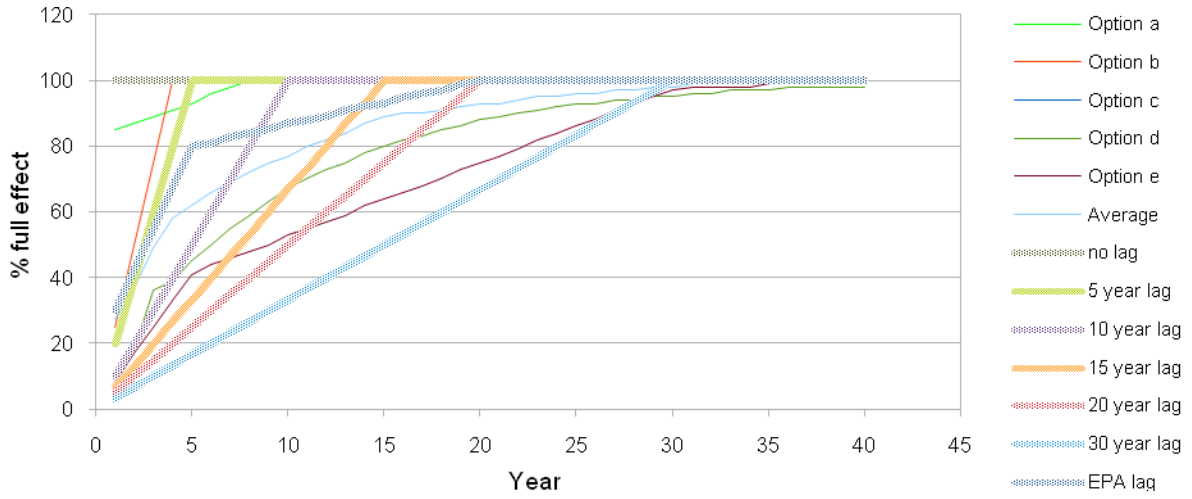
For example, there is evidence from several different study designs for substantial effects of a reduction in the first few years, to the far left of the envelope. The options could be weighted if desired although determining appropriate weights would not be easy to do.

Table 17 Various alternative lag structures based on the literature, the EPA and 0-30 year lags (proportion of effect in cumulative % per year)

Lag/year	none	a	EPA	ave	b	5 yr	10 yr	d	e	c	15 yr	20 yr	30 yr
1	100	85	30	27	25	20	10	10	8	7	7	5	3
2	100	87	43	37	50	40	20	18	17	13	13	10	7
3	100	89	55	49	75	60	30	36	25	20	20	15	10
4	100	91	68	58	100	80	40	39	33	27	27	20	13
5	100	93	80	62	100	100	50	45	41	33	33	25	17
6	100	96	81	66	100	100	60	50	44	40	40	30	20
7	100	98	83	69	100	100	70	55	46	47	47	35	23
8	100	100	84	72	100	100	80	59	48	53	53	40	27
9	100	100	85	75	100	100	90	63	50	60	60	45	30
10	100	100	87	77	100	100	100	67	53	67	67	50	33
11	100	100	88	80	100	100	100	70	55	73	73	55	37
12	100	100	89	82	100	100	100	73	57	80	80	60	40
13	100	100	91	84	100	100	100	75	59	87	87	65	43
14	100	100	92	87	100	100	100	78	62	93	93	70	47
15	100	100	93	89	100	100	100	80	64	100	100	75	50
16	100	100	95	90	100	100	100	82	66	100	100	80	53
17	100	100	96	90	100	100	100	83	68	100	100	85	57
18	100	100	97	91	100	100	100	85	70	100	100	90	60
19	100	100	99	92	100	100	100	86	73	100	100	95	63
20	100	100	100	93	100	100	100	88	75	100	100	100	67
21	100	100	100	93	100	100	100	89	77	100	100	100	70
22	100	100	100	94	100	100	100	90	79	100	100	100	73
23	100	100	100	95	100	100	100	91	82	100	100	100	77
24	100	100	100	96	100	100	100	92	84	100	100	100	80
25	100	100	100	96	100	100	100	93	86	100	100	100	83
26	100	100	100	97	100	100	100	93	88	100	100	100	87
27	100	100	100	97	100	100	100	94	91	100	100	100	90
28	100	100	100	98	100	100	100	94	93	100	100	100	93
29	100	100	100	98	100	100	100	95	95	100	100	100	97
30	100	100	100	99	100	100	100	95	97	100	100	100	100
31	100	100	100	99	100	100	100	96	98	100	100	100	100
32	100	100	100	99	100	100	100	96	98	100	100	100	100
33	100	100	100	99	100	100	100	97	98	100	100	100	100
34	100	100	100	99	100	100	100	97	98	100	100	100	100
35	100	100	100	99	100	100	100	97	99	100	100	100	100
36	100	100	100	99	100	100	100	98	99	100	100	100	100
37	100	100	100	99	100	100	100	98	99	100	100	100	100
38	100	100	100	100	100	100	100	98	100	100	100	100	100
39	100	100	100	100	100	100	100	98	100	100	100	100	100
40	100	100	100	100	100	100	100	98	100	100	100	100	100

a Majority of effect in first 2 years, with small longer term components c.f. Laden *et al* (2006)
b Builds up over first 4 years c.f. Puett *et al* (2009)
c Nothing to distinguish years 1-5, 6-10,11-15 i.e. evenly spread over 15 years (Krewski, 2009)
d Exponential decay using time constant from Dublin study (Roosli *et al,* 2005)
e Sharp drop in cv risk for first 5 years with longer tail for cv and lung cancer (smoking cessation)
ave Average of options a-e at each year.
EPA 30% year 1; 50% years 2-5 (12.5% per year); 20% years 6-20 (1.33% per year)
Information is given in order of the effect in the first year - this ranking may not apply to all years.

Figure 10 Various possible lag structures (options a-e) compared with their average, the EPA lag structure and 0-30 year lags



88. The figure also shows the pattern for the average across the different options. This is not really a central estimate that has stronger validity than the other options since it has averaged very different options. However, it does generate a result in the middle of the envelope which could be used in combination with the range.

89. The lag structure proposed by the EPA Health Effects Sub-Committee is also shown. It can be seen that this is more weighted towards shorter lags than the average of the 5 options above. EPA proposed 30% of the risk reduction in Year 1, reflecting short-term effects; 50% of the risk reduction distributed across Years 2-5; i.e. at 12.5% per year, reflecting other cardiovascular effects; and 20% of the risk reduction distributed across Years 6-20, reflecting lung cancer effects, with a recommendation to use smoothed annual values (EPA, 2004). The detailed reasoning leading to the specific proportions chosen is not given (it was presumably based on expert judgement). However, the references listed indicate that the intervention studies were considered in addition to an abstract that was a precursor of Roosli *et al* (2005) and an abstract that was a precursor of Schwartz *et al* (2008). The Health Effects Sub-Committee (HES) reconfirmed their support for this view in June 2010 (EPA, 2010a) recommending that the EPA cites and includes information from Laden *et al* (2006); Schwartz *et al* (2008) and Puett *et al* (2009)[3]. The HEI report by Krewski *et al* (2009) does not appear to have been considered. Although the HEI report predates the HES Committee meeting and the date of the letter, it may have been published too late for the preparatory work. Although HES encouraged EPA to look at the smoking cessation literature, this does not appear to form part of the reasoning leading to the proposed EPA lag structure. These two points would both weigh more towards longer lags if the evidence was considered to be on an equal

[3] The reference list only gives the reference for Puett *et al* (2008). This paper was on PM_{10} rather than $PM_{2.5}$. It is unclear which reference was actually meant.

footing with the evidence already considered by the EPA. Nonetheless, the 'average' lag structure and the EPA lag structure are similar.

90. HES also strongly recommended to EPA that sensitivity analyses were done on possible alternative lag structures (EPA, 2004). Documents subsequently provided to HES by the EPA (EPA 2010b) indicated that alternative lags had also been considered including no lag, a 5 year distributed lag and exponential decay functions based on Roosli *et al* (2005). The time constants used for the latter included one based on the Dublin study, one based on Laden *et al* (2006) and a third one smaller than that for the Dublin study. Extracts from these three EPA documents are given in Annex 3. (An 8 year lag and 15 year lag are also included in EPA cost-benefit analysis work (EPA, 2006).)

6. Conclusions

91. This review has shown that the examination of cessation lags in studies of air pollution and health is very difficult. It is unclear to what degree the analyses of time-dependence in the cohort studies of air pollution can be taken at face value as they are also influenced by factors unrelated to lags:

- different ranges in pollutant concentrations at different time-periods
- correlations between exposures at different time-periods
- different degrees of measurement error for exposure measures from closer and more distant time-periods

The studies often involve quite complex statistical approaches to try to deal with these issues and these approaches are debated. This also means that views on lags can change over time.

92. Bearing these caveats in mind, it does seem that there is a fair amount of evidence for a good proportion of the benefits from a reduction in $PM_{2.5}$ appearing in the first few years. This has been shown in a variety of study designs. On the other hand, some studies based on cohorts have not been able to show that using previous exposure in the last few years fits the data any better than exposure averaged over the whole follow-up period. In addition, lung cancer risks are less likely to be quickly reversed.

93. Given all the complexities in analysis of the air pollution literature, the smoking cessation literature is somewhat clearer. Higher exposures and a different composition of pollutants are involved but the pattern of health outcomes affected is similar[4]. The literature suggests that heavier smokers may have longer cessation lags (i.e. it may overestimate lags for air pollution) but also that a longer duration of smoking gives longer cessation lags (air pollution exposure is of long duration). The smoking cessation literature suggests quite marked

[4] With the exception of COPD mortality which is not an established outcome of long-term exposure in the air pollution literature.

reductions in risks in the first few years but a long 'tail' such that there is still a small raised risk 30 years or more after quitting smoking.

94. These various strands of evidence have been used to propose 5 alternative options for lag structures. The range of curves generated by these 5 options fits within an envelope defined by a range of simpler lags from no lag to a 30 year lag. The average of these lag structures is somewhat to the right (towards longer lags) of a lag structure used by the EPA perhaps due to consideration of a recent report and of the smoking cessation literature. While neither of these options forms a 'central estimate' in the statistical sense, either could be used to represent the middle of the uncertainty envelope defined by the range from no lag to a 30 year lag. Given the uncertainties in the evidence, it would be unwise to consider just one lag structure, unless it can be shown that different assumed lag structures make little difference to the overall health impact calculated.

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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.

Annex 2 Cohort studies of $PM_{2.5}$ and all-cause mortality – information on age-dependence or time-dependence

Author (Date)	Method of exposure assessment	Years of pollution measurement/ modelling	Cohort	Follow-up	Control for confounders	Time-dependence	Age-dependence
Pope *et al* (1995)	4 year median of $PM_{2.5}$ annual averages allocated to metropolitan area.	Measured 1979-1983.	ACS.	1982-1989	Individual confounders including smoking, BMI and education.	No information.	No information.
Krewski *et al* (2000)	4 year median of $PM_{2.5}$ annual averages allocated to metropolitan area.	Measured 1979-1983.	ACS, divided into random subsets for time-dependence analysis.	1982-1989	Individual confounders including smoking, BMI and education.	Concentration response curve given for cumulative exposure to $PM_{2.5}$ although this was not defined. The curve rose and flattened off at about 15 $\mu g/m^3$. Health Review Committee considered interpretation unclear.	Risks similar in those under 50, 50-60 and over 60.
Pope *et al* (2002)	Average of measured $PM_{2.5}$ 1979-1983, 1999-2000 and an average across both periods.	Measured 1979-1983 and 1999-2000.	ACS.	1982-1998	Individual confounders including smoking, BMI, diet and education.	Some suggestion of higher relative risks for the more recent 1999-2000 exposure.	Relative risks for cardio-pulmonary mortality higher in over 70s and higher for lung cancers in those 60-70 but confidence intervals overlap. Net effect for all-cause mortality, no trend with age.

Author (Date)	Method of exposure assessment	Years of pollution measurement/ modelling	Cohort	Follow-up	Control for confounders	Time-dependence	Age-dependence
Jerrett *et al* (2007)	$PM_{2.5}$ concentrations imputed from TSP and PM_{10}, measured $PM_{2.5}$ and measured sulphate.	Modelled annual averages for 1972-2000 in 51 cities that also had 1999-2000 measured $PM_{2.5}$ and 1980 measured sulphate.	Subset of ACS cohort.	1982-1986, 1987-1990, 1991-1994, 1995-1998 and 1999-2000	44 individual covariates including smoking.	Pattern of relative risks over time unchanged when a 5 year lag rather than no lag was used (caveat many other factors are influencing the pattern of relative risks over time.) Lung cancer pattern did shift with a 5 year lag.	Relative risk higher in under 65s in overall analysis. This was not always true for subgroups according to education and for exposure from different time-periods.
Krewski *et al* (2009)	$PM_{2.5}$ concentrations imputed from TSP and PM_{10}, measured $PM_{2.5}$ and measured sulphate.	1972-2000	Nutrition cohort plus another cohort. Subsets of ACS cohort.	1977 (15 years before first death) to 2000	44 individual covariates including smoking.	Exposure 1-5 years, 6-10 years and 11-15 years before death was considered. No time-window stood out as having a greater hazard ratio or a better fit except possibly lung cancer at 1-5 years in one of the cohorts.	No information.
Dockery *et al* (1993)	Monitoring of $PM_{2.5}$ in each city.	1979-1985	Six Cities.	1974-1991	Individual confounders such as smoking, BMI and education.	No information.	No information.

Author (Date)	Method of exposure assessment	Years of pollution measurement/ modelling	Cohort	Follow-up	Control for confounders	Time-dependence	Age-dependence
Krewski *et al* (2000)	Monitoring of $PM_{2.5}$ in each city.	1979-1985	Six Cities, divided into subsets for time-dependence analysis.	1974-1989	Current and former smoking, BMI.	Flexible spline modelling taking into account non-linear effects of continuous independent variables showed a drop in the log hazard ratio over the first 5 years of follow-up followed by a rise after 10-12 years of follow-up. This could be due to a combination of an effect of lags and of changes in pollution over time.	Some indication of greater risk in those under 40 but interaction with age not significant.
Villeneuve *et al* (2002)	Monitoring in each city 1979-1987 (1980-1985 for all cities); missing data e.g. for years before and after measurement period used regressions of $PM_{2.5}$ over time.	1979-1988 average; <1979, 1979, 1980.....1989, ≥1990	Six Cities.	1974-1989	Includes adjustment for individual smoking, education, bmi etc (at baseline and at 3, 6 and 12 years).	Use of time-dependent estimates of levels of fine particles attenuated the relative risks and provided poorer goodness of fit (higher value) than using a fixed mean level over the follow-up period. Consistent with the cumulative or life-long exposure to $PM_{2.5}$ as an important predictor of mortality but caveats noted.	Relative risk greater in the under 60s than the over 60s.

Author (Date)	Method of exposure assessment	Years of pollution measurement/ modelling	Cohort	Follow-up	Control for confounders	Time-dependence	Age-dependence
Laden *et al* (2006)	Monitoring in each city 1979-1987 (1980-1985 for all cities); estimated from PM_{10} 1985-1998. Annual average of quarterly average of daily averages in each city plus overall average for each exposure period and average over entire period.	1980-1985, 1990-1998 and 1979-1998.	Six Cities age 25-74	1974-1989 (period 1); 1990-1998 (period 2) and 1974-1998.	Includes adjustment for individual smoking, education, bmi etc (at baseline).	Significant reduction in risk for decrease in concentration from period 1 to period 2, controlled for period 1 i.e. effect partially reversible over a decade or so. Not the case for lung cancer. Relative risk for exposure in year before death similar to overall relative risk for whole period, suggesting exposure in last year important.	No information.
Schwartz *et al* (2008)	As Laden *et al* (2006).	Annual averages 1979-1998.	Six Cities.	1974-1998	Includes adjustment for individual smoking, education, bmi etc (at baseline).	Effect almost entirely due to exposure within the last 2 years. For lung cancer, the effect was accounted for by exposure within the previous 3 years.	No information.

Author (Date)	Method of exposure assessment	Years of pollution measurement/ modelling	Cohort	Follow-up	Control for confounders	Time-dependence	Age-dependence
Beelen *et al* (2008)	Estimated from PM_{10} using ratio based on later monitoring data in the Netherlands.	1992-1996	Netherlands cohort study on diet and cancer, 55-69 years.	1987-1996	Includes adjustment for individual smoking, income, education, bmi etc.	Difficult to evaluate which time-period was important due to high correlation between periods.	No information.
Janes *et al* (2007)	Single monitor per county. Average over preceding year or 2 years calculated every month. Smoothing used to deal with missing data.	1999-2002	65+ Medicare, replacing cohort.	2000-2002	None beyond age and sex.	Argues estimates from national and local (within county) trends should match but no effect of local trend was found and the authors considered that the effect of a national trend was more likely to be confounded. Concluded no effect of previous 1 or 2 years exposure.	Results were split by age but interpretation unclear if arguing no effect.
Eftim *et al* (2008)	2000-2002 average based on yearly county-specific averages.	2000-2002, Sensitivity 1999-2001.	65+ Medicare, replacing cohort.	2000, 2001, 2002.	Only indirect control for smoking (lung cancer/ COPD rates).	Gives relative risks for 2000, 2001, 2002 against 2000-2002 ave $PM_{2.5}$. Results similar across years. Results unchanged if used 1999-2001 exposure.	No information.

Author (Date)	Method of exposure assessment	Years of pollution measurement/ modelling	Cohort	Follow-up	Control for confounders	Time-dependence	Age-dependence
Zeger *et al* (2008)	2000-2005 average based on yearly zip code-specific averages.	2000-2005	65+ Medicare, replacing cohort.	2000-2005	Only indirect control for smoking (lung cancer/ COPD rates).	No information.	Positive and significant for 65-74 and 75-84 but not 85+.
Enstrom (2005)	4 year average measured $PM_{2.5}$ at county level.	1979-1983	California Cancer Prevention study 1, elderly – mean 65 years in 1973.	1973-2002	8 individual variables including smoking at baseline in 1959 plus smoking from 1972.	Subgroup analysis for 1973-1982 and 1983-2002. RR positive and statistically significant 1973-1982 but not 1983-2002.	Subgroup analysis for ages 43-64 and 65-99. RR positive and statistically significant only for youngest age group.
Naess *et al* (2007b)	Air dispersion model at building points weighted according to building occupants.	1992-1995	50-74 years.	1992-1998	No control for smoking but argue correlation of smoking with pollution levels is low and is partially taken into account by adjustment for SES.	No information.	No information.

Author (Date)	Method of exposure assessment	Years of pollution measurement/ modelling	Cohort	Follow-up	Control for confounders	Time-dependence	Age-dependence
Naess *et al* (2007a)	Air dispersion model at building points weighted according to building occupants.	1992-1995	51-90 years.	1992-1998	No control for smoking but argue correlation of smoking with pollution levels is low and is partially taken into account by adjustment for SES.	Noted only looking at a short time-period (3 years) so not addressing longer-term exposures.	Higher risks age 51-70 than 71-90 in men and women.
Jerrett *et al* (2005)	kriging to zip code level using year 2000 data ?annual average (averaging time not stated).	2000	Subset of Los Angeles residents from ACS cohort.	1982-2000	44 individual confounders (including smoking) and 8 ecological variables.	Information on other studies in discussion section.	Results not stratified by age.
Jerrett *et al* (2009)	Interpolation from 14 TEOMs in Toronto.	2002	Respiratory clinic patients Toronto Western hospital, mean age 60 IQR 49-69.	1992-2002	Several individual and neighbour-hood confounders including smoking.	Insufficient exposure contrast so results not presented for $PM_{2.5.}$	Insufficient exposure contrast so results not presented for $PM_{2.5.}$

Author (Date)	Method of exposure assessment	Years of pollution measurement/ modelling	Cohort	Follow-up	Control for confounders	Time-dependence	Age-dependence
Puett *et al* (2009)	GIS spatial smoothing model relating measurements to population density, distance from road, land use, emissions, windspeed and precipitation on a monthly basis using 1999-2002 data. Pre 1999 used ratio $PM_{2.5}/PM_{10}$ on a seasonal basis.	1999-2002 and 1988-1998	Nurses' health study women born 1921-1946 in 11 contiguous states north east and mid-west US, biennial question-naires, age 62.4+/- 7.6 years.	1992-2002	Several individual and neighbour-hood confounders including smoking. Individual confounders updated every 6 months.	Looked at exposure 1 month, 3 months, 1, 2, 3 and 4 years prior to death controlling for year and season and coarse particles. Effect very small at 1 and 3 months but stronger after 12 months and longer. Results only presented graphically and Cis overlap but there is a sense of a trend flattening off at 3-4 years.	No information.
Ostro *et al* (2010)	Allocation to nearest monitor	2002-2007	Californian teachers study, women, current and former school-teachers, age 22-104 years, median 54 years.	2002-2007	16 individual confounders including smoking, plus contextual variables.	No information.	No information.

Author (Date)	Method of exposure assessment	Years of pollution measurement/ modelling	Cohort	Follow-up	Control for confounders	Time-dependence	Age-dependence
McDonnell *et al* (2000)	Estimated from daily airport visibility data 1966-1993 based on daily 1979-1993 $PM_{2.5}$ and airport visibility data. Monthly averages for nearest airport allocated to home addresses. Also, long-term average 1973-1977.	1966-1993	Seventh day adventists recruited in 1977, 27 years or older in 1977, living near airports for 80% of the months from 1973-1977.	1977-1992 (repeat question-naires 1987, 1992).	Several individual confounders including smoking.	Considered time-varying pollution levels but just gave one overall result (higher risk using time-varying levels than using overall average but wider confidence intervals). Also looked at long-term average (1973 to time of event) *vs.* average 1, 2 or 3 months before event. Results were similar leading to conclusion that the effect is a long-term one.	No information.

ANNEX 3 EXTRACTS FROM EPA DOCUMENTS ON CESSATION LAGS

(1) Letter of December 6 2004

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460
OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

December 6, 2004

EPA-COUNCIL-LTR-05-001
The Honorable Michael O. Leavitt
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

SUBJECT: Advisory Council on Clean Air Compliance Analysis Response to Agency Request on Cessation Lag

Dear Administrator Leavitt:

In a letter of August 11, 2004, the Office of Air and Radiation and Office of Policy, Economics and Innovation jointly asked the Health Effects Subcommittee (HES) of the Advisory Council on Clean Air Compliance Analysis to comment on an EPA proposal. This proposal, developed in collaboration with OMB, concerns the cessation lag of $PM_{2.5}$. The cessation lag is defined as the time pattern of reductions in risks of mortality that would be expected after a decrease in ambient particulate matter smaller than 2.5 μm in aerodynamic diameter, *i.e.* $PM_{2.5}$. The letter requested the Council's Subcommittee to consider whether a proposed lag structure is generally consistent with our recommendations regarding a previous charge question on this issue.

Our previous comments on this issue noted that because some fraction of the mortality risk associated with $PM_{2.5}$ is the result of long-term exposures and disease processes such as chronic respiratory disease and cancer, the reduction in mortality risk that occurs when exposures are reduced may take several years to be fully realized. The EPA described a proposed lag structure that would allocate 20% of the benefits in the first year, a further 50% equally divided in the years 2 through 5, and the final 30% equally divided in the years 6 through 20. While we believe this proposal is broadly consistent with our recommendations, and preferable to the 5-year distributed lag used earlier, we would suggest a slight modification to this proposal. We have reviewed newly available evidence on this issue and considered several intervention studies examining reductions in exposure to either air pollution or from direct smoking. (See attachment.)

While there is still considerable uncertainty about the cessation lag, the air pollution evidence is generally suggestive of greater impacts in the first year relative to the proposed lag structure in question. In fact, some recent abstracts suggest that substantial benefits might occur in the first year. Therefore, the Advisory Council on Clean Air Compliance Analysis recommends that EPA use a primary case where 30% of the mortality reductions occur in the first year, 50% occur equally in years 2 through 5, and the remaining 20% occur equally over years 6 through 20.

These proposed changes to the cessation lag (both the EPA proposal and the HES recommended modification) do not change the estimates of total mortality reductions expected as a result of reductions in $PM_{2.5}$, but they both represent changes in the estimated timing of the expected mortality reductions. The HES recognizes that measures of health benefits in physical terms are not the final step in benefit-cost analysis, where all benefits need to be valued. The time profile assumed for health benefits may have implications for "net present value" calculations. However, this final step of economic valuation does not lie within the scope of expertise of the HES. The charge to the HES on this matter specifically concerns the pattern of health benefits in physical terms, so we limit our comments to this question.

We also urge EPA to: (1) review and keep abreast of the emerging literature in this area; (2) provide the best available justification for the lag structure they use; and (3) strongly consider conducting sensitivity analyses of other possible lag structures. EPA should also consider using smoothed distributions.

With regard to the suggestion to review emerging literature, it should be noted that, in addition to the literature from PM intervention studies, information from the smoking cessation literature is considered very relevant to the PM/mortality cessation lag question. Therefore, we recommend that EPA conduct a systematic review of the literature on the time course of health benefits following cessation of active and passive smoking to better account for this potentially useful information.
Sincerely,

/s/ /s/

Trudy Cameron, Ph.D.
Chair
Advisory Council on Clean Air Compliance Analysis

Bart Ostro, Ph.D.
Chair
Health Effects Subcommittee

Attachment:
Studies Considered by HES on PM-Mortality Cessation Lag

Studies Considered by the Health Effects Subcommittee on the PM-Mortality Cessation Lag

Clancy, L., Goodman, P., Sinclair, H., and Dockery, D.W. (2002). Effect of Air-Pollution Control on Death Rates in Dublin, Ireland: An Intervention Study. The Lancet 360: 1210-1214.

Fry, C., Hoelscher, B., Cyrys, J., Wjst, M., Wichmann, H. and Heinrich, J. (2003). Association of Lung Function with Declining Ambient Air Pollution. Environmental Health Perspectives 111: 383-387.

Heinrich, J. Hoelscher, B., Frye, C., Meyer, I. Pitz, M. Cyrys, J., Wjst, M. Neas, L., Wichmann, H.E. (July 2002). Improved Air Quality in Reunified Germany and Decreases in Respiratory Symptoms. Epidemiology 13: 394-401.

Heinrich, J., Hoelscher, B., and Wichmann, H.E. (2000). Decline of Ambient Air Pollution and Respiratory Symptoms in Children. American Journal of Respiratory Critical Care Medicine 161: 1930-1936.

Hurley, Fintan. (2004). Does Reducing Air Pollution Really Lead to Improvements in Health? Excerpt from a report entitled Evaluation of the Air Quality Strategy prepared for the Department for Environment, Food and Rural Affairs in the United Kingdom. The full report will be published in the coming months at http://www.defra.gov/uk.

Lan, Q., Chapman, R.S., Schreinemachers, D.M., Tian, L., and He, X. (2002). Household Stove Improvement and Risk of Lung Cancer in Xuanwei, China. Journal of the National Cancer Institute 94: 826-836.

Leksell, Ingemar and Rabl, Ari. (2001). Air Pollution and Mortality: Quantification and Valuation of Years of Life Lost. Risk Analysis 21: 843-857.

Roosli, M., Kunzli, N. and Braun-Fahrlander, C. (2004). Use of Air Pollution "Intervention-Type" Studies in Health Risk Assessment. Abstract presented at the 16th Conference of the International Society for Environmental Epidemiology, August 1 – 4, 2004.

Schwartz, Joel and Laden, Francine. (2004). Dose, Time and Death: Association with PM2.5 in Cohort Study. Presentation to 16th Conference of the International Society for Environmental Epidemiology, August 1 – 4, 2004.

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(2) Extract from August 2010 EPA Office of Air and Radiation Revised Draft Report 'The Benefits and Costs of the Clean Air Act 1990 to 2020.' (Supplied to the Health Effects Sub-Committee)

Revised Draft 812 Report (2010)Available at http://www.epa.gov/oar/sect812/aug10/fullreport.pdf

Pg 5-21: When valuing premature mortality for PM, we assume a lag between reduced PM exposure and the resulting reductions in incidences of premature mortality.[48] This lag does not affect the number of estimated incidences, but does alter the monetization of benefits. Because we value the "event" rather than the present risk, in this analysis we assume that the value of avoided future premature mortality should be discounted. The primary estimate reflects a 20-year distributed lag structure, which was recommended by the SAB HES (2004). Under this scenario, 30 percent of the mortality reductions occur in the first year, 50 percent occur equally in years two through five, and the remaining 20 percent occur equally in years six through 20. Our valuation of avoided premature mortality applies a five percent discount rate to the lagged estimates over the periods 2000 to 2020, 2010 to 2030 and 2020 to 2040. We discount over the period between the initial PM exposure change (2000, 2010, or 2020) and the timing of the resulting change in incidence.

[48] Note that we do not employ a cessation lag for ozone mortality due to our reliance on short-term studies to estimate these benefits.

Pg 5-24: Running the simulation beyond 2020 allows us to estimate the full effect of changes that begin in 2020, which because of the cessation lag are not fully realized until many years after the end of the study period. Comparing the estimated population in each age cohort across the two scenarios allows us to estimate gains in life-years (i.e., one additional person in a cohort for one year yields a life year gained), and summing across cohorts and years yields cumulative estimates.

Pg 5-30, Pg 7-16: *New Cessation Lag Structure for PM Mortality:* The Second Prospective relies on the use of a 20-year distributed lag structure assumption for the cessation lag between changes in PM exposure and resulting changes in premature mortality. This estimate represents a shift from the First Prospective, which applied a 5-year distributed lag based on smoking cessation literature. The 20-year distributed lag is based on recommendations from the SAB HES, is derived from air pollution literature and attempts to more closely reflect the disease processes that occur from PM exposure.[55]

[55] Science Advisory Board (2004). *Advisory on Plans for Health Effects Analysis in the Analytical Plan for EPA's Second Prospective Analysis—Benefits and Costs of the Clean Air Act, 1990-2020: Advisory by the Health Effects Subcommittee of the Advisory Council on Clean Air Compliance Analysis*. EPA-SAB-COUNCIL-ADV-04-002.

Pg 5-34: *PM/Mortality Cessation Lag*
The timing of the cessation lag between PM exposure and mortality remains uncertain. Our primary monetized estimate of PM/mortality benefits assumes a 20-year distributed lag (30 percent of the mortality reductions occur in the first year, 50 percent occur equally in years two through five, and the remaining 20 percent occur equally in years six through 20). We tested the sensitivity of this assumption by calculating monetized mortality benefits based on alternative cessation lag structures. We selected two alternative lag structures – a 5-year distributed lag (which was employed in the First Prospective) and a smooth function (which assumes an exponential decay model and is based on an analysis by Roosli et al., 2005; see Chapter 6 of *Uncertainty Analyses to Support the Second Section 812 Benefit-Cost Analysis of the Clean Air Act* for further details). We also calculated benefits assuming no cessation lag. Application of alternative cessation lag structures had a smaller impact on the benefits estimates than the C-R function, resulting in benefits estimates that range from 22 percent lower up to 16 percent higher than the primary estimate.

Pg 5-39:

POTENTIAL SOURCE OF ERROR	DIRECTION OF POTENTIAL BIAS FOR NET BENEFITS ESTIMATE	MAGNITUDE OF IMPACT ON NET BENFITS ESTIMATE	DEGREE OF CONFIDENCE
Assumption that PM-related mortality occurs over a period of 20 years following the critical PM exposure. Analysis assumes that 30% of mortality reductions in the first year, 50% over years 2 to 5, and 20% over the years 6 to 20 after the reduction in PM2.5	Unable to determine based on current information	Potentially major. PM/mortality is the largest contributor to monetary benefits. Our quantitative sensitivity analysis indicated that alternative plausible cessation lag structures could alter the benefits estimate between 25% lower to 13% higher than the primary estimate.	Medium. Recent epidemiological studies (e.g., Schwartz, 2008) have shown that the majority of the risk occurs within 2 years of reduced exposure. However, our default lag assumes 43% of mortality reductions would occur within the first 2 years. The evidence directly informing the cessation lag structure is somewhat limited, but the current lag is supported by the SAB.

On the benefits side, Table 7-7 and Figure 7-3 show that the most influential assumptions affecting benefits are the choice of the C-R function, the cessation lag model for the accrual of benefits, and the VSL distribution. While the two most extreme results from EPA's Expert Elicitation (EE) study imply substantial effects of C-R choice (about 80 percent in either direction) most of the alternatives from the EE study and the published epidemiological studies suggest effects on benefits of about 40 percent or less in either direction. By themselves, longer cessation lag alternatives can reduce monetized benefits by as much as a 25 percent and if coupled with a change in the C-R function, by close to half; however, the SAB Health Effects Subcommittee advised that much of the risk reduction benefits from PM2.5 controls are more likely to accrue sooner rather than later. Accelerating benefits increases benefits by about 13 percent when maintaining the same C-R function, but could

increase them by as much as half when using a smooth function based on the Laden Six Cities follow-up effect estimate.

No Lag, No Discounting
5 Year Distributed Lag,
Smooth Function - k = 0.08
Smooth Function - k = 0.10
Smooth Function - k = 0.57

- **Extract from Letter of 16th June 2010**

Cessation Lag

Agency-supplied background: The Primary Estimates for PM mortality reflect an assumed lag between cessation of exposure and realization of the change in health effect incidence. Based in part on prior Council HES advice, the primary estimates in the draft benefits report reflect a 20-year distributed lag. Specifically, 30 percent of the total reduced incidences is assumed to occur in the first year following the exposure change. Another 50 percent of the total incidence changes is be spread evenly over years two through five. The remaining 20 percent of the incidence change is spread evenly over years six through twenty. The effect of the cessation lag is realized through discounting (at a 5 percent rate) of the monetized value of future-year incidence changes (i.e., there is no need, and no intent, to represent the discounted values as reflecting direct discounting of incidences *per se***).** In addition, the draft uncertainty report evaluates the effect of alternative lag structures. These alternatives include the 5-year distributed lag applied in the First Prospective Study and a set of smoothed lag functions derived from consideration of the results of available cohort and intervention studies.

Charge question 2b: Does the Council HES support the use of the 20-year distributed lag structure described above for generation of the Primary Estimates of the monetary value of PM mortality incidence reduction and the specific alternative lag functions presented in the draft uncertainty report? If not, are there alternative study choices and/or methods for organizing and presenting results that the Council HES recommends EPA consider?

HES response: EPA has done an admirable job responding to the suggestions of earlier reviews by the Council and NAS. However, EPA should cite and include information from the recent analyses of the Nurses' Health Study (Puett et al., 2009) and the Harvard Six Cities Study (Schwartz et al., 2008; Laden et al., 2006). These studies suggest that most of the health effects of exposure (and benefits from reduction) occur within a few years. EPA assumes that 80% of the risk reduction occurs in the first five years. However, the EPA analysis of alternative assumptions about the lag using a given cohort study indicates that the 20-year distributed lag default assumption generates a result that is close to the mean of a range of reasonable assumptions. Therefore, in the face of uncertainty, this lag structure is appropriate.

The HES suggests that if the decay function approach is used, EPA should ensure that its choice of parameter *k* is consistent with its choice of risk coefficient, in terms of the cohort studies used to generate both.