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Epidemiological evidence of the effects of ultrafine particle exposure

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In epidemiological studies associations have been observed consistently and coherently between ambient concentrations of particulate matter and morbidity and mortality. With improvement of measurement techniques, the effects became clearer when smaller particle sizes were considered. Therefore, it seems worthwhile to look at the smallest size fraction available today, namely ultrafine particles (UPs, diameter below 0.1 μm) and to compare their health effects with those of fine particles (FPs, diameter below 2.5 μm). However, there are only few studies available which allow such a comparison.

Four panel studies with asthma patients have been performed in Germany and Finland. A decrease of peak expiratory flow and an increase of daily symptoms and medication use was found for elevated daily particle concentrations, and in three of these studies it was strongest for UPs. One large study on daily mortality is available from Germany. It showed comparable effects of fine and ultrafine particles in all size classes considered. However, FPs showed more immediate effects while UPs showed more delayed effects with a lag of four days between particulate concentrations and mortality. Furthermore, immediate effects were clearer in respiratory cases, whereas delayed effects were clearer in cardiovascular cases.

In total, the limited body of studies suggests that there are health effects, due to both UPs and FPs, which might be independent from each other. If this is confirmed in further investigations, it might have important implications for monitoring and regulation, which until now does not exist for UPs. Data from Germany show that FPs cannot be used as indicator for UPs: the time trends for FPs decreased, while UPs was stable and the smallest size fraction of UPs has continually increased since 1991/92.

Keywords: ultrafine particles; fine particles; short-term effects; mortality; respiratory diseases; cardiovascular diseases

1. Introduction

The aim of this overview is the evaluation of the available epidemiological knowledge on health effects of ultrafine particles in ambient air. This is only possible in the context of particle epidemiology in general. Therefore, at the beginning a short summary of relevant studies is given, where the particle mass with a diameter below 2.5 or 10 μm ($PM_{2.5}$, PM_{10}) or total suspended particulates (TSP) have been measured.

The paper will be restricted to short-term effects, since until now no studies on long-term effects have been available where ultrafine particles have been measured.

Furthermore, the role of copollutants will not be considered here, but we will address the question, if there are associations between ambient particles and morbidity or mortality, can they be attributed in part or totally to the ultrafine fraction?

We will use the following definitions:

ultrafine particles (UPs) have a diameter below 0.1 μm;

fine particles (FPs) have a diameter between 0.1 and 2.5 μm. They are mainly represented by $PM_{2.5}$;

coarse particles (CPs) have a diameter above 2.5 μm.

Furthermore we look at the following parameters:

number concentration (NC) is the concentration of the number of particles in 1 cm^3;

mass concentration (MC) is the mass of particles measured in $\mu g\, m^{-3}$.

As will be shown below, in a given volume the number of UPs is much higher than the number of FPs. Therefore, UPs are represented by the number concentration. In contrast, the mass of UPs is much smaller than the mass of FPs, and FPs are represented by the mass concentration.

(*a*) *Epidemiological knowledge on particle effects*

Epidemiological studies allover the world have consistently observed short-term effects of particulate matter on daily mortality (Dockery & Pope 1994; Schwartz 1994; Bascom *et al*. 1996; Katsouyanni *et al*. 1997; Pope & Dockery 1999). Often an immediate association was observed resulting in the largest effect estimates for the concurrent day or one day after. A recent review estimated that an increase of PM_{10} by 10 $\mu g\, m^{-3}$ is associated with a 0.8% increase in mortality. The summary estimate for respiratory disease mortality was *ca.* 3% and for cardiovascular disease mortality *ca.* 1.3% (Pope & Dockery 1999). In studies where both PM_{10} and $PM_{2.5}$ were available to characterize the ambient concentrations of particles mass, there were indications that $PM_{2.5}$ was more strongly associated with mortality than PM_{10} (Dockery *et al*. 1992; Schwartz *et al*. 1996).

A pooled analysis based on data from four large, western European cities (London, Barcelona, Paris and Athens) as part of the APHEA project estimated that the risk of mortality increased in association with SO_2 and black smoke independently of each other (Katsouyanni *et al*. 1996, 1997). In the absence of more detailed air pollution measurements, black smoke might be regarded as a surrogate measure for ambient particles in urban air.

The impact of particulate matter on respiratory symptoms has been reinforced by studies on exacerbation of respiratory diseases from the 1960s to the 1990s (Dockery & Pope 1994; Bascom *et al*. 1996; Pope & Dockery 1999; Peters *et al*. 1997*b*, *c*). However, a biological mechanism linking the association between exacerbation of cardiovascular diseases and inhalation of ambient particulate matter had to be established. Seaton *et al*. (1995) have hypothesized that pulmonary inflammation may trigger systemic hypercoagulability. During the 1985 Europe-wide air pollution episode, the WHO MONICA survey (*Monitoring of trends and determinants in cardiovascular*

disease) was conducted in Augsburg, Germany. Increases in plasma viscosity (Peters *et al.* 1999*a–c*) have been observed in randomly selected healthy adults in association with high particulate air pollution in both men and women from Augsburg. The odds of observing plasma viscosity levels above the 95th percentile tripled during the air pollution episode. Analyses of the C-reactive protein concentrations of healthy, middle-aged men (aged 45–64) based on data from the same study, showed an odds ratio of 3.5 for C-reactive protein concentrations above the 90th percentile. In addition, the TSP were associated independently from the episode with elevated CRP concentrations. Both CRP and plasma viscosity have been identified to be independent cardiovascular risk factors for subsequent myocardial infarctions (Danesh *et al.* 1998; Koenig *et al.* 1998). Plasma viscosity characterizes the physical properties of the blood. Elevated plasma viscosity increases the shear forces at an atherosclerotic lesion (Koenig & Ernst 1992). C-reactive protein is an acute phase reactant released as part of an inflammatory cascade. Its increase in association with particulate air pollution might point towards the inflammatory processes that particles elicit in the alveoli. A study published last year based on the Whitehall study also showed an increase of fibrinogen in association with nitrogen dioxide (Pekkanen *et al.* 1999*b*). Fibrinogen is also considered to be an acute phase reactant, and is one of the main determinants of plasma viscosity (Koenig & Ernst 1992). However, a study particularly designed to investigate the effects of ambient air pollution on blood in a panel of elderly subjects in Edinburgh was unable to confirm these associations (Seaton *et al.* 1999). Instead a decrease in red blood cells was observed in the blood samples repeatedly collected from panel members.

Toxicological studies conducted by Godleski and co-investigators suggested that concentrated ambient particles might alter the autonomic nervous system response (Stone & Godleski 1999). Epidemiological evidence was found for increased heart rate (Pope *et al.* 1999*a*; Peters *et al.* 1999*c*). The data collected in the MONICA study, Augsburg, in a random sample of the population (Peters *et al.* 1999*c*), as well as in a panel study in elderly subjects (Pope *et al.* 1999*a*), cohere. Three panel studies on the alteration of the autonomic control by ambient particles in elderly subjects have been reported on (Liao *et al.* 1997; Pope *et al.* 1999*b*; Gold *et al.* 2000). Heart rate variability was calculated based on either 24 holter EKG recording or 5–6 min intervals of EKG recording. An overall decrease in the standard deviation of all normal R–R intervals was observed (Liao *et al.* 1997; Pope *et al.* 1999*b*; Gold *et al.* 2000). However, the results differed with respect to measures that capture the sympathetic and parasympathetic portions of the nervous system control. Differences in the subjects, the EKG recordings and analyses or the different pollution mixtures and levels might account for these inconsistencies (Pope 2000). Additional evidence for the impact of particulate air pollution on arrhythmia was found in a follow-up study of patients with implanted cardioveter defibrillators (Peters *et al.* 2000). One hundred patients with a history of coronary artery disease and often syncope were enrolled into the study. Therapeutic interventions due to sustained tachycardia or defibrillation were analysed, and statistically significant odds ratios were noted in association with increased concentrations of $PM_{2.5}$ and NO_2.

Both mechanisms, the changes in coagulability of the blood and the alteration of the autonomic nervous control of the heart, might potentially increase the likelihood of ischemic events and arrhythmia, especially in persons with manifest atherosclerotic disease.

(b) *Possible role of ultrafine particles*

Ambient concentrations of particles are classically characterized by their mass concentrations. However, depending on their sizes, quite substantial differences in numbers or surfaces might constitute the same mass. While only one particle per cm^3 with a diameter of 2.5 μm is sufficient to result in a mass concentration of 10 $\mu g\, m^{-3}$, more than two million particles of a diameter of 0.02 μm are needed to obtain the same mass concentration (Oberdörster *et al.* 1995).

Ultrafine particles are deposited in the deep lung (ICRP 1994; US EPA 1996) and have been hypothesized to be responsible for the associations between particle matter and health outcomes at the current ambient concentrations (Oberdörster *et al.* 1995; Seaton *et al.* 1995). There are a number of potential mechanisms that can contribute to increased toxicity of UPs.

(i) For a given aerosol mass concentration, there is a much higher particle number and a much larger surface area when compared with larger sized particles. Since fine and ultrafine particles can act as a carrier to the deep lung for adsorbed reactive gases, radicals, transition metals or organic compounds, the larger surface area of ultrafines can transport more toxic surface adsorbed materials than larger particles.

(ii) Deposition of inhaled ultrafine particles is very high in the respiratory tract. Predicted deposition of inhaled 0.02 μm particles can be up to 50% in the alveolar region of the human lung and it is also very high in the lower tracheobronchial tree.

(iii) For particles not readily soluble in the epithelial lining fluid, the surface area provides the interface between the retained particles and cells, fluids, and tissues of the lungs; hence the dramatically increased surface area of ultrafine particles is likely to increase surface dependent reactions.

(iv) Protection resulting from the avid phagocytosis by alveolar macrophages is impaired since ultrafine particles are less well recognized by these cells, while there are many more ultrafine particles spread over the surface area of the alveolar epithelium less likely to be phagocytized when compared with larger particles.

(v) After deposition ultrafines penetrate more rapidly into interstitial sites. Preliminary evidence that ultrafine particles can be translocated to remote organs such as the liver and heart has been collected.

2. Epidemiological studies on ultrafine particles

(a) *Particle measurements in these studies*

Since 1991, daily measurements of UPs and, more general, of particle size distributions have been performed in the framework of epidemiological studies. The first equipment used was the mobile aerosol spectrometer (MAS). As described elsewhere (Brand *et al.* 1991, 1992; Tuch *et al.* 1997; Wichmann *et al.* 2000*a*), it consists of two instruments covering different size ranges. Particles in the size range 0.01 to 0.5 μm are measured using a differential mobility analyser (DMA) combined with a

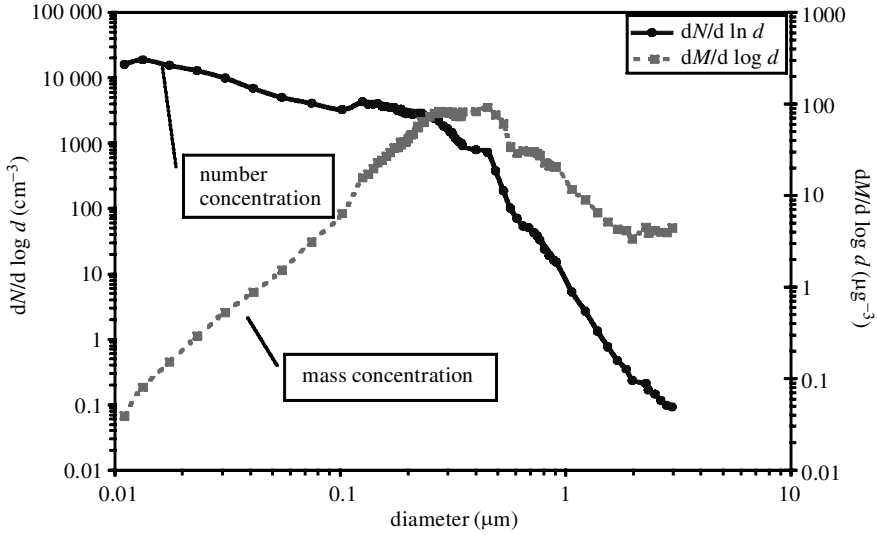

Figure 1. Typical particle number and mass distribution averages from approximately 10 000 single measurements, Erfurt. From Wichmann *et al.* (2000*a*).

condensation particle counter (CPC). This set is termed differential mobility particle sizer (DMPS). Particles in the size range from 0.1 up to 2.5 μm are classified by an optical laser aerosol spectrometer (LAS-X). The DMA allows the segregation of particle fractions of uniform electrical mobility from a polydisperse aerosol. The number of particles selected by the DMA is counted by the CPC in 13 discrete size ranges. The LAS-X classifies particles according to their light scattering into 45 size-dependent channels. MAS yields a differential particle number concentration. Based on parallel measurements of $PM_{2.5}$, the mean density of ambient particles has been determined as 1530 kg m^{-3}, which is in excellent agreement with the literature value of 1500 kg m^{-3}. The differential mass distribution is calculated on this basis.

MAS measurements have been performed in Erfurt since 1991/92 in the framework of several epidemiological studies (Peters *et al.* 1997*a*; Von Klot *et al.* 2000; Wichmann *et al.* 2000*a*, *b*) and also in three places in Sachsen-Anhalt, Eastern Germany (Pitz *et al.* 2000). A typical distribution of the particle number and the particle mass over the size range from 0.01 to 2.5 μm is shown in figure 1. In the years 1995–98 in Erfurt, 58% of the number concentration (NC) was found between 0.01 and 0.03 μm and 88% were UPs (between 0.01 and 0.1 μm). In contrast, only 3% of the mass was found below 0.1 μm, 78% between 0.1 and 0.5 μm and 95% below 1 μm. In other words, $PM_{0.5}$ equals $0.81PM_{2.5}$ and PM_1 equals $0.95PM_{2.5}$ in this study (Wichmann *et al.* 2000*a*).

The annual means of the number and mass concentrations are shown in table 1. UPs varied between 10 000 and 20 000 particles per cm^3 with a 24 h maximum of 50 000 particles per cm^3 and was stable over time. In contrast, FPs decreased substantially during the period of observation.

In the European ULTRA study, measurements of UPs have been performed in Finland, The Netherlands and Germany (Pekkanen *et al.* 1999*a*; Kreyling *et al.* 1999; Ruuskanen *et al.* 2000). In parallel to MAS in Erfurt, a similar device has been used in Alkmaar (denoted DAS) and a third spectrometer in Helsinki (denoted EAS),

Table 1. *Ambient concentrations of UPs and FPs measured in the framework of epidemiological studies*
(UP = NC0.01–0.1, FP = MC0.01–2.5 = '$PM_{2.5}$'.)

	Erfurt[a] (winter)		Sachsen-Anhalt[b]	
	1991/92	1997/98	1993	1999
UP (cm^{-3})	13 100	19 200	15 500	15 000
FP ($\mu g\ m^{-3}$)	82.1	25.3	47.9	22.6

	Helsinki[c] (SF) winter 1996/97	Alkmaar[c] (NL) winter 1996/97	Erfurt[c] (D) winter 1996/97
UP (cm^{-3})	16 200	18 300	17 700
FP ($\mu g\ m^{-3}$)	9.4	27.0	41.9

[a] Tuch *et al.* (1997), Wichmann *et al.* (2000*b*).
[b] Pitz *et al.* (2000).
[c] Ruuskanen*et al.* (2000).

which measured the particle size distribution in the size range 0.01–10 μm by an electrical method alone. (In an earlier side-by-side comparison, the different measurement principles had shown good agreement both in the number concentration of UPs and the total number concentration (Tuch *et al.* 2000*a*, *b*).) The concentrations of UPs in the three locations were comparable, whereas the concentrations of FPs differed substantially between the cities (table 1).

For source apportionment, in addition to the measurement of particle size distributions and gases, elemental composition in five size fractions has been determined. Particles have been collected with a Berner impactor in the size range between 0.05 and 1.4 μm and have been analysed by proton-induced X-ray emission (PIXE) spectrometry (technique described in Wichmann *et al.* (2000*b*)). In Erfurt, measurements have been performed every 10th day from September 1995 to August 1997 and every day from September 1997 to December 1998. Three sources have been considered, namely natural dust, domestic heating/fuel combustion of brown coal and oil, and motor vehicle exhausts. Using information based on crustal enrichment factors (enrichment of an element in the aerosol sample compared with the composition of the natural crust), correlations between the components, and patterns of the concentrations during the day, during the week and in summer and winter, the following associations have been found. In Erfurt, natural dust is especially represented by silicon, aluminium and titanium. Combustion of brown coal and oil is represented by sulphur, vanadium, nickel and sulphur dioxide. Motor vehicle exhausts are best characterized by the number concentration of the smallest available size fraction, namely NC0.01–0.03, followed by UPs, lead, NO, NO_2, CO and finally $PM_{2.5}$ (Wichmann *et al.* 2000*b*).

(*b*) *Observed health effects*

Until now only a few epidemiological studies have been published which address the role of ultrafine particles. These deal with short-term effects in adults and children with asthma and daily mortality.

Table 2. *Effects of UPs and FPs on PEF of asthmatics in epidemiological studies* (Δ is the interquartile range; $*$, $p < 0.05$.)

	Δ	morning PEF coefficient ($l\ min^{-3}$)	evening PEF coefficient ($l\ min^{-3}$)
Adults with asthma Erfurt 1991/92[a]			
UP	9200 cm^{-3}	−2.55*	−3.58*
FP	50 $\mu g\ m^{-3}$	−1.42*	−2.18*
PM_{10}	50 $\mu g\ m^{-3}$	−1.51	−2.31*
Adults with asthma Helsinki 1996/97[b]			
PNC	7300 cm^{-3}	−1.16*	−1.66*
FP	6.6 $\mu g\ m^{-3}$	0.32	−0.41
PM_{10}	9.3 $\mu g\ m^{-3}$	1.68*	1.13*
Children with asthma symptoms Kuopio 1994[c]			
NC0.01–0.03	20 700 cm^{-3}	−0.73	0.35
NC0.03–0.1	13 100 cm^{-3}	−0.48	0.10
PM_{10}	13 $\mu g\ m^{-3}$	−2.24*	0.04

[a] Peters *et al.* (1979): 5 days mean, UP = NC0.01–0.1, FP = MC0.1–0.5.
[b] Penttinen *et al.* (2000): 5 days mean, PNC is the total particle number count, FP = MC0.1–0.5.
[c] Pekkanen *et al.* (1997): 4 days mean.

(i) *Study on adults with asthma in Erfurt, Germany 1991/92*

In Erfurt, 27 non-smoking asthmatics recorded the peak expiratory flow (PEF) and respiratory symptoms daily during the winter season 1991/92 (Peters *et al.* 1997*a*). Most of the particles were in the ultrafine fraction, whereas most of the mass was attributable to particles in the size range 0.1–0.5 μm. Since these two fractions did not have similar time courses, comparison of their health effects was possible (correlation coefficient, $r = 0.51$). Both fractions were associated with a decrease of PEF and an increase in cough and feeling ill during the day. Health effects of the number of ultrafine particles were larger than those of the mass of the fine particles. The effects were strongest for the five days mean of the particle concentrations (tables 2 and 3, figure 2).

(ii) *Study on adults with asthma in Erfurt, Germany 1996/97*

Daily medication use was reported in 58 asthmatic adults in Erfurt from October 1996 to March 1997 (Von Klot *et al.* 2000). Number and mass concentrations in the size range of 0.01–2.5 μm diameter were determined concurrently. Overall prevalence of bronchodilator use and inhaled corticosteroid were analysed with a logistic regression model controlling for trend, temperature, weekend, holidays and autocorrelation. The results are shown in table 2. Corticosteroid use and bronchodilator use both increased in association with cumulative exposure over 14 days of UPs and FPs. A comparable effect was found for cumulative exposure over 5 days. The data

Table 3. *Symptoms and medication used in asthmatics depending on UPs and FPs* (Δ is the interquartile range; $*$, $p < 0.05$.)

Adults with asthma Erfurt 1991/92[a]			
	Δ	feeling ill during the day OR [95% CI]	cough OR [95% CI]
UP	9200 cm^{-3}	1.44 [1.15, 1.81]*	1.26 [1.06, 1.50]*
FP	50 $\mu g\ m^{-3}$	1.21 [1.06, 1.38]*	1.02 [0.91, 1.15]
PM_{10}	50 $\mu g\ m^{-3}$	1.47 [1.16, 1.86]*	1.30 [1.09, 1.55]*
Adults with asthma Erfurt 1996/97[b]			
	Δ	corticosteroid use OR [95% CI]	bronchdilator use OR [95% CI]
UP	7700 cm^{-3}	1.34 [1.22, 1.47]*	1.09 [0.99, 1.21]
FP	20 $\mu g\ m^{-3}$	1.29 [1.21, 1.38]*	1.03 [0.96, 1.11]
Adults with asthma Helsinki 1996/97[b]			
	Δ	asthmatic symptoms % coefficient	cough % coefficient
PNC	7300 cm^{-3}	0.001	0.076*
FP	6.6 $\mu g\ m^{-3}$	−0.010*	−0.008
PM_{10}	9.3 $\mu g\ m^{-3}$	−0.010	−0.016

[a] Peters *et al.* (1979): 5 days mean, UP = NC0.01–0.1, FP = MC0.1–0.5.
[b] Von Klot *et al.* (2000): 14 days mean, UP = NC0.01–0.1, FP = MC0.01–0.5 = '$PM_{2.5}$'.
[c] Penttinen *et al.* (2000): 5 days mean, PNC is the total particle number count, FP = $PM_{2.5}$.

suggest that asthma medication use increases with particulate air pollution. The effect might be more delayed but stronger on anti-inflammatory medication than on bronchodilators.

(iii) *Study on adults with asthma in Helsinki, Finland 1996/97*

Seventy-eight adult asthmatics were followed with daily peak-flow (PEF) measurements and symptoms and medication diaries for six months in the winter and spring season 1996/97 in Helsinki (Penttinen *et al.* 2000). The associations between daily health end-points and indicators of air pollution were examined by multivariate, autoregessive linear regression. Daily mean number concentration, but not particle mass (PM_{10}, $PM_{2.5}$), was negatively associated with daily PEF deviations. The strongest effects were seen for particles in the ultrafine range. No significant effect of particulate pollution on symptoms or bronchodilator use was seen (tables 2 and 3).

(iv) *Study on children with asthma symptoms in Koupio, Finland 1994*

The effects of daily variations in particles of different sizes on peak expiratory flow (PEF) were investigated during a 57-day follow-up of 39 asthmatic children

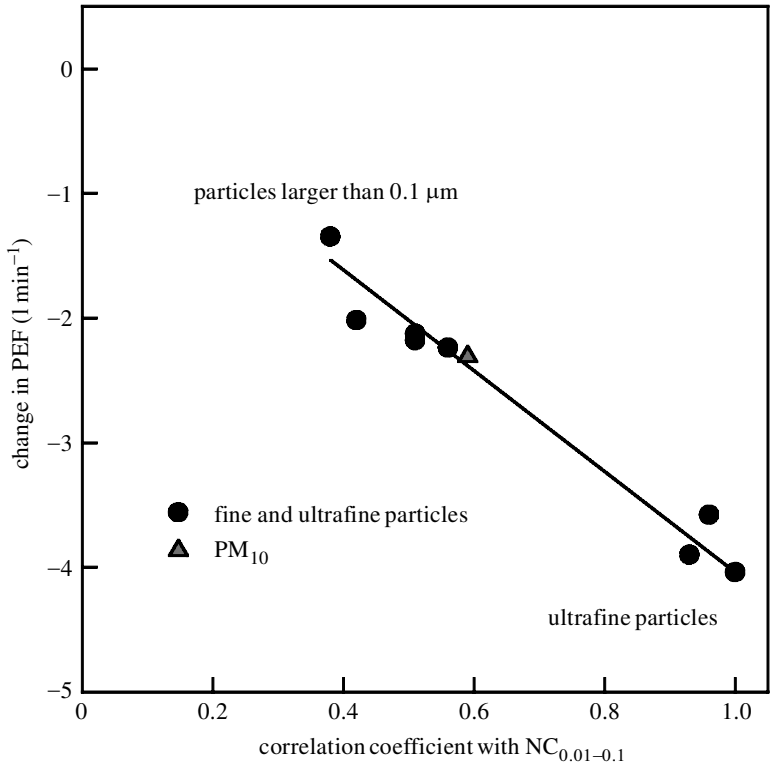

Figure 2. Changes in evening peak expiratory flow (PEF) by correlation between all size fractions and the number concentration of ultrafine particles (NC0.01–0.1). From Peters *et al.* (1979).

aged 7–12 years in 1994 in Koupio. In addition to PM_{10} and black smoke (BS) concentrations, an electrical aerosol spectrometer (EAS) was used to measure particle number concentrations in the size range of 0.01–10 μm. All pollutants tended to be associated with declines in morning PEF. In this study, the concentration of UPs was less strongly associated with variations in PEF than PM_{10} or BS (table 2).

(v) *Mortality study in Erfurt, Germany 1995–98*

Mortality data were collected prospectively over a 3.5 year period from August 1995 to December 1998. Death certificates were obtained from the local health authorities. The death certificates were aggregated to daily time-series of total counts or counts for subgroups. These were compared with particle data: besides $PM_{2.5}$ and PM_{10}, size specific number and mass concentration data in six size classes between 0.01 and 2.5 μm were derived from measurements with the MAS (Wichmann *et al.* 2000*a*). Furthermore, elemental composition was analysed by PIXE, as described above (Wichmann *et al.* 2000*b*).

Some of the UP and FP concentrations are given in table 1. All particulates had a strong seasonality with maximal concentrations in winter. The UP concentrations showed a strong day of the week effect with concentrations during the weekend 40% lower than during the week. This and a clear increase of the UP concentrations during the rush hours suggests that the main source for UPs was automobile traffic.

The association with daily mortality was analysed using Poisson regression techniques with generalized additive modelling (GAM) to allow non-parametric adjustment for the confounders. The pollutants were included either untransformed or log transformed, depending on goodness of fit. Mortality increased in association with ambient particulates after adjustment for season, influenza epidemics, day of week and meteorology. In a sensitivity analysis, the results proved stable against changes of the confounder model.

As shown in figure 3*a*, associations between particle number and particle mass concentrations have been observed in different size classes, and both immediate effects (lags 0 or 1 days) and delayed effects (lags 4 or 5 days) were found. There was a tendency for more immediate effects of the mass concentrations (i.e. in the larger size ranges) and for more delayed effects of the number concentrations (i.e. in the smaller size ranges). However, this pattern could not be separated clearly, and distributed lag models comprising the days 0 to 5 showed similar results.

The effects could be found for total mortality but also for respiratory and cardiovascular causes (figure 3*b*). There was a tendency for more immediate effects on respiratory causes and more delayed effects for cardiovascular causes. Again this could not be distinguished statistically.

(*c*) *Ongoing studies*

(i) *Study on adults with cardiovascular diseases in three European cities (EU-ULTRA) 1996–1999*

In the first part of this study, UP and FP measurements have been compared in Finland, The Netherlands and Germany (Pekkanen *et al.* 1999*a*; Ruuskanen *et al.* 2000). The results are shown in table 1. In the epidemiological part, a panel study of 150 elderly with cardiovascular diseases was performed in the winter season 1998/99, using symptom diaries and performing biweekly EKG and lung function measurements. The analysis is ongoing.

(ii) *Study on survivors of acute myocardial infarction in Augsburg, Germany 1999–2001*

A case crossover study is performed based on the Coronary Event Registry in Augsburg. Cases are survivors of an acute myocardial infarction. Measurements of fine particle mass and total number concentration are performed on an hourly basis.

(iii) *Study on cardiovascular diseases and COPD in Erfurt (as part of the EPA Rochester ultrafine particle centre) 2000–2004*

In the first part, a panel of 50 patients with adult cardiovascular patients is observed for six months. In the second phase a corresponding protocol is used for adult patients with chronic obstructive pulmonary disease (COPD). Daily respiratory and cardiovascular symptoms are recorded, biweekly EKGs and blood parameters are determined. Fine and ultrafine particles are measured using the MAS device, as well as $PM_{2.5}$, PM_{10} and PIXE. The aim of the study is the characterization of the association between ambient particle exposure and changes in biomarkers of inflammation of the cardiorespiratory system in patients with stable coronary artery disease and/or COPD.

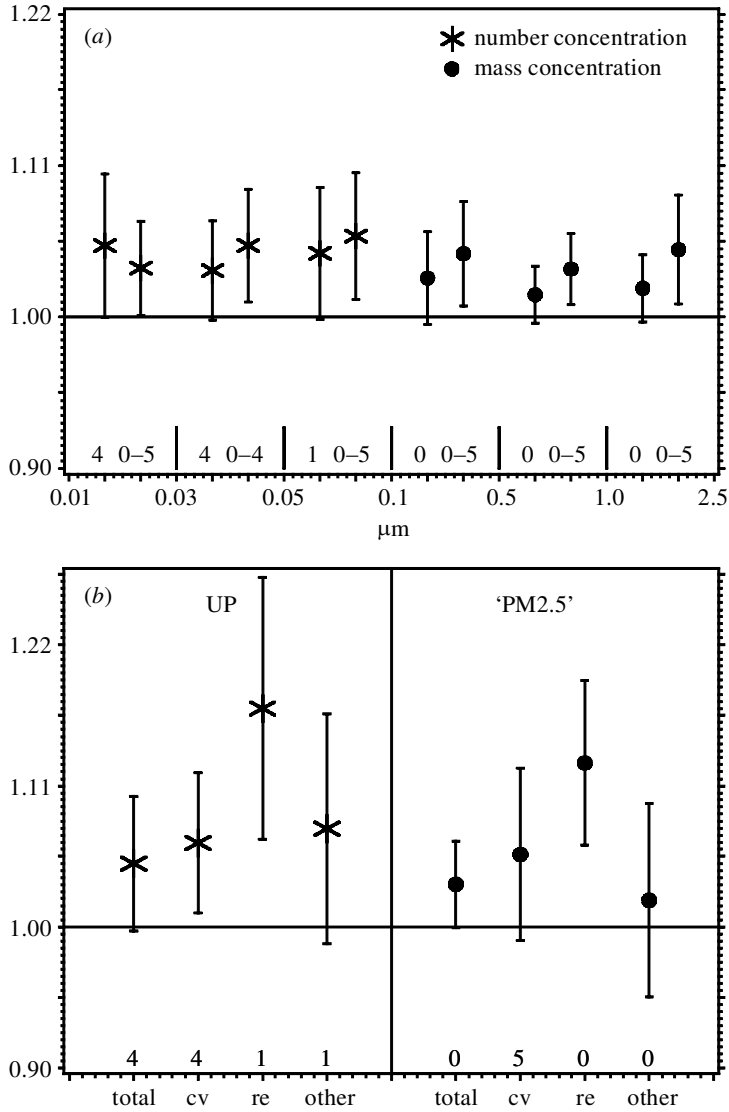

Figure 3. (*a*) Effects of different size classes of UPs and FPs on daily mortality in Erfurt, 1995–1998. Left, best one-day lag; right, distributed lag model. The lags (days) are given at the bottom. (*b*) Effects of UPs and FPs on mortality for prevalent diseases (total, cardiovascular, respiratory, others). Best day-lag model. There seems to be a stronger immediate effect (lag 0 or 1 days) on respiratory causes and a stronger delayed effect (lag 4 or 5 days) on cardiovascular causes. Modified from Wichmann *et al.* (2000*a*).

3. Discussion

(*a*) *Ultrafine particles in ambient air*

The ambient aerosol is a dynamic system which may change its concentration and size distribution due to coagulation and chemical reactions. Because of their high diffusivity UPs coagulate with other aerosol particles depending on the ambient aerosol

conditions such as concentration, size distribution, thermodynamic parameters, etc. (Fuchs 1964; Willeke & Baron 1993).

Measurements of ultrafine particles in the framework of epidemiological studies are only available for a limited number of places in Europe like Erfurt (Tuch *et al.* 1997; Wichmann *et al.* 2000*a*, *b*) as well as the ULTRA study in Germany, Finland and The Netherlands (Tuch *et al.* 2000*a*, *b*; Ruuskanen *et al.* 2000; Pekkanen *et al.* 1999*a*; Mirme *et al.* 2000) and three places in Sachsen-Anhalt (Pitz *et al.* 2000). These data show a surprisingly homogeneous picture, but the number of places is not sufficient to see which range exists within Europe. Furthermore, no data of the spatial distribution of UPs within a city are available. It is important to note that the correlation of UPs and FPs is surprisingly low, suggesting that different sources may be relevant and that the coagulation of UPs to FPs is a complex process.

(*b*) *Health effects of fine and ultrafine particles*

(i) *Lesson from the asthma panel studies*

From the studies described above the following can be learned:

- there are clearer effects on adults with asthma than on children with asthma symptoms;
- effects of both UPs and FPs are observed, and the effects of UPs are slightly stronger;
- cumulative effects over 5 days (for medication use up to 14 days) are stronger than same-day effects;
- in two pollutant models, the effect on the same day is stronger for FPs, whereas the cumulative effect is stronger for UPs (Peters *et al.* 1997*a*).

(ii) *Lesson from the mortality study*

From the only available mortality study (Wichmann *et al.* 2000*a*, *b*) we learn:

- there are particle effects on total mortality as well as on respiratory and cardiovascular causes;
- effects of both UPs and FPs are observed;
- there are immediate effects (lag 0–1 day) and delayed effects (lag 4–5 days), which can be combined into cumulative effects (by distributed lag models);
- there is a tendency that FPs show slightly stronger immediate effects and that UPs show slightly stronger delayed effects;
- there is a tendency that mortality of respiratory cases is more immediately affected, whereas mortality of cardiovascular cases is more delayed;
- in two pollutant models, immediate (lag 0 day) and delayed effects (lag 4 days) are independent (Wichmann *et al.* 2000*a*).

(iii) *Which pathophysiological mechanisms are plausible?*

Based on the knowledge from animal experiments and on the pathway of particles in the respiratory tract, the following mechanisms would be plausible.

- Since FPs are deposited in the small airways, one would expect to see effects there. These should be proportional to the volume (mass) deposited. One could think of soluble toxic agents. The larger a particle is, the more material can be dissolved from it. This would be directly available to the respiratory system and the dose would depend on the mass concentration. These soluble compounds could initiate inflammation and lead to an acute local inflammatory response in the lung and thereby may contribute to the exacerbation of pre-existing diseases (Bates 1992).

- UPs are deposited mainly in the alveolar region. Since the mass of UPs is negligible, mass-related effects are less probable. Therefore, not the soluble but the insoluble compounds are expected to be relevant. For this causal fraction, time would be required to translocate the particles to sites of reaction and/or initiation of chain of reactions. UPs are phagocytized less readily by alveolar macrophages and are found not only on the epithelium but in interstitial sites (Ferin *et al*. 1991; Stearns *et al*. 1994). At the same time inflammatory indicators may be upregulated, suggesting that the increased access of UPs to the interstitium triggered an inflammatory response. In other words, UPs may be translocated to reactive sites in and beyond the epithelium which may activate endothelial and circulating leukocytes and endothelial adhesion molecules in the blood, alter blood coagulability (Utell & Frampton 1999), and this process may need more time to become effective. These events could lead to an exacerbation of pre-existing cardiovascular disease.

(iv) *Do the epidemiological data support the described mechanisms?*

The following observations are in favour of the mechanisms described in § 3 *b* (iii):

- the tendency of more direct effects of FPs in asthmatics and on mortality with respiratory causes;

- the tendency of more delayed effects of UPs on mortality with cardiovascular causes;

- the fact that these two mechanisms seem to be independent and show a positive interaction.

The following observations cannot be easily explained by these mechanisms:

- there are also delayed or cumulative effects of FPs (although weaker);

- the delayed or cumulative effects are not only seen in cardiovascular mortality but also in patients with asthma.

The following data would be very important to test the hypotheses in § 3 *b* (iii), but are missing:

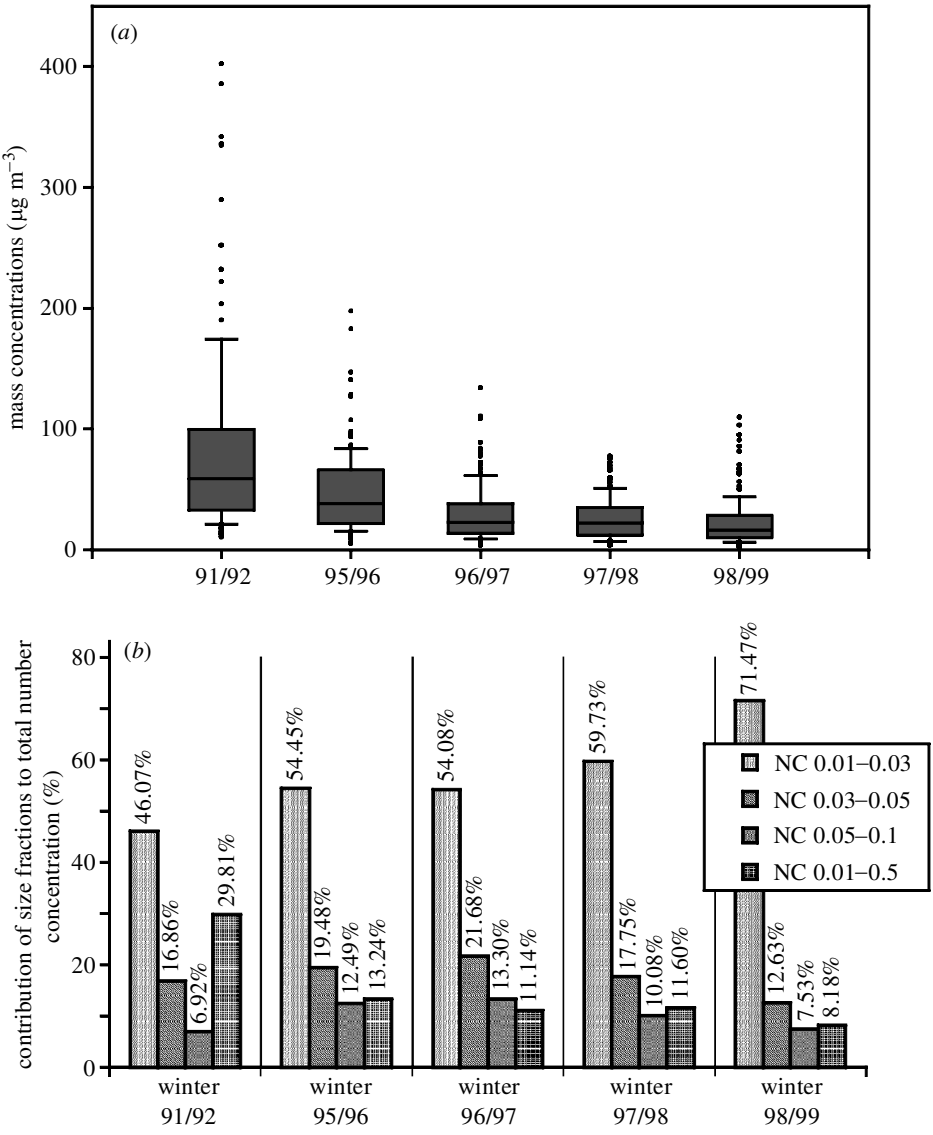

Figure 4. (*a*) Seven years trend of the mass concentration (MC 0.01–2.5 = $PM_{2.5}$ of FPs in Erfurt, winters 1991/2 to 1998/9. From Wichmann *et al.* (2000*a*). (*b*) Seven years trend of the relative particle number concentration (in %); different size ranges (0.01–0.03, 0.03–0.05, 0.05–0.1. 0.1–0.5 µm diameter). The concentration of UPs is approximately constant (see table 1) and the fraction in the smallest size fraction increases steadily. From Wichmann *et al.* (2000*a*).

- data on panel studies with cardiovascular patients are missing, which could test whether or not delayed effects of UPs are found;
- measurements of the soluble fraction of relevant components as transition metals in FPs and of the non-soluble fractions in UPs are missing, in the context of epidemiological studies.

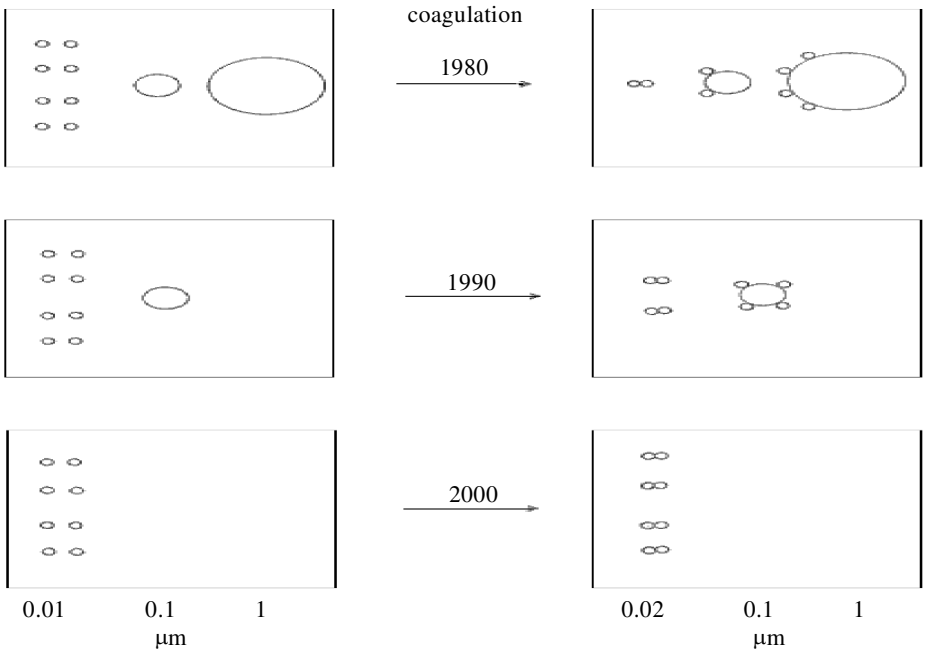

Figure 5. Simplified model of the coagulation dynamics in Erfurt from 1980 to 2000. In 1980, large particles have been in the air, which effectively scavenged the ultrafine particles, leading to a short half-life of UPs. In 2000, mainly very small particles are in the air. They coagulate much slower and the coagulation products are still UPs. In total, in the year 2000, the half-life of UPs is clearly longer than in the year 1980, i.e. if the production rate is constant, the measure ambient concentration of UPs increases. From Wichmann *et al.* (2000*a*).

In conclusion, the available literature suggests that there are health effects of UPs in ambient air, in addition to effects of FPs. However, the database is too sparse to allow clear conclusions on the mode of action.

4. Regulatory implications

Given the indications that ultrafine particles may be relevant for human health, it is not sufficient to study only the mass of fine particles, for example $PM_{2.5}$ (Wichmann & Peters 1999; Tuch *et al.* 2000*a*, *b*). This may be illustrated by the development in Erfurt as shown in figure 4. The mass of fine particles was clearly reduced since 1991/92. However, during the same period the number concentration of ultrafine particles was not decreased, and especially the fraction of very small particles between 0.01 and 0.03 µm diameter increased steadily over the seven years of observation. This makes clear that, with respect to regulation, the reduction of the fine mass does not automatically mean that the number of ultrafine particles is also reduced. Therefore, to identify the relevant particle fraction with respect to human health is crucial for sound regulatory activities.

The ambient aerosol is a dynamic system which may change its concentration and size distribution due to sources and due to coagulation and chemical reactions. Hence, specific pollution control measures to reduce fine particle mass concentration, which

effectively reduces the FPs concentration, may paradoxically increase the persistence and thus number concentration of UPs. The drastic reduction of larger particles in the last 20 years in Erfurt may have reduced the scavenging of ultrafine particles and thus prolonged their half-life in the atmosphere. As a result, even if emissions of UPs were constant, their ambient concentration nevertheless may have increased. This is shown schematically in figure 5.

It is important to realize that technologies different from the ones currently used to reduce the mass emission are needed to reduce the particle number emission.

References

Bascom, R., Bromberg, P. A., Costa, D. A., Devlin, R., Dockery, D. W., Frampton, M. W., Lambert, W., Samet, J. M., Speizer, F. E. & Utell, M. 1996 Health effects of outdoor air pollution. *Am. J. Respir. Crit. Care Med.* **153**, 3–50.

Bates, D. V. 1992 Health indices of the adverse effects of air pollution. The question of coherence. *Environ. Res.* **59**, 336–349.

Brand, P., Gebhart, J., Below, M., Georgi, B. & Heyder, J. 1991 Characterization of environmental aerosol on Helgoland Island. *Atmos. Environ.* A **25**, 581–585.

Brand, P., Ruoß, K. & Gebhart, J. 1992 Technical note: performance of a mobile aerosol spectrometer for *in situ* characterization of an environmental aerosol in Frankfurt city. *Atmos. Environ.* A **26**, 2451–2457.

Danesh, J., Collins, R., Appleby, P. & Peto, R. 1998 Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *J. Am. Med. Ass.* **279**, 1477–1482.

Dockery, D. W. & Pope C. A. 1994 Acute respiratory effects of particulate air pollution. *A. Rev. Public Health* **15**, 107–132.

Dockery, D. W., Schwartz, J. & Spengler, J. D. 1992 Air pollution and daily mortality: association with particulates and acid aerosols. *Environ. Res.* **59**, 362–373.

Ferin, J., Oberdörster, G., Soderholm, S. C. & Gelein, R. 1991 Pulmonary tissue access of ultrafine particles. *J. Aerosol Med.* **4**, 57–68.

Fuchs, N. A. 1964 *The mechanic of aerosols*, pp. 288–302. Oxford: Pergamon.

Gold, D. R., Litonjua, A., Schwartz, J., Lovett, E., Larson, A., Nearing, B. D. *et al.* 2000 The relationship between paticulate pollution and heart rate variability. *Circulation.* (In the press.)

ICRP (International Commission of Radiological Protection) 1994 Human respiratory tract model for radiological protection. (ICRP Publication no. 66.) *Ann. ICRP* **24**, 36–52.

Katsouyanni, K. (and 12 others) 1996 Short term effects of air pollution on health: a European approach using epidemiologic time series data: the APHEA protocol. *J. Epidemiol. Commun. Health* (Suppl.) **50**, 12–18.

Katsouyanni, K. (and 12 others) 1997 Short term effects of ambient sulfur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. *Br. Med. J.* **314**, 1658–1663.

Koenig, W. & Ernst, E. 1992 The possible role of hemorheology in altherothrombogenesis. *Atheroclerosis* **94**, 93–107.

Koenig, W., Sund, M., Filipiak, B., Döring, A., Löwel, H. & Ernst, E. 1998 Plasma viscosity and the risk of coronary heart disease: results from the MONICA–Augsburg cohort study, 1984 to 1992. *Arterioscler. Thromb. Vasc. Biol.* **18**, 768–772.

Kreyling, W. G., Khlystov, A., Mirme, A., Tuch, T., Ruuskanen, J., Vallius, M., Ten Brink, H., Roth, C., Kos, G. A. & Pekkanen, J. 1999 Exposure assessment for fine and ultrafine particles in ambient urban aerosoles. In *Proc. Third Colloquium on Particulate Air Pollution and Human Health in Durham, UC Irvine*, 4-80–4-91.

Liao, D., Cai, J., Rosamond, W. D., Barnes, R. W., Hutchinson, R. G., Whitsel, E. A. *et al*. 1997 Cardiac autonomic function and incident coronary heart disease: a population-based case-cohort study. The ARIC Study. Atherosclerosis Risk in Community Study. *Am. J. Epidemiol.* **145**, 696–706.

Mirme, A., Tuch, T., Khlystov, A., Kos, G., Ten Brink, H. M., Ruuskanen, J., Kreyling, W. G. & Pekkannen, J. 2000 Intercomparison of aerosol spectrometers for ambient air monitoring. *Atmos. Environ.* (Submitted.)

Oberdörster, G., Gelein, R. M., Ferin, J. & Weiss, B. 1995 Association of particulate air pollution and acute mortality: involvement of ultra-fine particles? *Inhal. Toxicol.* **7**, 111–124.

Pekkanen, J., Timonen, K. L., Ruuskanen, J., Reponen, A. & Mirme, A. 1997 Effects of ultrafine and fine particles in an urban air on peak expiratory flow among children with asthmatic symptoms. *Environ. Res.* **74**, 24–33.

Pekkanen, J., Brunekreef, B. & Wichmann, H. E. 1999*a* Exposure and risk assessment for fine and ultrafine particles in ambient air (ULTRA). Final report, EU Environment Programme Contract ENV4-CT95-0205, Brussels.

Pekkanen, J., Brunner, E., Anderson, H. R., Tittanen, P. & Atkinson, R. W. 1999*b* Air pollution and plasma fibrinogen. *Am. J. Respir. Crit. Care Med.* **54**, 1027–1032.

Penttinen, P., Timonen, K. L., Tiittanen, P., Mirme, A., Ruuskanen, J. & Pekkanen, J. 2000 Fine and ultrafine particulate matter in ambient air are associated with peak flow decreases in adult asthmatic subjects. *Am. J. Respir. Crit. Care Med.* (In the press.)

Peters, A., Wichmann, H. E., Tuch, T., Heinrich, J. & Heyder, J. 1997*a* Respiratory effects are associated with the number of ultra-fine particles. *Am. J. Respir. Crit. Care Med.* **155**, 1376–1383.

Peters, A., Dockery, D. W., Heinrich, J. & Wichmann, H. E. 1997*b* Medication use modifies the health effects of particulate sulfate pollution in children with asthma. *Environ. Health Perspect.* **105**, 430–435.

Peters, A., Dockery, D. W., Heinrich, J. & Wichmann, H. E. 1997*c* Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children. *Eur. Respir. J.* **10**, 872–879.

Peters, A., Döring, A., Wichmann, H. E. & Koenig, W. 1997*d* Increased plasma viscosity during the 1985 air pollution episode: a link to mortality? *Lancet* **349**, 1582–1587.

Peters, A., Perz, S., Döring, A., Stieber, J., Koenig, W. & Wichmann, H. E. 1999*a* Activation of the autonomic nervous system and blood coagulation in association with an air pollution episode. In *Proc. Third Colloquium on Particulate Air Pollution and Human Health, 6–8 June 1999, Durham* (ed. R. Phalen & Y. Bell), 8-71–8-85.

Peters, A., Perz, S., Döring, A., Stieber, J., Koenig, W. & Wichmann, H. E. 1999*b* Increases in heart rate during an air pollution episode. *Am. J. Epidemiol.* **150**, 1094–1098.

Peters, A., Wichmann, H. E. & Koenig, W. 1999*c* Air pollution exposure influences cardiovascular risk factors: a link to mortality? In *Proc. Int. Inhal. Symp. Hanover, Germany.*

Peters, A., Liu, E., Verrier, R. L., Schwartz, J., Gold, D. R., Mittleman, M. *et al*. 2000 Air pollution and incidence of cardiac arrhythmia. *Epidemiology* **11**, 11–17.

Pitz, M., Heinrich, J., Tuch, T., Kreyling, W. G. & Wichmann, H. E. 2000 Change of particle size distribution in Sachsen-Anhalt between 1993 and 1999. (Submitted.)

Pope, C. A. 2000 Epidemiology of fine particulate air pollution and human health: biological mechanisms and who's at risk? *Environ. Health Perspect.* (In the press.)

Pope, C. A. & Dockery, D. W. 1999 Epidemiology of particle effects. In *Air pollution and health* (ed. S. T. Holgate, J. M. Samet, H. S. Koren & R. L. Maynard), pp. 673–705. San Diego: Academic Press.

Pope, C. A., Dockery, D. W., Kanner, R. E., Villegas, G. M. & Schwartz, J. 1999*a* Oxygen saturation, pulse rate, and particulate air pollution. *Am. J. Respir. Crit. Care Med.* **159**, 365–372.

Pope, C. A., Verrier, R. L., Lovett, E. G., Larson, A. C., Raizenne, M. E., Kanner, R. E. *et al*. 1999*b* Heart rate variability associated with particulate air pollution. *Am. Heart J.* **138**, 890–899.

Ruuskanen, J. (and 12 others) 2000 Concentrations of ultrafine, fine and $PM_{2.5}$ particles in three European cities. *Atmos. Environ.* (In the press.)

Schwartz, J. 1994 Air pollution and daily mortality: a review and meta analysis. *Environ. Res.* **64**, 36–52.

Schwartz, J., Dockery, D. W. & Neas, L. M. 1996 Is daily mortality associated specifically with fine particles? *J. Air. Waste. Management Ass.* **46**, 927–939.

Seaton, A., MacNee, W., Donaldson, K. & Godden, D. 1995 Particulate air pollution and acute health effects. *Lancet* **345**, 176–178.

Seaton, A., Soutar, A., Crawford, V., Elton, R., McNerlan, S., Cherrie, J. *et al*. 1999 Particulate air pollution and the blood. *Thorax* **54**, 1027–1032.

Stearns, R. C., Murthy, G. G. K., Skornik, W., Hatch, V., Katler, M. & Godleski, J. J. 1994 Detection of copper oxide particles in the lungs of hamsters by electron spectroscopic imaging. *ICEM* **13**, 763–764.

Stone, P. H. & Godleski, J. J. 1999 First steps toward understanding the pathophysiologic link between air pollution and cardiac mortality. *Am. Heart J.* **138**, 804–807.

Tuch, T., Brand, P., Wichmann, H. E. & Heyder, J. 1997 Variation of particle number and mass concentration in various size ranges of ambient aerosols in Eastern Germany. *Atmos. Environ.* **31**, 4193–4197.

Tuch, T., Mirme, A., Tamm, E., Heinrich, J., Heyder, J., Brand, P., Roth, C., Wichmann H. E., Pekkanen, J. & Kreyling, W. G. 2000*a* Comparison of two particle size spectrometers for ambient aerosol measurements. *Atmos. Environ.* **34**, 139–149.

Tuch, T., Kreyling, W. G., Peters, A., Heinrich, J., Heyder, J. & Wichmann, H. E. 2000*b* Reduction of particle mass parallels increase in particle number in the atmosphere. (Submitted.)

US EPA 1996 Air quality criteria for particulate matter research. Triangle Park Research: EPA.

Utell, M. J. & Frampton, M. W. 1999 Clinical relevance of particle related effects. *J. Aerosol Med.* **12**, 104 (Abstract 56).

Von Klot, S., Wölke, G., Tuch, T., Heinrich, J., Docker, D. W., Schwarz, J., Wichmann, H. E. & Peters, A. 2000 Short-term effects of ultrafine and fine particles on medication use in asthmatic adults. *Proc. Conf. American Thoracic Soc.* 2000 Toronto (Abstract).

Wichmann, H. E. & Peters, A. 1999 Epidemiological studies on health effects of fine and ultrafine particles in Germany. In *The health effects of fine particles: key questions and the 2003 Review Report of the Joint Meeting of the EC and HEI, 14–15 January 1999, Brussels, Belgium. HEI Commun.* **8**, II-163–172.

Wichmann, H. E., Spix, C., Tuch, T., Wölke, G., Peters, A., Heinrich, J., Kreyling, W. G. & Heyder J. 2000*a* Daily mortality and fine and ultrafine particles in Erfurt, Germany, Part A: Role of particle number and particle mass. HEI report.

Wichmann, H. E., Spix, C., Tuch, T., Wittmaack, K., Cyrys, J., Wölke, G., Peters, A., Heinrich, J., Kreyling, W. G. & Heyder, J. 2000*b* Daily mortality and fine and ultrafine particles in Erfurt, Germany, Part B: Role of sources, elemental composition and other pollutants. HEI Report.

Willeke, K. & Baron, P. A. (eds) 1993 *Aerosol measurements: principles, techniques and applications*. New York: Van Nostrand Reinhold.

Discussion

H. R. Anderson (*St George's Hospital Medical School, Cranmer Terrace, London, UK*). Your studies in Erfurt have found clear associations between health effects in adult asthmatics, but similar studies among children in Kuopio, Finland, have

not been so conclusive. Studies of hospital admissions for asthma also tend to find associations between particles and admissions in adults but not in children. Can you think of any explanation for this difference between adults and children?

H.-E. Wichmann. Indeed, the effects of ultrafine particles seem to be more pronounced in asthmatic adults than in asthmatic children. I have no explanation for this result.

D. Costa (*US EPA, NC, USA*). The aerometric data from the first half of this issue suggest that the ultrafine PM is quite variable in concentration and time over the course of the day. Yet your early data showed correlations with five-day averages. Does this suggest that the ultrafine effects on impact is cumulative?

H.-E. Wichmann. Our data suggest cumulative effects on daily mortality. The influence of cumulative exposure over five days seems stronger than the influence of every single day. This is true both for fine and ultrafine particles. However, if one considers single-day effects, these seem to be more immediate for fine particles (lag 0 days) and more delayed for ultrafine particles (lag 5 days).

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