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Differential epidemiology of ambient aerosols

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There is now a large body of epidemiological evidence associating exposure to ambient particles with short- and long-term effects on health. Most authorities consider that at least some of these associations represent a causal relationship with particles. The size fraction of particles that could potentially harm health is PM_{10}, since only particles less than this size can plausibly reach the small airways and alveoli. Studies of mechanisms and theoretical considerations suggest that the fine ($PM_{2.5}$) and ultrafine ($PM_{0.1}$) particles are probably more important than larger particles, because of their relatively greater numbers and deeper penetration of the lung. Because of limited population exposure data, there is little direct epidemiological evidence about the effects of ultrafine particles. Indirect evidence falls into three groups. The first comes from studies that have directly compared the coarse ($PM_{2.5–10}$) with the fine ($PM_{2.5}$) fractions; the findings of these few studies have not been consistent. The second comes from studies of chemical species or measures of particles (sulphates, acid aerosol and black smoke) that reside mainly in the fine fraction; many of these have found associations with adverse health effects. The third group are those few studies that have compared the effects of size/number concentrations with size/mass concentrations; the findings of these have either been inconclusive or have suggested that numbers may be more important than mass.

Inference about the toxic component of particles will depend on all the evidence, especially from toxicology, as well as epidemiology. At present, epidemiological evidence points towards the fine fraction being important, but an effect of the coarse fraction cannot be excluded. Because of a lack of data, epidemiology has little to say about the relative importance of the ultrafine fraction. This is an urgent research need.

Keywords: air pollution; epidemiology; particles; PM_{10}; $PM_{2.5}$

1. Introduction

The development of our knowledge about the health effects of ambient air pollution has depended on two very different scientific disciplines. One may broadly be described as toxicology, which is laboratory based and experimental in concept. The other is epidemiology, which is population based and observational in concept. While toxicology is important for telling us whether an environmental agent might be important, and possible mechanisms of effect, epidemiology is important for telling us whether effects actually occur in the real-life situation. The earliest evidence of adverse effects came from simple epidemiological analyses of major air pollution episodes, notably the 1952 London air pollution episode (Ministry of Health 1954).

Around the same time it was observed that ill health and mortality tended to be higher in polluted areas (Gardner *et al.* 1969; Lave & Seskin 1970). As pollution improved in western developed countries, evidence for health effects, using the crude epidemiological techniques available at the time, became marginal, and this was interpreted as indicating that there was no longer a problem. The resurgence of concern about air pollution is due in part to the development and application of more sensitive statistical tools for the epidemiological analysis of time-series and cohort data, which have identified associations at levels of pollution well under guideline values. Toxicology has, until recently, contributed mainly to the understanding of the mechanism of effects of pollutant gases, such as ozone, or selected chemically pure particles such as sulphuric acid, or titanium dioxide. More recently, experimental techniques have been developed to study ambient particles themselves. At present there is intense interest in identifying the important toxic components of the particle mixture and the field is becoming driven by mechanistic theories relating to aspects such as the chemistry, size and number concentration of particles. This, in turn, presents new challenges to epidemiology to raise and test hypotheses in exposed populations. In this paper I shall first review briefly the development of epidemiological knowledge of the health effects of inhalable particles, and then focus on epidemiological evidence concerning the responsible fraction, in terms of size, chemistry and numbers.

2. Evidence that ambient particles have health effects

(*a*) *Short-term associations: air pollution episodes*

One method of epidemiological enquiry is to analyse data arranged as a time-series to look for short-term associations between air pollution and health outcomes. The earliest form of this approach is seen in reports of air pollution episodes, where a simple graphical display alone may be sufficient to show a convincing increase in daily mortality or some other outcome coinciding with a major increase in air pollution, such as the 1952 London episode. This is not a very sensitive way of detecting smaller effects and it is not always possible to exclude other explanations, such as a coincidental respiratory epidemic, or the effects of the weather conditions which predisposed to the episode in the first place: these will include cold in the case of winter episodes and heat in the case of summer episodes. The majority of major episodes comprise elevated concentrations of both particles and gases and there is no way of satisfactorily separating out the effects of the various components in a single episode analysis. In special situations such as certain types of volcanic eruption, where the population is exposed mainly to particles, adverse health effects have been found, which suggests that particles alone are sufficient to have effects (Baxter *et al.* 1983).

(*b*) *Short-term associations: ecological time-series analyses*

These are regression analyses that use aggregated data such as daily counts of mortality or hospital admissions from a large population, usually a city, obtained from routine health data systems. The method is statistically powerful and enables a range of potential confounding factors to be controlled for. Confounding factors are those that may be related to both air pollution and the outcome of interest, and failure to control for them could lead to spurious associations. They include time trends,

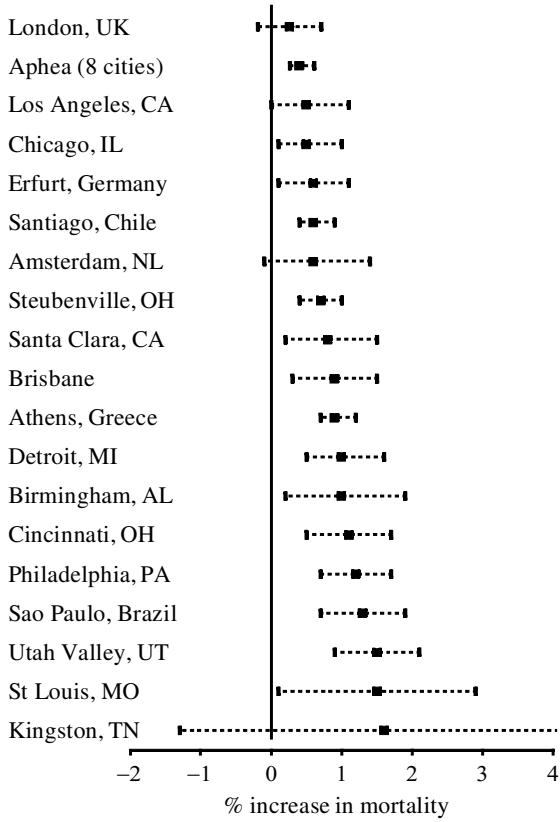

Figure 1. Particulate matter with aerodynamic diameter less than 10 μm (PM_{10}) and daily mortality from cities around the world. Expressed as a percentage change in daily mortality associated with a 10 μg m^{-3} increase in PM_{10}.

seasonal variations, weather, day of the week, and epidemics of respiratory disease. It is the development of appropriate statistical methodology that has brought to light associations between daily mortality and air pollution at low (i.e. below guidelines) levels. These studies identify short-term associations in a statistical sense but from the point of view of the individual, the health effects may be either transient, e.g. a stay in hospital, or permanent (as in the case of mortality). It is likely that the increase in events such as admissions and mortality is due to air pollution acting as an added factor in a situation already loaded with other risk factors.

Typically, the exposure data for such analyses come from stations which routinely monitor background pollution. It is likely that this will lead to misclassification of individual exposure. In most circumstances, this will bias the effect estimate towards the null. This has implications for comparing different fractions of the particle mixture. Use of a community monitor also carries the risk of bias in the estimate of community exposure, the effect of which on the estimate of health risk of air pollution could be up or down.

A large number of such studies have now been reported from cities throughout the world (figure 1). There is a remarkably consistent tendency to positive effects, not only for mortality but for hospital admissions and emergency room visits (Ameri-

can Thoracic Society 1996; Dockery & Pope 1994; Pope *et al*. 1995*a*; USEPA 1996; Department of Health Committee on the Medical Effects of Air Pollutants 1995*a*). When looked for, it has also been common to observe similar associations with pollutant gases such as SO_2, O_3 and, to a lesser extent perhaps, CO and NO_2. In most cases the associations with particles are more or less maintained after controlling for covarying pollutants.

(*c*) *Short-term associations: panel studies*

The other time-series technique is to study relationships at an individual level by following a panel of subjects over time and monitoring such outcomes as lung function, symptoms and medication use. These have also been found to be associated with air pollution (see references above), though not so consistently. For example, a very large and carefully conducted European study of children, the Pollution Effects on Asthmatic Children in Europe (PEACE) study, did not observe an association between particles and health effects (Roemer *et al*. 1998). Pollutant gases, especially ozone, have also been found to be associated with such outcomes. The method only identifies short-term associations. It is likely that most of the outcomes recorded are short-term physiopathological adaptations or represent the functioning of defence mechanisms, but longer-term effects cannot be excluded, especially if exposure to pollutants is associated with other pathogenic factors.

The causality of associations identified by ecological and panel time-series studies have been questioned, mainly on the basis of inadequate control for confounders, or failure to separate particle effects from those of other pollutants in the mixture (Gamble & Lewis 1996). Most authorities believe that this is not the case (Department of Health Committee on the Medical Effects of Air Pollutants 1995*a*), and for the purposes of this paper I shall accept that we are discussing a real effect on health, and not a spurious and, therefore, non-causal association.

I have already referred to some evidence that particles alone may be associated with health effects. In most situations, however, populations are exposed to particle–gas mixtures and it is important to consider the possibility that these particle associations are explained by some gaseous component of the mixture that is correlated with particles. One potential candidate is ozone, for which there is strong evidence of ambient toxicity. In most environments there is little correlation between ozone and particles on a daily basis and multi-pollutant regression models including both pollutants usually find that the effects of one are independent of those of the other (see, for example, Anderson *et al*. 1996). On the other hand, many studies, of which those from Philadelphia, PA, are good examples, have found that particle effects are reduced somewhat in models including SO_2 (Kelsall *et al*. 1997). One technical problem is that the risks identified by the time-series studies are small, often with wide confidence intervals and there is a complex and varying covariation with gaseous pollutants; these factors conspire to make it difficult to disentangle, in statistical terms, the separate effects. There are a few circumstances in which exposure to gaseous pollutants is very low and here associations with particles are still observed (Pope *et al*. 1992).

To summarize so far, it is established that there is consistent evidence of short-term associations between ambient particles and health, and that although gases also show associations, there is sufficient evidence to show that particles have effects that are independent of gases.

Most academic and regulatory authorities consider that the associations could be causal, though this inevitably remains a debated issue because of personal differences in the interpretation of observational evidence of small increased risks. Factors that tilt in favour of causality are the consistency of findings across many cities, climates, pollution sources and investigators, a specificity for cardiorespiratory diseases, the exposure–response relationship, and the growing toxicological evidence for biological plausibility.

(*d*) *Associations with chronic disease*

The other epidemiological strategy for studying air pollution compares the health of populations exposed, long term, to different levels of pollution. Comparisons can only be made at a group level because the exposure is at a group level. This approach addresses more important health outcomes, such as mortality rates and chronic illness, but is hampered by the potential for confounding by factors common to both the outcome and pollution level (social class for example). The most satisfactory techniques are those that compare the prevalence or incidence of disease according to different levels of exposure while controlling for confounding factors at an individual level (smoking, household environment, occupation, etc.). These studies have found associations between air pollution and premature mortality, the incidence and prevalence of chronic respiratory disease, respiratory symptoms and reduced lung function (Dockery *et al*. 1989, 1993; Raizenne *et al*. 1996; Pope *et al*. 1995*b*; Abbey *et al*. 1995; Ackermann-Liebrich *et al*. 1997). Interestingly, however, there is very little evidence to suggest that air pollution affects the incidence of asthma, though it does play a role in exacerbations (Department of Health Committee on the Medical Effects of Air Pollutants 1995*b*). The majority of prevalence and cohort studies have identified particles as important, though a role for gases cannot be excluded. As for the time-series studies, the causality of associations is open to different interpretations, but most authorities accept at least the possibility of causality.

3. Which component of the particle mixture is important?

Having concluded that ambient particles in low concentrations may be toxic to humans, the next step is to consider the relative importance of different components of this very complex mixture of air pollutants. In considering the effects of particles on the lung, heart and blood, the first consideration is that of size. Particles of diameter greater than 10 μm have a low probability of reaching the intra-thoracic airways. This is the reason for the widespread adoption of PM_{10} as a measure of particles. The proportion of particles delivered to the air-exchanging parts of the lung increases with decreasing size of particle. Although very fine particles account for a small part of the total mass, either in the ambient aerosol or deposited in the lung, they account for the greatest number. Theoretical reasons now backed by some experimental evidence support the idea that large numbers of ultrafine particles may present the most risk (Seaton *et al*. 1995).

Apart from the size and number of particles, the chemical composition of particles must be considered. PM_{10} comprises particles from two very different sources and this is reflected in a bimodal size/mass distribution with a dip at *ca*. 2–3 μm. The so-called coarse mode or fraction ($PM_{2.5–10}$) is mainly from the degradation of crustal material

Table 1. *Main measures of particles available for epidemiological investigation*

particle measure	comments
black smoke	Reflectance principle. Used in Europe for many years. Measures primary black carbonaceous particles under 4.5 μm in diameter. Resembles coefficient of haze in North America. Gradually going out of use in favour of PM_{10}.
TSP[a]	Gravimetric. No size cut-off, includes particles greater than PM_{10}. Common in North America and parts of Europe. Now being phased out by PM_{10}.
acid	Secondary pollutant mainly from oxidization of SO_2 to H_2SO_4.
sulphate	Results from ammonia reacting with H_2SO_4.
PM	Particulate matter of specified mean aerodynamic diameter. Gravimetric. Most commonly PM_{10}, but increasing information on $PM_{2.5}$.
particle numbers	Still essentially a research application.
other measures	These include chemical constituents such as nitrates, metals. Little epidemiological data.

[a] Total suspended particles.

and is composed of chemicals such as carbonates, silicates, etc. The fine mode ($PM_{2.5}$) is, in contrast, the result of condensations and aggregations of the gaseous products of combustion (APEG 1999). These may be divided into the primary fraction, which is derived directly from combustion (elemental carbon), and the secondary fraction, which is due to photochemistry and other processes acting on gaseous emissions. Relevant examples of the secondary generation of particles are sulphuric acid and ammonium sulphate from the oxidization of sulphur dioxide, and nitric acid and nitrate from the oxidization of oxides of nitrogen.

If this were not complicated enough, there are a host of trace metals and organic compounds in the mixture, and individual particles are not chemically homogeneous. There may be adsorption of other particles or gaseous pollutants onto a central particle core.

The epidemiology of ambient particles is limited by the availability of appropriate measures. This in itself begs the question of what is appropriate in health terms, since we have little prior information from toxicology about the likely components. The measures most commonly encountered in epidemiological studies are listed in table 1.

4. Fine or coarse particles?

(*a*) *Daily mortality and hospital admissions*

Overall, the results from studies that have directly compared the fine and coarse fractions have been mixed (table 2). A meta analysis of six eastern US cities that had taken part in a planned study of air pollution and health found that the associations between fine particles and daily mortality were larger and more significant than those of coarse particles (Schwartz *et al*. 1996). In two-pollutant models, the

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Table 2. *Selected time-series studies that have compared the effects of the fine particle fraction* ($PM_{2.5}$) *with those of the coarse fraction* ($PM_{2.5-10}$)

('RR' denotes relative risk; 'OR' denotes odds ratio; 'MLR' denotes mean least-squares regression; and 'CI' denotes confidence interval.)

study description	reference	outcome and pollution increment (interpercentile range) for which the relative risk is estimated	type of estimate (95% CI)	$PM_{2.5}$	$PM_{2.5-10}$
six eastern US cities	Schwartz *et al.* (1996)	daily all-cause mortality (5–95)	RR	1.058 (1.042, 1.074)	1.02 (0.992, 1.049)
Birmingham, UK 1994–1996	Anderson *et al.* (unpublished data)	daily all-cause mortality (10–90)	RR	1.006 (0.985, 1.027)	0.993 (0.958, 1.029)
		daily cardiovascular mortality (10–90)	RR	1.009 (0.979, 1.04)	0.992 (0.955, 1.035)
		daily respiratory mortality (10–90)	RR	0.999 (0.946, 1.055)	0.924 (0.861, 0.991)
Toronto 1992–1994 (summers)	Burnett *et al.* (1997)	daily respiratory admissions (25–75)	RR	1.037 (1.015, 1.059)	1.023 (1.010, 1.036)
		daily cardiac admissions (25–75)		1.031 (0.997, 1.066)	1.036 (1.015, 1.057)
Birmingham, UK 1994–1996	Anderson *et al.* (unpublished data)	daily respiratory admissions (10–90)	RR	1.012 (0.991, 1.034)	1.002 (0.975, 1.031)
		daily cardiovascular admissions (10–90)	RR	1.005 (0.974, 1.016)	1.007 (0.963, 1.023)
Harvard Six Cities	Schwartz & Neas (2000)	lower respiratory symptoms (25–75)	OR	1.33 (1.11, 1.58)	1.14 (0.98, 1.66)
Diary Study		cough without other respiratory symptoms (25–75)	OR	1.16 (0.99, 1.36)	1.20 (1.07, 1.35)
Philadelphia	Schwartz & Neas (2000)	peak flow (ml) (25–75)	MLR	−0.68 (−1.14, −0.22)	0.30 (−1.18, 1.78)
Philadelphia	Neas *et al.* (1999)	afternoon peak flow ($l\,min^{-1}$) (25–75)	MLR	−0.51 (−2.26, 1.24)	0.30 (−0.76, 1.35)
		next morning peak flow ($l\,min^{-1}$) (25–75)	MLR	−1.84 (−3.72, 0.04)	−0.69 (−1.83, 0.44)
Kuopio	Tiittanen *et al.* (1999)	morning peak flow ($l\,min^{-1}$) (lag 1) (25–75)	MLR	−1.06 (−2.08, −0.41)	−0.86 (−1.82, 0.10)
		cough (lag 2) (25–75)	OR	1.13 (1.01, 1.26)	1.15 (1.04, 1.27)

effects of $PM_{2.5}$ tended not to be affected when $PM_{2.5–10}$ was added to the model, whereas those of $PM_{2.5–10}$ were reduced to near zero when PM_{10} was included in the model. On the other hand, in an earlier report from one of these cities (St Louis; see Dockery *et al.* (1992)), it was noted that the associations between effects of both coarse and fine particles on daily mortality were similar when considered simultaneously in the model. The only other data on mortality are unpublished, from Mexico City and Birmingham, UK. In Mexico City, it was found that coarse particles were associated with daily mortality from all causes, and from respiratory and cardiovascular diseases more strongly than fine particles. When the two fractions were considered together, coarse particles were dominant (Loomis 2000). In Birmingham, UK, neither the fine nor coarse fractions were positively associated with all-cause or disease-specific mortality, and two pollutant models did not further clarify their relative importance. There were, however, hints of differences in the behaviour of the two modalities, the most notable being that the coarse fraction showed a significant *negative* association with respiratory mortality (H. R. Anderson *et al.*, unpublished data; see also table 2).

In an attempt to look at this question in a different way, Schwartz *et al.* (1999) studied the effect of periodic dust storms on mortality in Spokane, WA. These produce high levels of PM_{10}, but, being of crustal origin, are likely to be of coarse rather than fine mode particles. No effect on mortality was found and Schwartz concluded that this indicates that coarse particles are not the toxic component of PM_{10}. The relevance of these findings to the coarse mode found in more usual urban situations is unclear.

Results from the few hospital-admissions studies that have addressed this question tend not to show a clear difference between the coarse and fine fractions. In an analysis of summer hospital admissions to Toronto hospitals in 1992–1994 (Burnett *et al.* 1997), the fine and coarse fraction both showed statistically significant associations of a similar size with respiratory admissions. In the case of cardiac admissions, coarse particles had a slightly larger effect, which was significant, while the effect of fine particles fell below significance. The confidence intervals of the fine and coarse particle estimates overlapped considerably (table 2). These results conflict somewhat with an earlier study from Toronto for the years 1986–1988, in which fine but not coarse particles were significantly associated with cardiorespiratory admissions, though the overlapping of the confidence intervals indicates that this could be a chance difference (Thurston *et al.* 1994).

Table 2 shows the results from Birmingham, UK (H. R. Anderson *et al.*, unpublished data). Here it was found that neither the fine nor the coarse fraction had a significant association with either respiratory or cardiovascular outcomes, and in the case of cardiovascular admissions, the estimates were very similar in size. Lastly, in a study of asthma admissions in Seattle, WA, it was found that both the fine and coarse particle fractions had significant positive effects and that it was not possible to distinguish between them (Sheppard *et al.* 1999).

(*b*) *Panel studies*

Schwartz & Neas (2000) have recently reported a reanalysis of three panel studies, all carried out in the eastern US. The largest of these is of 1844 children in six cities, who kept a diary of respiratory symptoms (the Harvard Six City Diary Study). The

investigators measured various particle indicators at a central monitor placed in a residential area of each community. There was a low correlation between the coarse and fine fractions. When all lower respiratory symptoms were considered, $PM_{2.5}$ showed the larger and significant effect, and had the most stability in two pollutant models (table 2). For the symptom of cough without other symptoms, the strongest effect was with nephelometry (a light-scattering method of measuring mainly submicronic particles), followed by a significant effect of coarse particles; the effect of $PM_{2.5}$ was similar to that of the coarse fraction but was not statistically significant. It is not clear why this particular single respiratory question was selected for analysis.

In two separate panel studies ($n = 83,104$) conducted in Pennsylvania, also reported in Schwartz & Neas (2000), peak expiratory flow rates (PEFRs) for the evening and next morning were analysed in relation to $PM_{2.1}$, $PM_{2.5–10}$ and sulphate. In the combined estimate for both panels, the effect of the fine fraction was negative and significant, whereas that of the coarse fraction was positive and non-significant, though the respective 95% confidence intervals overlapped (table 2). Further panel studies from Philadelphia, PA, during the summer period strengthen the impression that it is difficult to show a clear difference between the effects of coarse and fine fractions (Neas *et al*. 1999). In this study, the effects of fine particles, while larger than those of coarse particles, were non-significant, and clearly not statistically significantly different from those of the coarse particles (table 2).

Similar results were found in the very different environment of Kuopio, Finland, in which a panel of 49 children with chronic respiratory symptoms were studied (Tiittanen *et al*. 1999). In this case, the correlations between $PM_{2.5}$ and $PM_{2.5–10}$ were quite high (above 0.9). There were significant associations between cough symptom for both $PM_{2.5}$ and $PM_{2.5–10}$ after a lag of two days. The authors observed, more generally, that there were inconsistent associations at a variety of lags with all of the fractions studied. Different conclusions were drawn from a panel study in Mexico City (Gold *et al*. 1999), where effects were found with $PM_{2.5}$ but not with $PM_{2.5–10}$.

(*c*) *Numbers or mass?*

There is considerable current interest in the idea that high numbers of ultrafine particles are the most potentially toxic component of the ambient aerosol. Methods of counting particles do so within size categories and this gives an opportunity to compare the effects of particles in different size ranges using numbers or mass. An influential early report that addresses this question is that by Peters *et al*. (1997) among a panel of adults in the city of Erfurt. They measured the number concentrations and mass concentrations within size categories 0.01–2.5 (fine particles), 0.01–0.1 (ultrafine particles) and 0.5–2.5 μm, along with PM_{10} measured with a Harvard Impacter. These measures were analysed in relation to the symptoms and lung function of 27 non-smoking adults with chronic respiratory disease. Ultrafine particles made up 73% of particles but contributed only 1% to the mass of fine particles. Most of the mass provided by particles was between 0.5 and 2.5 μm in diameter. The time courses of changes in the number and mass concentrations were only moderately correlated, allowing their separate contributions to health effects to be analysed. The health effects of the number of ultrafine particles tended to be greater than that of the mass effects of fine particles and of PM_{10}. The study did not directly address the effects of coarse particles.

In the study of Tiittanen *et al.* (1999), particle numbers were also studied, but no coherent pattern of results emerged to give substantial support for any particular metric over another. In another panel study in Kuopio, Pekkanen *et al.* (1997) concluded that the number concentration of ultrafine particles was no more associated with variations in lung function than was PM_{10}, or black smoke. Taken together, these three studies provide only modest epidemiological support for the hypothesis that it is the number concentration of ultrafine particles, rather than the mass concentration of the aerosol, that is important in driving the health effects.

(*d*) *Chronic effects*

(i) *Cohort studies*

The results from three major cohort studies, all from the US, have all provided evidence for associations between fine particles and health effects. All have allowed for confounding at an individual level. Abbey *et al.* (1995) have followed a cohort of non-smoking Seventh Day Adventists to examine the association between $PM_{2.5}$ (estimated from an airport visibility index) and PM_{10}, and the incidence of chronic respiratory disease. While associations were reported for both particle indices, no direct comparison of fine with coarse particles was made (Abbey *et al.* 1995). The Six Cities Study examined the association between air pollution and mortality in a cohort of 8111 adults over 14–16 years. Significant associations were found with $PM_{10/15}$, $PM_{2.5}$ and sulphate, with similar rate ratios and confidence intervals. These associations were greater than those with total particles or acid aerosol. There was a specificity for deaths from lung cancer and cardiorespiratory causes (Dockery *et al.* 1993). Finally, in the largest cohort study, over half a million adults living in 151 metropolitan areas were followed from 1982 to 1989, using annual concentrations of sulphate (151 areas) and fine particles (50 areas) as indicators of air pollution exposure. Mortality was increased in association with both measures to a similar extent, but the effect of sulphates on cancer was greater (Pope *et al.* 1995*b*).

(ii) *Prevalence studies*

Chronic respiratory symptoms and lung function measures are conveniently measured by prevalence surveys and allow the opportunity to compare areas with different air pollution exposures. The best modern studies control for confounding factors such as smoking, passive smoking, gas cooking, dampness, etc. A number of studies have used measures of fine particles and most have found either associations with symptoms or decrements in lung function, or both (Dockery *et al.* 1989). However, there is only one study, that by Raizenne *et al.* (1996), that directly compares the coarse and fine fraction. This was a study of children in 26 cities of the eastern US and Canada. There was a clear association between fine particles and lung function, but none was found for the coarse fraction; this is fairly convincing evidence that fine particles are more important.

5. Other measures of fine particles

Apart from measures of $PM_{2.5}$ or other size fractions, we can also deduce something about the effect of fine particles from measures of sulphate, acid aerosol and black

smoke, all of which reflect particles found mainly in the fine fraction, and for which there are sufficient epidemiological data.

(*a*) *Sulphate and acid aerosols*

These are largely the result of the oxidation of SO_2 to sulphuric acid with subsequent reactions with ammonia, in particular, to form sulphates of various types. Nitric acid and nitrates also occur in the UK, but generally in lower concentrations than sulphate (APEG 1999). These are secondary pollutants and tend to have a regional distribution. The amount of associated acid varies according to the opportunities for neutralization and is generally higher in the eastern US, where most studies have been done, than in Europe, where farming activity produces enough ammonia to neutralize the acid.

Particle-associated acidity was a feature of the major air pollution episodes of the past, and it has been postulated that acid aerosol is harmful to health (Lippmann 1989). Without reviewing the evidence here, it is sufficient to say that a number of time-series studies support this view. One example is the study of hospital admissions in Toronto (referred to above; see Thurston *et al*. (1994)), in which the ranking of effects of particles was

$$H^+ > \text{sulphate} > PM_{2.5} > PM_{10} > TSP$$

(though the effect of ozone was ten times greater). This was also found in later studies of Toronto (Burnett *et al*. 1997). On the other hand, the study of mortality in six eastern cities, also referred to earlier (Schwartz *et al*. 1996), found much lower and non-significant associations with H^+ than with sulphate and $PM_{2.5}$. In the Harvard Six Cities cohort study, fine particles, sulphates and inhalable particles were more strongly associated with mortality than acid aerosol. The results of panel studies in the eastern US show variable results. Little evidence is available from Europe.

There is probably stronger evidence to relate ambient sulphate to health effects, but it must be borne in mind that sulphate and acidity are closely associated in some atmospheres. Sulphate has been associated with daily mortality and hospital admissions in daily time-series studies (Schwartz *et al*. 1996; Thurston *et al*. 1994) and lung function in some panel studies in the US (Neas *et al*. 1995; Schwartz & Neas 2000) and Europe (Peters *et al*. 1996). The results tend to be less substantial and robust than those for $PM_{2.5}$. In cross-sectional studies, sulphate has been associated with mortality (Ozkaynak & Thurston 1987). More substantially, sulphate was associated with increased mortality in the American Cancer Society cohort study, with similar relative risks as for $PM_{2.5}$ (Pope *et al*. 1995*b*). In the recent studies from Birmingham, UK, sulphates showed inconsistent associations with mortality, but with a notable seasonal interaction, with larger effects in the warm season. There were weak effects on hospital admissions (H. R. Anderson *et al*., unpublished data).

(*b*) *Black smoke*

The Black Smoke method, which uses a reflectance technique, has been the standby for particle measurement for many years in the UK and some other European countries. Unlike sulphate and acid, the method measures primary pollution from black carbonaceous particles. In cities such as London it is mainly measuring diesel exhaust

particles. The inlet cut-off is at 4.5 μm, but most of the particles are probably in the fine fraction. It is, therefore, a measure of fine black primary particles. Most daily time-series studies have observed associations between black smoke and daily mortality and hospital admissions (Katsouyanni *et al*. 1997; Spix *et al*. 1998). In recent studies of London daily mortality, it was found that the effects of black smoke were more robust than those of PM_{10} (Bremner *et al*. 1999). In Amsterdam, the effects of black smoke and PM_{10} were almost identical (Verhoeff *et al*. 1996). This suggests that black smoke represents an important component of the toxic material included in PM_{10}. The results from panel studies have been more mixed. Many studies have found associations with lung function decrement and symptoms, whereas the European PEACE study of 14 centres found little evidence of associations between PM_{10} or black smoke and lung function and symptoms in panels of children with respiratory disease (Roemer *et al*. 1998).

6. Interpretation and conclusion

The epidemiology of particle fractions is very patchy, due to a lack of appropriate measures and some inherent limitations of the epidemiological approach. Virtually nothing is known about ultrafines, apart from information now emerging from studies of particle number concentrations.

There is abundant evidence of short-term associations between ambient particles and mortality on hospital admissions and emergency-room visits. The evidence concerning short-term associations with lung function and respiratory symptoms is less consistent but generally persuasive. All of the major cohort studies have found associations between exposure to particles and mortality or disease incidence. Most authorities regard these associations as at least partly causal, and there is emerging mechanistic evidence from experimental studies which supports this view.

Epidemiological studies have made a contribution to understanding which component or components of the mixture are important. Firstly, this has been through studies using measurements of size-fractionated particles, mainly $PM_{2.5}$ (fine fraction). These have found that the associations with the fine fraction are similar to those of PM_{10}, which suggests that the $PM_{2.5}$ fraction is toxic. What these studies rarely address is whether the coarse fraction is also important, and there is not enough evidence at present to be sure that it is not. The second strand of evidence is that related to species of particles that are mainly fine; those that have been amenable to epidemiological study are mainly sulphate, acid and black smoke. Associations have been reported for all of these measures. Finally, the emerging evidence on particle numbers suggests that numbers of fine particles may be more important than mass.

It is important to mention a potential statistical problem with comparing different particle measures. This starts with the different behaviour of fine versus coarse particles in the atmosphere (Wilson & Suh 1997). The former have a low settling velocity and penetrate indoors quite effectively, whereas the latter settle out quite quickly. This means that concentrations of fine particles are more uniformly spread over large areas such as cities, and it follows from this that the community monitor or monitors used for epidemiological studies probably represent the population exposure more accurately than do monitors of coarse particles. Misclassification of exposure will, in most circumstances, bias the effect estimates of air pollution to the

null. This argument has been used to postulate that the larger estimates for fine compared with coarse fractions reflect differential exposure misclassification rather than differences in toxicity (Lipfert & Wyzga 1997). Schwartz *et al*. (1996) have disputed this and the issue remains unresolved.

It is concluded that fine particles are associated with health effects, and that both secondary and primary particles may be important. It has not been shown that coarse particles are not important. The epidemiological evidence concerning the ultrafine fraction is meagre and will remain so until adequate series of data are available for epidemiological analysis.

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Discussion

H.-E. Wichmann (*GSF – Institute of Epidemiology, Neuherberg, Germany*). You mentioned that in the APHEA study, effects of black smoke on daily mortality have been observed in western Europe, but not in eastern Europe. I wonder whether the new insights into ultrafine particles could help us understand this. If we look at the atmosphere in eastern Europe at the time of APHEA study, there were many larger particles in the air which might have scavenged the ultrafine particles, leaving no room for health effects of the ultrafines. In contrast, in western Europe, there were probably many more ultrafines in the air, which might have contributed to daily mortality, and, since they are correlated to black smoke, this might have been attributed to black smoke.