Abstract

Aerosol mass and chemistry are of concern in setting a particulate matter (PM) standard at 1.0 μm (PM_1), or 2.5 μm ($PM_{2.5}$) and in correlating human health effects with an aerosol measurement (PM_1, $PM_{2.5}$, or PM_{10}). Phoenix aerosol was sampled using a $PM_{10}/PM_{2.5}/PM_1$ trichotomous sampler. During the period from May through October 1995, separate 24-hour samples of PM_1, $PM_{1-2.5}$, $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10}, were obtained on Teflon filters, weighed, and chemically analyzed. Chemical composition of the $PM_{1-2.5}$ fraction was compared with that of the PM_1 and $PM_{2.5-10}$ fraction in order to estimate the contribution of coarse mode aerosol and fine mode aerosol to the $PM_{1-2.5}$ intermediate size range. For the period studied, the PM_{10} concentrations averaged approximately 32 $\mu g/m^3$, consisting of approximately 69% $PM_{2.5-10}$, 8% $PM_{1-2.5}$, and 18% PM_1. Weight gain and chemical analysis of the filter samples (by ion chromatography, XRF, and PIXE) were used to calculate a fine mode and coarse mode contribution to the intermediate $PM_{1-2.5}$ region. Based on the assumption that the intermediate region consists of a simple mixture of the tail ends of the coarse and fine mode distributions, the intermediate region consisted of roughly 75% coarse mode and 25% fine mode aerosol. The contribution of coarse mode to the intermediate mode is correlated with wind speed and wind direction, time of year, and measured PM concentrations. An equation is developed and presented to correct for the contribution (or "intrusion") of coarse mode aerosol into a $PM_{2.5}$ measurement, in order to obtain a better estimate of true fine mode aerosol concentration. The equation developed is of the form:

$$PM_{fine} = (PM_{2.5})_{corr} = (1 + C_l)(PM_{2.5})_{meas} - C_l(PM_{10})_{meas}$$

Introduction

Scientific data suggests that ambient aerosols are best characterized by a bimodal (or multimodal) size distribution[1]. There are two main mass distributions present: coarse mode aerosol from dispersion mechanisms (i.e. wind-blown dust from mining activities, road building, farming, roadway traffic, sea spray, aerial spraying or handling of granular raw materials), and fine mode aerosol from condensation mechanisms (i.e. combustion and atmospheric reactions). Depending upon local atmospheric conditions and location of sources, data suggests that the fine mode aerosol can often be approximated with a log-normal distribution having a mass mean diameter (MMD) of 0.1-1 μm, and a geometric standard deviation (σ_g) of about 2 to 3[1]. Measurement data also suggest that coarse mode aerosol may be represented by a log-normal distribution having an MMD of 10-30 μm and a σ_g of about 2 to 3 [2]. The minimum point separating these two aerosol mass modes is between approximately 1 and 2.5 μm. The source and composition of particles in this intermediate size range of 1 to 2.5 μm is of particular interest in the move to introduce a new ambient air quality standard at either PM_1 or $PM_{2.5}$. Aerosol in this range can be attributed to the high end of fine mode aerosol and the low end of coarse mode aerosol. In fact this region can be considered as an aerosol mixture region because condensation aerosols don't normally grow above 2.5 μm (excluding water), and significant concentrations of dispersion aerosols are not normally generated below about 1 μm. Neither gravity, coagulation, or rainfall causes a rapid loss of the 1-2 μm aerosol. Concentration changes in this intermediate size range mainly result from atmospheric dilution (winds and atmospheric instability). Thus in determining a new particulate matter standard, the composition and source of this intermediate $PM_{1\text{-}2.5}$ range is of great interest and is the focus of this study.

This study uses PM_1 and $PM_{2.5\text{-}10}$ as indicators of the fine and coarse mode aerosols discussed above. Carryover of fine mode aerosol distribution into the $PM_{2.5\text{-}10}$ and carryover of coarse mode aerosol into the PM_1 are both considered to be negligible. Thus the intermediate $PM_{1\text{-}2.5}$ size range is considered to a simple mixture of fine and coarse mode distribution tail ends. Quantitative mass measurements of PM_1, $PM_{1\text{-}2.5}$, and $PM_{2.5\text{-}10}$, on a filter surface suitable for chemical analysis, were obtained. Composition data for each particle size range was used to determine the "contribution" to this intermediate size range from the coarse and fine mode regions using a developed mathematical technique. Based upon water-soluble ion analysis, sulfate was selected as the best indicator of fine mode aerosol, while calcium (Ca), and silica (Si) were selected as the best elemental indicators of coarse mode aerosol.

METHODS

Sample Collection. Samples were collected in Phoenix, Arizona at a monitoring station located at West Earl Road and 36th Avenue. This location is in a residential area, located about 9 km northwest from downtown Phoenix (Figure 1). Samples were collected using a high-volume trichotomous sampler, which has cutpoints of PM_1, $PM_{2.5}$, and PM_{10} [3]. A diagram of the trichotomous sampler used is shown in Figure 2. The trichotomous sampler provides data not only for the three cutpoints, but also for the intermediate regions ($PM_{1\text{-}2.5}$ and $PM_{2.5\text{-}10}$). The cutpoints are achieved by using a standard Graseby-Andersen PM_{10} inlet, followed by two high-volume virtual impactors (HVVI) to achieve the $PM_{2.5}$ and PM_1 cutpoints. After passing through the PM_{10} inlet, air passes through the 2.5 µm HVVI. The HVVI splits the air into two streams, the "major" flow and the "minor" flow. The major flow portion carries the particles smaller than the cut off size ($PM_{2.5}$), while the minor flow portion carries all of the particles (in theory) larger than the cut off size ($PM_{2.5\text{-}10}$) into a quiescent cavity where they are then collected on filter media. Along with the $PM_{2.5\text{-}10}$ particles, a portion of the $PM_{2.5}$ particles are collected with the minor flow in proportion to the percentage of the minor flow to the total flow. The mass of these particles must be subtracted out in the $PM_{2.5\text{-}10}$ concentration calculations. After passing through the 2.5 µm HVVI, a small portion of the air is diverted through a filter to collect a $PM_{2.5}$ mass sample, and the remaining $PM_{2.5}$ air goes on to the 1.0 µm HVVI. The minor flow of the 1.0 µm HVVI collects the $PM_{1\text{-}2.5}$ particles (along with a portion of the PM_1 which is subtracted out in the mass concentration calculations) and the major flow carries the PM_1 to be collected on filters. The filters were color coded for identification purpose.

Sample Filters. All of the 47 mm filters used in this study were made of Teflon membrane to allow for conducting the desired chemical analysis (after weighing for mass data). The trichotomous sampler monitors and controls flowrates through each filter using a flow circuit consisting of an orifice flow meter and a Magnehelic pressure gauge.

Meteorology Measurements. Meteorological parameters were measured at a height of 10 m. Hourly values of wind speed and wind direction, temperature, and relative humidity were obtained. This hourly data was reduced to 24-hour averages according to the daily start and stop times of the trichotomous sampler, and used to obtain 3-hour maximum wind speeds and wind direction and 1-hour maximum wind speed and direction. Mass concentration and intermediate range intrusion calculations are correlated with meteorologic data and are presented in the Results section.

Sample Analysis. Net filter mass gains were determined using a calibrated balance. Weighing room temperature was maintained at 24 ± 3 degrees C with a relative humidity of 30 ± 10%. Approximately one out of ten filters were reweighed for quality control purposes. Three methods were used in the chemical analysis of the filters: ion chromatography (IC), x-ray fluorescence (XRF), and proton-induced x-ray emission (PIXE). IC was used to determine sulfate content, while the elemental analysis for Si and Ca was determined using XRF and PIXE.

Mass Calculations. The PM mass concentrations were determined by dividing the net weight gain on each filter by the total air volume passing through it in the sampling period (approximately 24 hours). As mentioned previously, HVVI mass concentrations were corrected for the minor flow rate used in the trichotomous sampler. Since most samples were not run for exactly 24-hours, each sample was divided by a correction factor to correct for the actual sampling time. The basic equation used for mass concentration calculations is:

$$PM_x = \frac{\Delta M}{v \times f} \qquad (1)$$

where:

	PM_x	=	PM mass concentration of size x [µg/m^3]
	Δm	=	net filter mass gain [µg]
	v	=	airstreamvolume sampled [m^3]
	f	=	correction factor [dimensionless]

It should be noted that for the minor flow rate samples of $PM_{1\text{-}2.5}$ and $PM_{2.5\text{-}10}$ the flowrate Q used in equation (1) is the equivalent flowrate from which the larger particles are collected, not simply the minor flowrate through the filter. This results because the HVVI impactor "concentrates" the larger particles in the virtual impactor receiving tube, so the mass collected on the filter is divided by the equivalent sampled flow rate. Figure 2 shows the values of Q and the filter color codes used to obtain the mass concentrations for each PM region.

Intermediate Mode "Contribution" Calculations. As stated previously, the contribution calculations assume that the intermediate $PM_{1\text{-}2.5}$ region is comprised entirely of the tail ends of the coarse and fine modes, and that the coarse and fine modes are fairly represented by the $PM_{2.5\text{-}10}$ and PM_1 samples obtained using the trichotomous sampler. To help explain this assumption, the size distributions of typical Phoenix fine and coarse mode can be plotted on log-

probability paper. Figure 3 shows fine and coarse mode distributions as described above. The plots assume reasonable values of mass medium diameter (MMD) and geometric standard deviation (σ_g). From these figures, it is seen that the tail of both distributions extends into the $PM_{1-2.5}$ µm size interval.

In testing the equations used to estimate coarse and fine mode aerosol contributions to $PM_{1-2.5}$, it is assumed that fine mode aerosol is represented by the sulfur and sulfate concentration in a PM_1 sample and the coarse mode aerosol is represented by the silica and calcium concentrations in a $PM_{2.5-10}$ sample. An algorithm was developed to determine the mass "contribution" or "intrusion" of both the PM_1 and $PM_{2.5-10}$ into the intermediate $PM_{1-2.5}$ region. The algorithm consists of solving the following two linear equations:

$$X + Y = I \tag{2}$$

$$(X \times S_X) + (Y \times S_Y) = I \times S_I \tag{3}$$

where:

X	=	contribution of coarse mode into $PM_{1-2.5}$ [µg/m^3]
Y	=	contribution of fine mode into $PM_{1-2.5}$ [µg/m^3]
I	=	$PM_{1-2.5}$ [µg/m^3]
S_X	=	fraction of species in $PM_{2.5-10}$ region
S_Y	=	fraction of species in PM_1 region
S_I	=	fraction of species in $PM_{1-2.5}$ region

Equations (2) and (3) are solved simultaneously to yield the X and Y unknowns.

Coarse Mode Intrusion Estimation Technique. Using the above calculation procedure and average concentration measurement for $PM_{1-2.5}$ and $PM_{2.5-10}$, a technique is developed to estimate a $PM_{2.5}$ concentration "corrected" for the intrusion of the coarse mode particles into the $PM_{2.5}$ region using only a PM_{10} and $PM_{2.5}$ measurement. This type of "correction" may be useful for the Western region of the United States if a $PM_{2.5}$ standard were implemented, since the purpose of the $PM_{2.5}$ standard is to protect human health from the effects of the fine mode aerosol which has been shown to adversely affect human health[4]. This correction could be used to "back-out" from a $PM_{2.5}$ mass measurement that portion of the $PM_{2.5}$ which is coarse mode aerosol.

This correction is developed by first obtaining an average ratio of $PM_{1-2.5}$ mass to

$PM_{2.5-10}$ mass. This gives a constant, R, shown by equation (4):

$$\frac{(PM_{1-2.5})_{ave}}{(PM_{2.5-10})_{ave}} = R \qquad (4)$$

An average coarse mode intrusion fraction (X/I), expressed as a fraction of $PM_{1-2.5}$ is then calculated. Multiplying R and X yields the coarse mode fraction (C_I) included in $PM_{1-2.5}$ as a fraction of $PM_{2.5-10}$, shown in equation (5):

$$C_I = R \times \frac{X}{I} \qquad (5)$$

This factor C_I is used to subtract out, from the measured $PM_{2.5}$ sample, that portion which is attributed to intrusion of coarse mode aerosol, as shown in equation (6):

$$(PM_{2.5})_{corr} = (PM_{2.5})_{meas} - C_I\, PM_{2.5-10} \qquad (6)$$

The $PM_{2.5-10}$ can then be calculated by subtracting the $PM_{2.5}$ from PM_{10}, yielding equation (7):

$$(PM_{2.5})_{corr} = (PM_{2.5})_{meas} - C_I \times [(PM_{10})_{meas} - (PM_{2.5})_{meas}] \qquad (7)$$

Combining terms yields equation (8) for the "corrected" $PM_{2.5}$, expressed in terms of measured $PM_{2.5}$ and PM_{10}:

$$(PM_{2.5})_{corr} = (1 + C_I)(PM_{2.5})_{meas} - C_I\,(PM_{10})_{meas} \qquad (8)$$

RESULTS

Mass Data and Correlation with Meteorological Data. The mass concentration measurements are summarized by month in Tables I and II. These tables show that during the 6-month period from May to October 1995 the major mass component of PM_{10} is the $PM_{2.5-10}$ particles (69%). $PM_{1-2.5}$ contains 8% of the PM_{10} mass, while PM_1 contains 18%. Meteorological data (24-hour average wind speed, maximum 1-hr wind speed, maximum 3-hr wind speed, and wind direction) were correlated with the sample mass results (which are 24-hour

concentrations) and the sample elemental analysis results. It was expected that the $PM_{2.5-10}$ concentrations would show a direct correlation with wind speed, since suspension of super-micron particles is expected during periods of increased wind speed. However, no significant correlation was obvious. Because of the 24-hour average mass data, increase in mass concentrations experienced in a one or three-hour period were "smoothed" over by hours of lower mass concentrations when the winds were lower. Unfortunately, average wind speed was low during the entire 6-month study period, no calm days were encountered and winds were, on average, from a southerly direction. Although mass concentrations varied by a factor of 10, the nature of the ambient aerosol was relatively consistent. Winter aerosol conditions (December, January, etc.) can be significantly different but were not measured in the study.

The elemental analysis of sulfates, S, Ca, and Si are summarized on a monthly basis in Table III. As stated previously, it is assumed that sulfate and S mass distributions approximate the fine mode aerosol distribution, while the Ca and Si mass distributions represent the coarse mode aerosol distribution. Table III shows that about 75% of the sulfate and S mass is in PM_1, while about 90% of the Ca and Si mass is in $PM_{2.5-10}$.

Intermediate Mode "Contribution" Results. Using equations (2) and (3), the coarse mode contributions were estimated using the sample mass and element concentration data. These results are summarized on a monthly basis in Table IV. The average contribution of coarse mode particulate in the $PM_{1-2.5}$ region is 75%. The daily average coarse mode contributions were correlated with meteorological variables, but no significant correlations were found. Figure 4 shows a plot of $PM_{1-2.5}$ mass concentration versus $PM_{2.5-10}$ mass concentrations. From this graph we can see that these variables are linearly related to one another for the time period of this study. Therefore, using equation (4), the ratio, R can be determined:

$$R = \frac{(PM_{1-2.5})_{ave}}{(PM_{2.5-10})_{ave}} = \frac{2.7}{22.6} = 0.12 \qquad (9)$$

Using equation (5), the average coarse mode particles included in the $PM_{2.5}$ (C_I) can be calculated:

$$C_I = R \times X = 0.12 \times 0.75 = 0.09 \qquad (10)$$

The equation for "corrected" $PM_{2.5}$, expressed in terms of only $PM_{2.5}$ and PM_{10} is:

$$(PM_{2.5})_{corr} = 1.09(PM_{2.5})_{meas} - 0.09(PM_{10})_{meas} \quad (11)$$

As stated previously, the average mass distribution data for coarse mode aerosol can be approximated by a log-normal distribution. The Phoenix coarse mode aerosol can be represented by a log-normal distribution with an MMD of about 20 µm, a geometric standard deviation of about 2.8, and an average concentration of about 100 µg/m^3. This distribution, shown in Figure 4, would produce the measured average $PM_{2.5-10}$ concentration of 22.6 µg/m^3 and a $PM_{1-2.5}$ average concentration of 2 µg/m^3, which is 75% of the measured $PM_{1-2.5}$ value of 2.7 µg/m^3. Over the 6-month sampling period the total coarse mode aerosol concentration would vary from approximately 30 to 300 µg/m^3, producing the measured range of $PM_{1-2.5}$ (0.8 to 8 µg/m^3) and PM_{1-10} (8 to 80 µg/m^3). In general, the coarse fraction of $PM_{1-2.5}$ (75%) was always about 10% of the $PM_{2.5-10}$ measured concentration.

CONCLUSION

While no correlations were established between the meteorological data and the mass concentrations, the mass data was used to estimate intrusion of coarse mode aerosol into the intermediate $PM_{1-2.5}$ range. The intrusion estimates allowed for a proposed equation to be used to back-out the coarse mode contribution of a $PM_{2.5}$ mass concentration measurement, provided that a PM_{10} measurement is also obtained.

The proposed "average" coarse mode aerosol size distribution is reasonable based upon the published measurements of others[5]. Use of the concept of some distribution shape, allows prediction of the coarse mode fraction below any selected particle size. The proposed distribution requires approximately 9% of the $PM_{2.5-10}$ mass to be in the $PM_{1-2.5}$ size range (and a negligible fraction less than PM_1, about 0.2% of the total coarse mode concentration).

The proposed "average" coarse mode size distribution does fit the Phoenix data and does account for the measured intrusion of coarse mode particles into the $PM_{1-2.5}$ size range (about 2 to 3% of the total coarse mode concentration).

The proposed equation to back-out the coarse mode particles from a measure of $PM_{2.5}$ particles does not depend upon any specific requirement for the fine mode aerosol. Therefore, the equation could be used in general to correct any $PM_{2.5}$ measure of fine mode aerosol, provided the coarse mode aerosol distribution is

similar to that obtained for Phoenix.

REFERENCES

[1] Lundgren, D.A.; Burton, R.M.: Effect of particle size distribution on the cut point between fine and coarse ambient mass fractions. Inhalation Toxicology. 7:131-148 (1995).

[2] Lundgren, D.A.; Paulus, H.J.: The mass distribution of large atmospheric particles. Journal of the Air Pollution Control Association. 25:1227 (1973)

[3] Marple, V.A.; Olson, B.A.; A high volume $PM_{10/2.5/1.0}$ trichotomous sampler-Proceedings of the International Speciality Conference, Air and Waste Management Association, Pittsburgh, PA, pp 237-361 (1995).

[4] Reichhardt, T; Weight of the health risks of airborne particulates. Environment Science and Technology. 29(8), 360A (1995)

[5] Lundgren, D.A., Hausknecht, J.J., and Burton, R.M. Large particle size distribution in five U.S. cities and the effect on a new ambient particulate matter standard (PM-10). Aerosol Science Technology. 7:467-473 (1984)

PERMISSIBLE DAILY AIRBORNE PARTICLE MASS LEVELS ENCOMPASS BRIEF EXCURSIONS TO THE 'LONDON FOG' RANGE WHICH MAY CONTRIBUTE TO DAILY MORTALITY AND MORBIDITY IN COMMUNITIES

Robert A. Michaels

RAM TRAC Corporation

Schenectady, New York

ABSTRACT

Recent studies associate 24-hour PM_{10} levels within EPA's 150-$\mu g/M^3$ standard with mortality and morbidity. These findings remain unexplained. This study documents the contribution of brief particle mass excursions to 24-hour average levels, and evaluates the possible public health significance of such excursions. Two technologies were identified for short-term measurement of particle mass. Ten 24-hour periods distributed among three locations were examined with PM_{10} <150 $\mu g/M^3$. At all three locations, and in six of 10 days, excursions exceeded 150 $\mu g/M^3$. Fifteen-minute excursions approached 2,000 $\mu g/M^3$, surpassing the 1952 London fog despite regulatory control of particles at the 24-hour time frame. Toxicology literature confirmed the harmfulness of brief exposure to particles in the range of observed excursions. Fine particle excursions are followed by prolonged internal exposure of lungs which cannot efficiently clear them. Prolonged internal exposure may correlate with prolonged, potentially lethal, cardiopulmonary stress, especially for the frail elderly and infirm. An examination of policy documents revealed consistency of observed short-term health effects of particles with EPA criteria for air pollutant standard setting. However, EPA has focused upon protracted toxicological causes, whereas this study suggests that shorter-term mechanisms may cause or contribute to causing the unexplained effects. The study thus supports the recommendation that EPA further consider imposing a one-hour particle standard, despite Agency uncertainty that *"the majority of effects"* observed after daily exposure would occur after briefer exposures. A one-hour mass limit of 300 $\mu g/M^3$ might enhance protection against acknowledged short-term effects, avoiding a burdensome change in the 150 $\mu g/M^3$ 24-hour mass limit.

KEY WORDS: airborne particle NAAQS, public health risk, excursions, epidemiology, PM-10, regulation, policy, air pollution risk management

INTRODUCTION

At Court direction, the U. S. Environmental Protection Agency (EPA) is reviewing the National Ambient Air Quality Standard (NAAQS) for airborne particles (1, 2, 54, 55). The present NAAQS limits particulate matter within a diameter of 10 microns (PM_{10}) to a time-weighted average mass limit of 150 $\mu g/M^3$ of air over 24 hours (and 50 $\mu g/M^3$ annually). It is based primarily upon epidemiological associations of particle elevations during air pollution episodes with elevated mortality and morbidity in communities (for example, see 18, 44, 45). Particle levels during the 1952 London fog, during which some 4,000 people died over a period of 10 days, have been estimated at 1,200 $\mu g/M^3$ (53; $PM_{10} \leq 1{,}200\ \mu g/M^3$). Recent studies associate significant elevations of morbidity and mortality with particle levels well within the NAAQS (reviewed by EPA, 1995; 60), and below levels which have been explainable by known toxicological mechanisms. The EPA must soon decide whether to control airborne particles to levels below those of demonstrated toxicological significance, and thereby risk further legal challenge.

EPA's *Clean Air Science Advisory Committee* (CASAC) advised the EPA to explain the basis for averaging times specified in the airborne particle standard (14):

> *"A number of the Panel members noted the absence of a sixth link, namely, the rationale for using a 24-hour averaging time for the NAAQS.... The justification for using any specific averaging time, including a 24-hour averaging time, is not established"* (page 3).

In response, the Agency considered applying a longer averaging time of up to several days and a shorter averaging time, such as one hour (57-60). The present study inquires whether 24-hour average particle levels educed via the U. S. EPA reference gravimetric monitoring method might encompass undetected shorter-term excursions sufficient to explain the observed adverse effects.

METHODS

The method of investigation consisted of evaluation of available analytical data and literature to resolve three technical issues. First, the study determined whether instrumentation is available to reliably and economically measure particle levels over short intervals. Second, it quantified short-term excursions of particle mass contributing to 24-hour averages well within the NAAQS. Third, it assessed the possible toxicological adequacy of such excursions, considering their relatively brief persistence, to cause mortality and/or morbidity.

The findings regarding the three issues elucidated above were evaluated relative to EPA policies and procedures for air pollutant standard setting under the Clean Air Act (3, 56) based upon the weight of evidence for the existence, nature, and magnitude of public health risks. Ultimately, the findings were evaluated relative to a major regulatory issue facing state health departments and the U. S. EPA. That issue is, in view of currently available data and instrumentation technologies, whether public health protection can be assured via the current airborne particle risk management approach, which limits particle excursions only to the degree that they produce exceedances of 24-hour and annual mass limits.

FINDINGS

Identification of Monitoring Technologies

Two relatively new particle monitoring technologies were found to be capable of reliably measuring airborne particle levels in real time or over short intervals (15, 16, 35-38, 43, 46-51, 58). Inertial monitors can measure particles virtually continuously, whereas beta attenuation monitors can do so over intervals of an hour or less under realistic conditions. Both technologies represent alternatives to the reference gravimetric method for monitoring airborne particles. The technologies reflect evolution of the older technologies most notably in three directions: 1. toward greater sensitivity associated with utilizing non-gravimetric physical principles for measurement; 2. toward continuous monitoring and reduced sampling time; and 3. toward greater automation and reduced expense of operation. Indeed, inertial instruments are deployed in the U. K. Automatic Urban Network (AUN), gathering particle data with a 15-minute time resolution (50). Using this short time resolution, AUN posts on the Internet one-hour-average values, updated hourly, at monitors in 18 cities (http://www.aeat.co.uk/products/centres/netcen/airqual/bulletins/pm10.html), adding power to ongoing U. K. studies of particle health effects.

Greater sensitivity of non-gravimetric instrumentation. Technologies for measuring particles have traditionally involved collection on a filter and measurement of the difference in filter weight before and after a known volume of air has been drawn through it. This traditional technology relies upon gravity to cause particles to affect a balance in proportion to their mass. The technology requires a relatively long sampling time, depending upon the ambient particle level, to assure sufficient particle mass collection

to register accurately using an instrument of specified sensitivity known as a mass microbalance.

One technology utilizes an inertial system of mass measurement (35, 36-38, 43, 46, 47, 50, 51). Inertial mass measurement relies upon the naturally constant frequency of a harmonic oscillator of fixed length and mass (43). A filter of known surface area is placed at the free end of a hollow tapered glass tube which is mechanically oscillated in a clamped-free mode. A detector quantifies reduction in the frequency of the oscillator, which occurs in proportion to the particle mass captured on the filter.

Another technology utilizes the phenomenon of beta radiation attenuation to measure particle mass. Beta attenuation utilizes a source which emits electrons (beta particles). A detector is placed near the source, and the source measured while a strip filter is interceded to collect particles. As particles accumulate, they absorb beta emissions, attenuating the signal detected in proportion to the thickness, and therefore the mass, of the deposited particle layer.

Increased automation. Inertial and beta decay detectors are more automated than gravimetric detectors. Their operating cost is comparable to (lower in the long-term than) that of now-prevalent manual samplers (U. S. EPA 1995; 58):

> *"The initial cost of an automated sampler is typically 2-3 times that of a manual, single channel PM_{10} sampler, but can be offset by the savings in operator labor costs"* (page 4-30).

Continuous monitoring and reduced sampling time. Inertial and beta

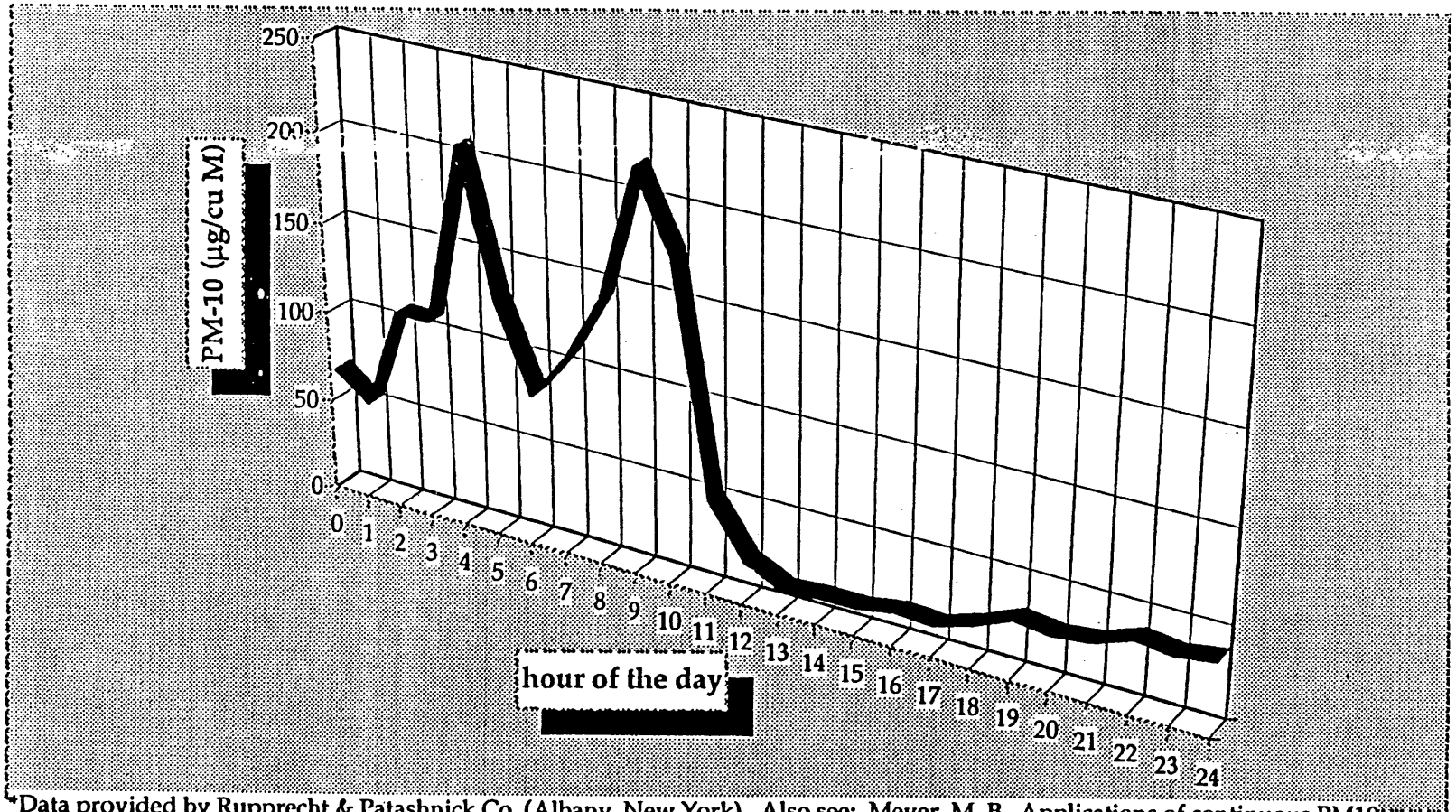
attenuation detectors are essentially continuous particle mass monitors. The inertial instrument appears to be more sensitive than the beta attenuation instrument because the amount of particle mass accumulation needed by the latter to accurately measure beta attenuation is greater than that required by the former to detect oscillation frequency reduction. The inertial instrument, therefore, represents a more perfect continuous monitor, inasmuch as it requires less sampling time to elapse before a significant mass response will be recorded. Nonetheless, both detector types respond in minutes compared with the gravimetric hi-vol detector, which may require hours to collect a reliably measurable sample under typical conditions. The trend toward reduced sampling time and continuous monitoring facilitates routine and economical short-term airborne particle mass monitoring with respect to selected particle size windows in the respirable range.

Airborne Particle Excursions

Data sets were screened to identify those which 1. were obtained using one or both of the identified technologies, 2. exhibited short time resolution, 3. encompassed at least one 24-hour period, and 4. revealed 24-hour airborne particle levels within the current NAAQS. Screening identified three locations, and 10 days, during which 24-hour average $PM_{10} < 150$ mg/M^3. At all three locations, and in six of the 10 identified cases meeting the screening criteria, excursions exceeding 150 µg/M^3 were noted (Figs. 1-3, Table 1).

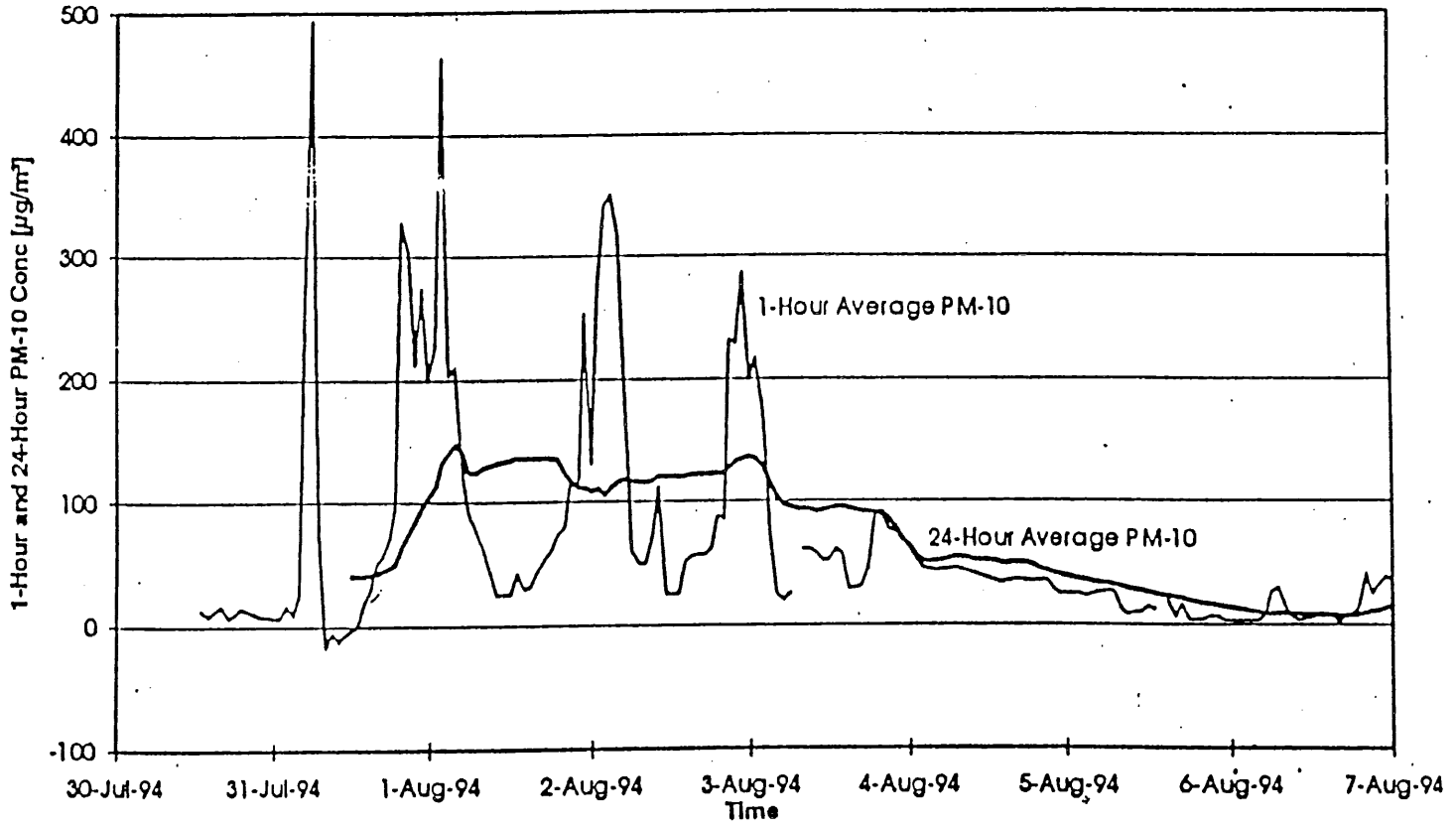
In Birmingham, Alabama on 16 April 1990 24-hour average PM_{10} was 70 µg/M^3, but two one-hour-average excursions exceeding 200 µg/M^3 were recorded (Fig. 1). In Penticton, British Columbia on approximately eight days between 30 July and 7 August 1994 24-hour average PM_{10} varied from close to zero to close to 150

Fig. 1. Hourly PM-10 Fluctuations in Birmingham, Alabama on 16 April 1990 with a 24-Hour PM-10 Average of 70 Micrograms Per Cubic Meter*



*Data provided by Rupprecht & Patashnick Co. (Albany, New York). Also see: Meyer, M. B. Applications of continuous PM10 measurements. Conf. on The Role of Meteorology in Managing the Environment of the 90s. Scottsdale, Arizona; 26-28 January 1993.

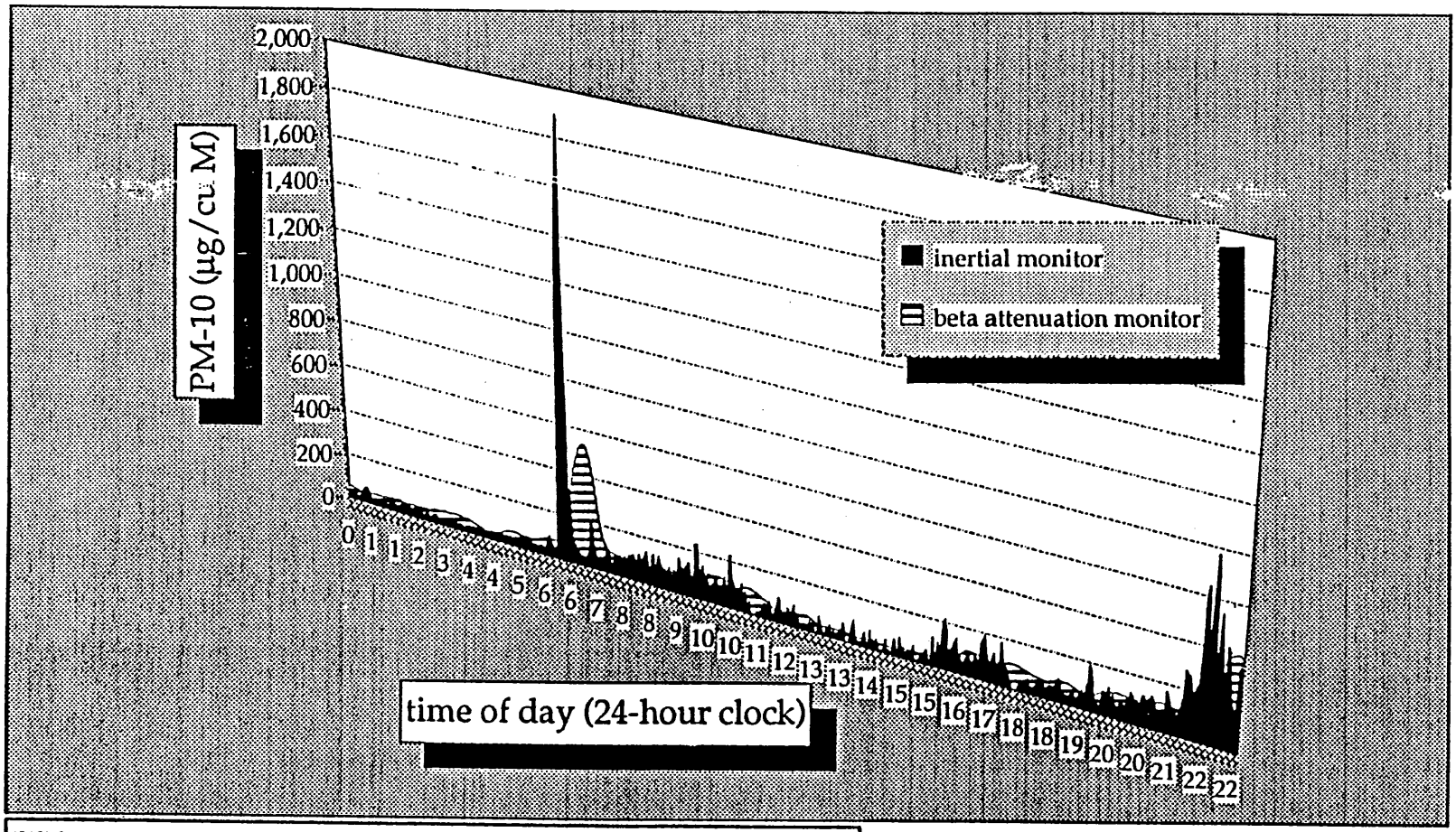
Fig. 2. Hourly and Daily PM_{10} Concentration In Penticton, British Columbia, 30 July to 7 August 1994*



*source:

Rupprecht, E., M. B. Meyer, and H. Patashnick. *Performance characteristics of a near real-time particulate mass monitor.* Conference on Particulate Matter: Health and Regulatory Issues. Pittsburgh, Pennsylvania 4-6 April 1995.

Fig. 3. Time Variation of 15-Minute Average PM-10; Zeebrugge, Belgium; 15 March 1993 (24-Hour Average = 101 μg/cu Meter)*



*With permission from the source: Institute of Hygiene & Epidemics, Belgium.

Table 1. Short-Term Particle Excursions Without Exceedance of the 24-Hour PM-10 Standard

location	source	date	24-hour average particle mass	airborne particle mass excursion	excursion averaging time	excursion-to-24-hour mass ratio	excursion-to-1952 London-Fog ratio**
...	...	...	(μg/cu M)	(μg/cu M)	(minutes)	...	...
Zeebrugge, Belgium	1	3/15/93	101	1,898	15	18.8	1.6
Penticton, British Columbia	3	7/31/94	50	500	60	10.0	0.4
Zeebrugge, Belgium	1	3/15/93	101	780	15	7.7	0.7
Zeebrugge, Belgium	1	3/15/93	101	648	15	6.4	0.5
Zeebrugge, Belgium	1	3/15/93	101	553	15	5.5	0.5
Penticton, British Columbia	3	8/1/94	100	460	60	4.6	0.4
Zeebrugge, Belgium	1	3/15/93	101	425	15	4.2	0.4
Zeebrugge, Belgium	1	3/15/93	101	355	15	3.5	0.3
Penticton, British Columbia	3	8/1/94	100	320	60	3.2	0.3
Birmingham, Alabama	2	4/16/90	70	222	60	3.2	0.2
Birmingham, Alabama	2	4/16/90	70	208	60	3.0	0.2
Penticton, British Columbia	3	8/2/94	120	350	60	2.9	0.3
Penticton, British Columbia	3	8/1/94	100	280	60	2.8	0.2
Zeebrugge, Belgium	1	3/15/93	101	283	15	2.8	0.2
Birmingham, Alabama	2	4/16/90	70	176	60	2.5	0.1
Penticton, British Columbia	3	8/3/94	120	290	60	2.4	0.2
Zeebrugge, Belgium	1	3/15/93	101	238	15	2.4	0.2
Zeebrugge, Belgium	1	3/15/93	101	230	15	2.3	0.2
Zeebrugge, Belgium	1	3/15/93	101	220	15	2.2	0.2
Zeebrugge, Belgium	1	3/15/93	101	220	15	2.2	0.2
Penticton, British Columbia	3	8/2/94	120	250	60	2.1	0.2
Penticton, British Columbia	3	8/3/94	120	240	60	2.0	0.2
Zeebrugge, Belgium	1	3/15/93	101	195	15	1.9	0.2
Zeebrugge, Belgium	1	3/15/93	101	193	15	1.9	0.2
Zeebrugge, Belgium	1	3/15/93	101	185	15	1.8	0.2
Penticton, British Columbia	3	8/3/94	120	210	60	1.8	0.2
Zeebrugge, Belgium	1	3/15/93	101	153	15	1.5	0.1
summary							
excursions detected		27:	Birmingham, 3/1 day; Penticton, 9/9 days; Zeebrugge, 15/1 day				
mean excursion (μg/cu M)		...	99	373	...	3.9	0.3
standard deviation (μg/cu M)		...	17	342	...	3.6	0.3
coefficient of variation		...	17	91	...	92	91
locations examined		3	...	...	...	...	...
fraction exhibiting excursions		1.00	...	...	...	...	...
days examined		10	...	...	...	...	...
fraction exhibiting excursions		0.60	...	...	...	...	...

*Sources: adapted from:

1. Institute of Hygiene and Epidemics, Belgium;
2. Meyer, M. B. Applications of continuous PM-10 measurements. Conference on the Role of Meteorology In Managing the Environment of the 90s. Scottsdale, Arizona; 26-28 January 1993;
3. Rupprecht, E.; M. B. Meyer, and H. Patashnick. Performance characteristics of a near real-time particulate mass monitor. Conference on Particulate Matter: Health and Regulatory Issues; Pittsburgh, Pennsylvania; 4-6 April 1995.

**Conservatively assumes London fog = 1,200 μg/cu M, but this estimate is probably total particulates rather than only PM-10. The deaths of approximately 4,000 people over 10 days in 1952 have been attributed to the London fog (see text for source).

$\mu g/M^3$, but excursions exceeding 150 $\mu g/M^3$ were recorded on four of the eight days (Fig. 2). These included three one-hour-average excursions to 300 $\mu g/M^3$ and two excursions to approximately 500 $\mu g/M^3$. In Zeebrugge, Belgium on 15 March 1993 24-hour average PM_{10} was 101 $\mu g/M^3$, but several 15-minute-average excursions exceeding 200 $\mu g/M^3$ were recorded (Fig. 3). In one excursion, the 15-minute average reached 2,000 $\mu g/M^3$, significantly exceeding the estimated magnitude, though not the persistence, of the 1952 London fog ($\leq$1,200-$\mu g/M^3$; 53).

Table 1 summarizes the observed excursions and quantifies their magnitude relative to 24-hour average and London fog particle mass benchmarks. Excursions attained levels from 0.1 to 1.6 times the London fog benchmark. Four of 27 excursions (15 percent) reached at least 0.5 of the London fog level. These estimates are based upon the conservative assumption that the average London fog particle mass estimate consisted of only PM_{10}, whereas PM_{10} may have represented only a fraction of this estimate.

Possible Toxicological Significance

Toxicology literature was evaluated, confirming that particle levels in the observed range of measured fine particle excursions can cause adverse health effects. Numerous studies of short-term effects exerted by airborne particles during controlled acute human exposures were identified. Many of these reported positive results (4, 7-12, 17, 19-22, 25-32, 34, 40, 61, 62, 64). Table 2 exemplifies the positive studies, ranking the tabulated examples, along with findings of daily mortality studies (for example, see 18) and the current PM_{10} standard (55), in increasing order of dose-times-exposure-duration product.

Table 2. Particle Effects Revealed In Controlled Acute Human Exposures

citation [*]	healthy subjects	asthmatic subjects	activity level	subject age span	particle type(s)	MMAD [**]	dose	duration	dose x duration	effect(s)
...	...	...	...	(y)	...	(μM)	(μg/cu M)	(min.)	(μg min/cu M)	...
Yang and Yang, 1994	30	25	at rest	23 - 48	TSP	...	202	30	6,060	healthy: no effects; asthmatic: reduced lung function (FEV1)
Utell, et al., 1989	0	15	exercise	19 - 50	NaCl, H2SO4, NH3	0.80	700	30	21,000	reduced lung function (FEV1)
Morrow, et al., 1994	0	17	exercise	20 - 57	NaCl, H2SO4	...	190	120	22,800	reduced lung function (FEV1)
Green, et al., 1989	24	0	exercise	18 - 35	activated carbon + formaldehyde	1.4	1,020	120	122,400	cough, reduced lung function (FVC, FEV3, peak flow)
...	...	...	...	...	...	10	50 - 100	1,440	72,000 - 144,000	daily mortality and morbidity begin
...	...	...	...	...	...	10	150	1,440	216,000	NAAQS for PM-10
Framptom, et al., 1992	12	0	exercise	20 - 39	NaCl + H2SO4	0.9	2,000	120	240,000	throat irritation; no effect on lung function
Balmes, et al. 1988	0	12	at rest	25 - 41	NaCl, 30 mOsm	5.3 - 6.1	5,900,000 to 87,100,000	...	≥5,900,000	increased specific airway resistance

*citations:

1. Balmes, J. R., et al. Acidity potentiates bronchoconstriction induced by hypoosmolar aerosols. American Reviews of Respiratory Disease, 138:35-9, 1988;
2. Framptom, M. W., et al. Sulfuric acid aerosol exposure in humans assessed by bronchoalveolar lavage. American Reviews of Respiratory Disease, 146:626-32, 1992;
3. Green, D. J., et al. Acute pulmonary response in healthy, non-smoking adults to inhalation of formaldehyde and carbon. Journal of Toxicology and Environmental Health, 28:261-75, 1989;
4. Morrow, P. E., et al. Effects of near ambient levels of sulphuric acid aerosol on lung function in exercising subjects with asthma and chronic obstructive pulmonary disease. Annals of Occupational Hygiene, 38(Supplement 1):933-8, 1994;
5. Utell, M. J., et al. Effect of inhaled acid aerosols on respiratory function: the role of endogenous ammonia. Journal of Aerosol Medicine, 2:141-7, 1989;
6. Yang, S.-C., and S.-P. Yang. Respiratory function changes from inhalation of polluted air. Archives of Environmental Health, 49:182-7, 1994.

**MMAD: mass median aerodynamic diameter

Table 2 indicates that adverse particle-associated health effects have been demonstrated beginning at levels as low as 202 $\mu g/M^3$ (64) and at exposure durations as short as 30 minutes (62, 64). These effects were documented in asthmatics at rest (64) or engaged in exercise (62). Participant ages in these studies varied from 19 to 50 (62) and 23 to 48 (64). Thus, no frail elderly, elderly, or infirm subjects were included in the studies. Other positive studies likewise involved asthmatic subjects exercising or at rest, of ages up to 57 years (12, 21, 25, 40). For ethical reasons, adverse effects, when observed, could not be allowed to progress to clinical significance. However, reported effects included increased airway resistance; reduced values of lung function parameters such as forced expiratory volume at one and three minutes (FEV_1, FEV_3), forced vital capacity (FVC), and peak flow; as well as such symptoms as throat irritation and coughing.

In addition to the clinical studies described above, Lawther, *et al.* (1970; 33) conducted an epidemiological study pointing to short-term toxicological actions of particles. They employed a diary method in which bronchitis patients recorded daily changes in the severity of their symptoms relative to their recollection of previous-day symptom severity. The diary method required participants to make an entry pertaining to a full day of symptom experience. Lawther, *et al.* reported a clear association of symptom severity with daily concentrations of smoke or sulfuric acid in London. They concluded, however, that this association could not be attributed to the measured 24-hour average concentrations, but more likely to *"the effects of brief exposures to the maximum concentrations occurring during the day"* (page 538), which may be several times the 24-hour average (63) which served merely as a surrogate parameter for such excursions. The basis for the Lawther, *et al.* conclusion included their (uncited) experimental work on normal subjects:

"... the measurements quoted in the present paper relate only to 24-

hour average concentrations of sulphur dioxide and other pollutants. The evidence that we have from experimental work on normal subjects suggests that the effects of inhaling prepared mixtures of pollutants are of rapid onset, and peak concentrations encountered during the day may therefore be more relevant than 24-hour averages. The effects that we have reported cannot be considered as the result of 24-hour exposures to at least 500 $\mu g/M^3$ of sulphur dioxide together with 250 $\mu g/M^3$ of smoke: they are more likely to reflect the effects of brief exposures to the maximum concentrations occurring during the day, and these may be several times the 24-hour averages" (page 538).

The studies described above demonstrate adverse health effects induced by short-term exposure to particles. However, exposure was routinely terminated to preclude symptoms from progressing to clinical significance. Identification of plausible mechanisms might enable prediction of the possible clinical and epidemiological significance of exposures which are not terminated in a timely manner (as part of an experimental protocol), or of similar exposures to more susceptible individuals.

Brief airborne exposures may be more toxicologically, and more clinically, significant for some individuals. Briefly intense airborne exposures may deposit an overwhelming number of particles per alveolar macrophage cell, inhibit particle clearance, and result in protracted internal pulmonary exposures. The duration of such exposures will be inversely proportional to the fine particle clearance rate. Individuals whose lung function is compromised may clear fine particles less efficiently and less rapidly than normal individuals under identical exposure conditions, increasing their effective exposure to fine particles, as indicated by Miller, *et al.* (1995; 39). They reported differentials favoring higher exposure of individuals having compromised respiratory systems,

including approximately three-fold increases in the number of 1-μ particles deposited per unit of respiratory surface area, per ventilatory unit, per alveolus, and per alveolar macrophage cell. They also reported similar findings with respect to 0.1-μ particles.

Prolonged internal exposure to fine particles may correlate with irritation and prolonged, potentially lethal, reductions in the alveolar surface area available for gas exchange, and therefore in the efficiency and rate of gas exchange. These challenges may result in cardiopulmonary stress, possibly provoking episodes of apnea and cardiac arrhythmias, especially for the frail elderly, the infirm, and generally for individuals suffering from preexisting respiratory disease (especially if severe). These factors, and possibly increased susceptibility to airborne pathogens (49), suggest the likelihood that short-term adverse effects observed at subclinical intensities in young asthmatics whose cardiopulmonary health is otherwise robust may be exacerbated in older individuals suffering from preexisting health deficits.

Elucidation of toxicological mechanisms by which fine particles induce adverse health effects observed clinically has been incomplete because of a dearth of animal models (53). However, investigations into airborne particle-induced effects on rats and dogs are reported under way at Harvard University's School of Public Health, and are closing this data gap. The ongoing research has been published in abstract form (24, 41, 42), and more completely in oral and written reports by John Godleski to CASAC (23). The findings implicate short-term, possibly electrophysiological mechanisms of fine-particle-induced cardiopulmonary malfunctioning, shown via electrocardiograms (EKGs).

Nearing, *et al.* (42) induced ST segment elevation and periods of apnea in dogs inhaling fly ash at 1,000 $\mu g/M^3$ for 3 d, 4 h/d. Nearing, *et al.* (41) also demonstrated

increased T-wave alternans amplitude, indexing vulnerability to ventricular fibrillation, in dogs inhaling fly ash at 3,000 $\mu g/M^3$ for 3 d, 3 h/d. Although ST segment elevation and T-wave alternans effects became most prominent by day three, they began to occur only hours after the onset of exposure.

Godleski, *et al.* (23, 24) used rats exhibiting either monocrotyline-induced pulmonary inflammation or SO_2-induced chronic bronchitis. Rats with respiratory pathology then inhaled particles concentrated from Boston air at 228 to 288 $\mu g/M^3$ for 3 h/d, 6 h/d. Breathing rates declined from 17.1/min. in controls to 9/min. in exposed rats. Apnea for up to 22 seconds occurred. Bronchoconstriction occurred in 80 percent of rats exhibiting respiratory disease, compared with 25 percent of controls. Rats exhibited no signs of distress, but deaths occurred on all exposure days, possibly as a result of particle-induced arrhythmias or other EKG-related cardiopulmonary malfunction. Godleski (23) indicated that mortality might also be consistent with systemic effects following particle induction of proinflammatory mediators, such as the cytokines interleukin-1 and tumor necrosis factor-alpha.

Possible Regulatory Significance

The findings reported in epidemiological and controlled human exposure studies must be evaluated relative to EPA policies and procedures for air pollutant standard setting (3, 56) based upon the weight of evidence for the existence, nature, and magnitude of public health risks. The Agency requested the American Thoracic Society (ATS) to define toxicological effects, and degrees of effect, which might qualify as forming the basis for limiting air pollutants, and both ATS (1985; 3) and the U. S. EPA (1989; 56) have published these guidelines.

According to U. S. EPA policy (56), air pollution limits must be set based upon a clinically significant adverse effect, not any effect, as defined by ATS (3):

> *"We define 'adverse respiratory health effects' as medically significant physiologic or pathologic changes..."* (page 666).

Many of the controlled human exposure studies focus upon asthmatics during exercise and at rest. These studies, described earlier in Table 2 and associated text, reveal symptoms of asthma exacerbation such as bronchoconstriction, increased airway resistance, reduced FEV_1 and FEV_3, reduced FVC, and reduced peak flow. The issue of whether these effects can form the basis for air pollutant standard setting under EPA's Clean Air Act implementation policies and procedures is resolved by ATS (3):

> *"the eye, nose, and throat irritation associated with ... urban 'smog' or photochemical oxidant air pollution is not medically important and is, therefore, not considered an 'adverse health effect' in relation to the Clean Air Act. This irritation certainly is annoying or bothersome, which puts it in the category of an effect on human welfare. However, irritation that triggers an asthmatic attack is an adverse health effect"* (page 666; emphasis added).

Clearly, the symptoms evoked by controlled clinical exposures as described and tabulated (Table 2) above do not include triggering an asthmatic attack. However, according to EPA and ATS guidelines, this clinical endpoint need not be (and for ethical reasons, cannot be) experimentally induced to be used in standard setting. Rather, the guidelines justify inferring greater severity of response with greater exposure. ATS

continues as follows:

> *This spectrum of biologic responses would be evoked more strongly as the concentrations of pollutants are increased"*
> (page 666; emphasis added).

CONCLUSIONS AND RECOMMENDATIONS

The findings of this study form the basis for drawing four principal conclusions about airborne particles: 1. Excursions of airborne particle mass may elevate PM_{10} by an order of magnitude relative to 24-hour average levels within the 150-$\mu g/M^3$ NAAQS. 2. Particle levels comparable to those reached during documented excursions can exert toxicological effects, including mortality in animals. 3. Such excursions might constitute a previously unrecognized cause of as-yet-unexplained mortality and morbidity revealed by epidemiology studies based upon 24-hour average particle levels. 4. U. S. EPA criteria for air pollutant standard setting include (and may require) use of toxicological effects associated with particles in the range of observed excursions.

Time Frames for Health Effect Detection Vs. Causation

The U. S. EPA's current NAAQS requires averaging PM_{10} mass over 24 hours and one year, precluding both detection and control of shorter-term exposures, which appear to be toxicologically significant. However, the Agency has not proposed to incorporate an airborne particle mass limit averaged over a shorter time than 24 hours (57). Indeed, the Agency's response to CASAC's advice to justify its averaging times suggests confusion between the averaging time appropriate for health effect causation (and prevention) vs. health effect detection:

"The current 24-hour averaging time is consistent with the majority of the results from community epidemiological studies, which have reported associations of 24-hour concentrations of PM_{10}, fine particles, and TSP [total suspended particulates] *with an array of health effects. Nevertheless, because some such studies have found a stronger association with a multiple day average.... the Staff considered whether a multiple day averaging time would be more appropriate... The 24-hour averaging time effectively protects against episodes lasting for several days while also protecting sensitive individuals who may experience effects after a single day of exposure. Thus, the staff concludes that a longer averaging time, such as 3 to 5 days, would not provide more effective protection than a 24-hour average"* (page VI-2; emphasis added).

The time frames over which adverse health effects are caused vs. manifested commonly bear little if any relation to one another. For example, a bullet wound may represent a nearly instantaneous cause of death. Alternatively, death may occur days after the instantaneous causal event. Likewise, diseases may result from instantaneous exposures to pathogens, but pathology typically develops after a significantly longer incubation period, and death (if it occurs) may occur over still longer time frames bearing no relation to the duration of the exposure event. As a corollary example, the availability of daily roadside counts of dead animals does not constitute evidence of a 24-hour lethality mechansim. Yet, the linkage of 24-hour mortality and morbidity data has been used to justify regulation of airborne particles as a long-term risk, but not as a short-term risk.

In the case of airborne particle associated health effects, exposure occurs at some background intensity over long periods, and episodically at sometimes lower and

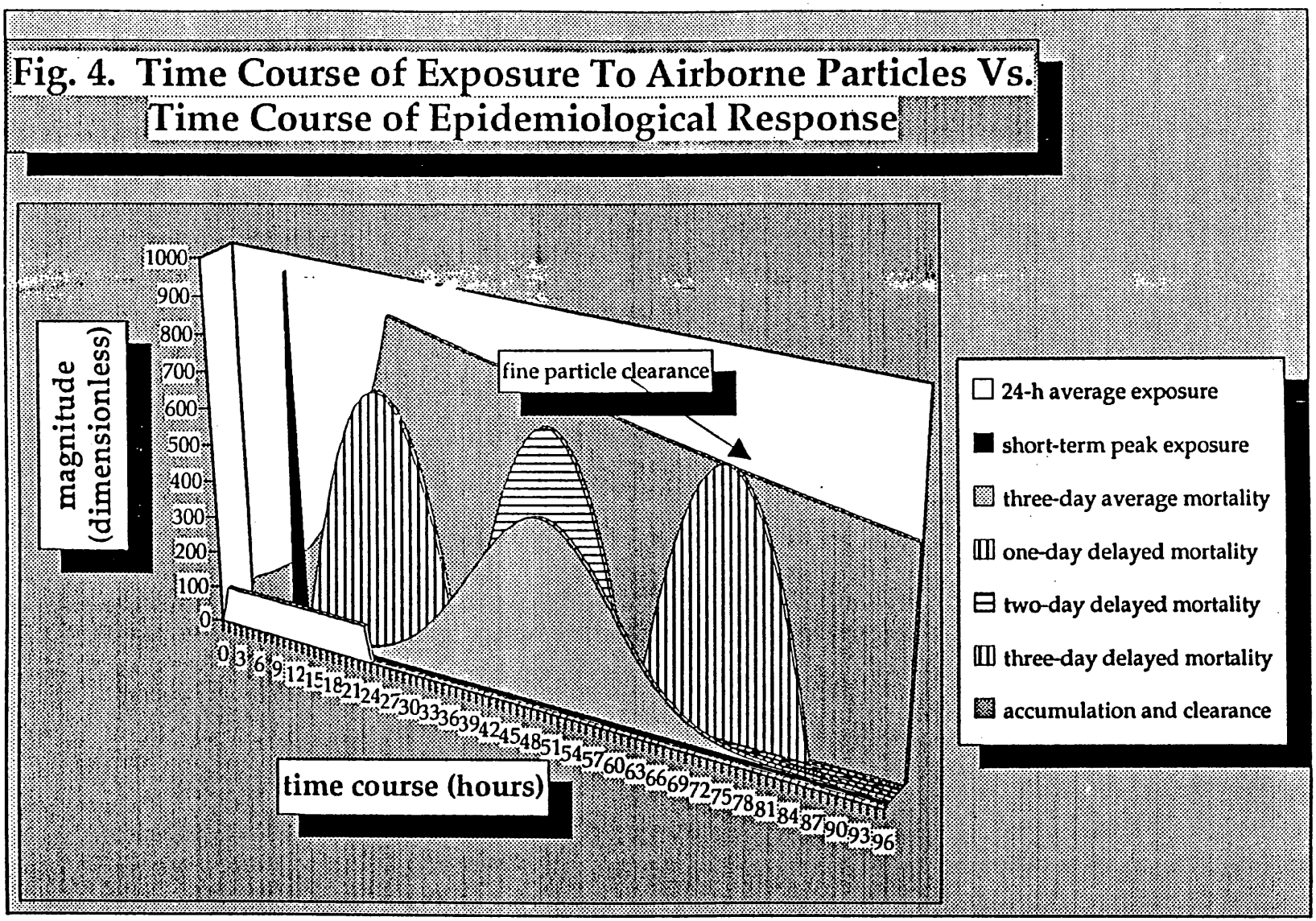
sometimes higher intensities. To illustrate, Figure 4 depicts exposure to a 24-hour average PM_{10} of 100 $\mu g/M^3$ with a brief (15-minute) excursion to 1,000 $\mu g/M^3$, approximately equivalent to that attained during the 1952 London fog (53), and approximately half that actually observed in the present study (Table 1). Figure 4 also illustrates the ensuing process of particle accumulation in the lungs, and the slower rate of particle clearance. Finally, alternative time courses for the manifestation of adverse health effects are shown.

Three similar peaks represent possible one-day, two-day, or three-day delays in postexposure mortality, similar to delays reported in some epidemiological studies. Inasmuch as no prior knowledge may be assumed of the occurrence or length of any mortality delay, a shallower curve is also depicted showing the statistical effect of averaging ('curve smoothing') over a three-day period. The curve illustrates that the longer-term averaging strategy offers a higher probability of encompassing a delayed mortality peak, if it occurs; whether it occurs after one, two, or three days postexposure. However, this benefit is offset by the reduced height of the curve, which illustrates how each 24-hour mortality peak in the depicted scenario is diluted over a 72-hour period. This will reduce the probability of statistically identifying a 24-hour peak due to its dilution with (ideally) a 48-hour period of background mortality incidence.

Recommendation 1

The purpose of the airborne particle standard, as suggested by Figure 4 and the above analysis of multiple-day averaging, is not to assist epidemiologists to detect health effects, but to prevent health effects from occurring. This policy choice should reduce attention to curve smoothing and the time frame for health effect detection, focusing attention instead upon shorter time frames for health effect causation and prevention.

Fig. 4. Time Course of Exposure To Airborne Particles Vs. Time Course of Epidemiological Response



Short-Term Vs. Long-Term Mechanisms of Action

EPA's *Criteria Document* addresses the time frame issue for health effect causation (58). However, short-term health effects are excluded from explicit consideration. Indeed, the document prefers the hypothesis of long-term causation:

> *"One of the best indications that there is a longer-term effect of PM is that the relative risks estimated in the long-term mortality studies are considerably larger than those in the acute mortality studies... This suggests that the long-term studies include the excess deaths inferred in acute studies, and also include some of the excess deaths attributable to air pollution that may occur during low-pollution baseline periods, and would not be inferred by the acute mortality studies"* (page 1-36).

Clearly, particle-induced health effects must be cumulative, so that exposures of longer duration will be associated with greater risks. This is widely accepted to be the case, for example, with respect to cigarette smoking. However, the issue of whether long-term or short-term risks are greater is irrelevant. The relevant issues are 1. whether excursion-associated relative risks correlate with sufficiently high absolute risks to public health to merit management via the NAAQS (CASAC too has recommended that EPA address this issue), and 2. whether observed mortality and morbidity can be plausibly explained without invoking short-term mechanisms of causation.

Recommendation 2

One implication of the present investigation is that the Agency should further

consider the short-term causation scenario in the context of standard setting. Short-term causation is dismissed in the *Staff Paper* (57):

> *"The staff has also considered the evidence regarding effects associated with PM exposures of durations less than 24 hours. Some investigators prior to the 1987 review (Lawther, et al., 1970) speculated that the observed health effects might be largely due to short-term peaks on the order of an hour. Controlled human and animal exposures to specific components of fine particles, such as acid aerosols, also suggest that some effects, such as bronchoconstriction, can occur after exposures of minutes to hours. Some epidemiological studies of exposures to acid aerosols have also found changes in respiratory symptoms in children using averaging times less than a 24-hour period (e.g., 12 hours). However, it is not clear whether the majority of effects that have been associated with daily exposure to PM, including mortality and various measures of morbidity, would occur after only short duration exposures. Moreover, a 24-hour average can be expected to provide significant protection from potential effects associated with short-duration peaks in most urban atmospheres."* (pp. VI-2 to VI-3, emphasis added).

Thus, EPA rejects short-term causation and, concomitantly, a one-hour mass limit, based upon three incorrect premises: 1. that Lawther, *et al.* (33) merely *"speculated"* that peak exposure rather than 24-hour exposure exacerbated bronchitis among the subjects of their investigation, 2. that standards for air pollutants must be based upon a *"majority"* of observed effects rather than just the one effect occurring at the lowest exposure level, and 3. that a 24-hour averaging time will protect against excursions, which is refuted by the present investigation.

Relative Vs. Absolute Risks

The technical basis for reexamining the airborne particle mass regulation has consisted primarily of frequently observed associations of morbidity and mortality with fine airborne particle mass levels. However, these associations, assuming they represent excess relative risks (which is in dispute) have not been quantified as potential absolute risks. This is significant for risk management, whether applied to occupational or to environmental settings. A high relative risk may represent a *de minimis* incremental absolute risk if the baseline absolute risk is low. Conversely, a low relative risk may represent an unacceptably high incremental absolute risk if the baseline absolute risk is high. To illustrate, the lifetime absolute risk of being struck and killed by a meteorite may be in the range of 150/trillion (1.5×10^{-10}). If the risk at the earth's poles is 100 times the average, this would produce a relative risk of 100, but an absolute risk of only 1.5×10^{-8}, orders of magntude below levels likely to be of concern for polar risk managers. In the case of particles, relative risks of a few percent may or may not be significant or acceptable, depending upon the baseline. However, the baseline has apparently not been established.

Recommendation 3

Quantify the baseline and incremental absolute risks corresponding to reported relative risks of mortality and morbidity associated with fine particles. The higher the absolute risk being managed, the higher the potential value of risk management procedures. As the value of risk management procedures increases, the significance of their cost declines. Further, as the significance of cost declines, the justification for taking pro-active, even speculative regulatory action may increase. Regulating airborne particles over a one-hour time frame may seem more attractive in the context of a major risk to public

health, and less attractive in the context of a lower risk, or in the context of an absence of quantitative risk estimates. CASAC too has recommended that EPA address this issue.

Risk Management Via PM_{10} Vs. $PM_{2.5}$

The EPA *Staff Paper* (57) presents the health risk management option of diverting NAAQS standard from PM_{10} to $PM_{2.5}$. This proposal has been controversial, but is irrelevant to the findings made, conclusions drawn, and recommendations advocated in the present study. The effects exerted by particles are widely acknowledged to result predominantly from the most respirable (fine) fraction of the inspired mixture. PM_{10} excursions undoubtedly encompass excursions of $PM_{2.5}$. Thus, the 24-hour PM_{10} standard of 150 $\mu g/M^3$ can be expressed as an equivalent one-hour standard of about 300 $\mu g/M^3$, which may be in turn formulated as a one-hour $PM_{2.5}$ mass equivalent if the NAAQS focus changes.

The present investigation has revealed that 1. airborne particle mass can be reliably and economically measured over short intervals, 2. significant airborne particle excursions occur over brief intervals of duration 15 minutes to one hour, 3. such excursions are potentially significant toxicologically, and 4. the effects known to be caused by short-term exposure to particles constitute appropriate clinical bases for standard setting under the Clean Air Act. These findings add to the risk management options available to the EPA. The EPA must soon decide whether to risk further legal challenge by managing airborne particles to levels below those of demonstrated toxicological significance. The present investigation enables the Agency to reject standard setting in the absence of demonstrated statistical and clinical significance of the health risks being managed. Alternatively, the Agency can choose to manage airborne particle risks based upon statistically and clinically

significant public health endpoints, avoidance of which is consistent with EPA policies and procedures for airborne pollutant standard setting under the Clean Air Act.

The cost of NAAQS compliance is large, and will increase if the 24-hour airborne particle mass limit is revised downward. The cost to the Agency will be large if the proposed standard is legally challenged, and larger if it does not prevail. Compliance with a one-hour mass limit of 300 $\mu g/M^3$ would be less burdensome than compliance with a 24-hour mass limit below 150 $\mu g/M^3$ because the effects of a one-hour limit would be limited primarily to equipment start-up and shutdown rather than continuous facility operation. The present study suggests that such a one-hour limit may eliminate the need to strengthen longer-term limits while being: 1. more effective at protecting health, 2. justified by available data, and 3. feasible.

LITERATURE CITED

1. **American Lung Association.** *Complaint in a civil case: American Lung Association Vs. Carol Browner, U. S. EPA;* U. S. District Court, District of Arizona, Case No. CIV-93-643-TUC-ACM, 11 pp., 12 October 1993;
2. **American Lung Association.** *The Perils of Particulates.* New York City, 24 pp., March 1994;
3. **American Thoracic Society.** *Guidelines as to what constitutes an adverse respiratory health effect, with specific reference to epidemiologic studies of air pollution.* American Reviews of Respiratory Disease, 131:666-8, 1985;
4. **Anderson, K. R., *et al.*** *Controlled exposures of volunteers to respirable carbon and sulfuric acid aerosols.* Journal of the Air & Waste Management Association, 42:770-6, 1992;

7. **Aris, R., *et al.*** *The effects of sequential exposure to acid fog and ozone on pulmonary function in exercising subjects.* American Reviews of Respiratory Disease, 143:85-91, 1991a;

8. **Aris, R., *et al.*** *Lack of bronchoconstrictor response to sulfuric acid aerosols and fogs.* American Reviews of Respiratory Disease, 143:744-50, 1991b;

9. **Avol, E. L., *et al.*** *Respiratory dose-response study of normal and asthmatic volunteers exposed to sulfuric acid aerosol in the sub-micrometer size range.* Toxicology and Industrial Health, 4:173-84, 1988a;

10. **Avol, E. L., *et al.*** *Short-term respiratory effects of sulfuric acid in fog: a laboratory study of healthy and asthmatic volunteers.* Journal of the Air Pollution Control Association, 38:258-63, 1988b;

11. **Avol, E. L., *et al.*** *Respiratory responses of young asthmatic volunteers in controlled exposures to sulfuric acid aerosol.* American Reviews of Respiratory Disease, 142:343-8, 1990;

12. **Balmes, J. R., *et al.*** *Acidity potentiates bronchoconstriction induced by hypo-osmolar aerosols.* Amer. Reviews of Respiratory Disease, 138:35-9, 1988;

14. **CASAC.** Letter from George T. Wolff, CASAC Chairperson, to EPA Administrator Carol M. Browner transmitting CASAC comments on the April 1995 draft *Air Quality Criteria for Particulate Matter.* Washington, DC; Clean Air Science Advisory Committee (CASAC), EPA-SAB-CASAC-LTR-95-005, 4 pp., 31 August 1995;

15. **Chow, J. C.** *Measurement methods to determine compliance with ambient air quality standards for suspended particles--summary of critical review.* Environmental Manager, 1:12-5, May 1995;

16. **Chow, J. C.** *Measurement methods to determine compliance with ambient air quality standards for suspended particles--critical review.* Journal of the Air

& Waste Management Association, 45(5):320-82, May 1995;

17. **Culp, D. L., *et al.*** *Composition of human airway mucins and effects after inhalation of acid aerosols.* Amer. Journal of Physiology, in press, 1995;

18. **Dockery, D. W., and C. A. Pope.** *Acute respiratory effects of particulate air pollution.* Annual Reviews of Public Health, 15:107-32, 1994;

19. **Fine, J. M., *et al.*** *The role of titratable acidity in acid aerosol-induced bronchoconstriction.* American Reviews of Respiratory Disease, 135:826-30, 1987a;

20. **Fine, J. M., *et al.*** *The roles of pH and ionic species in sulfur dioxide- and sulfite-induced bronchoconstriction.* American Reviews of Respiratory Disease, 136:1,122-6, 1987b;

21. **Framptom, M. W., *et al.*** *Sulfuric acid aerosol exposure in humans assessed by bronchoalveolar lavage.* American Reviews of Respiratory Disease, 146:626-32, 1992;

22. **Framptom, M. W., *et al.*** *Sulfuric acid aerosol followed by ozone exposure in healthy and asthmatic subjects.* Environmental Research, in press, 1995;

23. **Godleski, J. J.** Oral and written report to the PM_{10} Review Panel, U. S. EPA Clean Air Science Advisory Committee (CASAC). Research Triangle Park, North Carolina; 14 December 1995;

24. **Godleski, J. J., *et al.*** *Death from inhalation of concentrated ambient air particles in animal models of pulmonary disease.* New Orleans, Louisiana; American Thoracic Society 1996 International Conference, 11-15 May, abstract in press, 1996;

25. **Green, D. J., *et al.*** *Acute pulmonary response in healthy, non-smoking adults to inhalation of formaldehyde and carbon.* Journal of Toxicology and Environmental Health, 28:261-75, 1989;

26. **Hanley, Q. S., *et al.*** *Response of young asthmatic patients to inhaled sulfuric acid.* American Reviews of Respiratory Disease, 145:326-31, 1992;

27. **Koenig, J. Q., *et al.*** *Effects of inhalation of acidic compounds on pulmonary function in allergic adolescent subjects.* In: *Symposium on the Health Effects of Acid Aerosols.* Research Triangle Park, NC, October 1987. Environmental Health Perspectives, 79:173-8, 1989;

28. **Koenig, J. Q., *et al.*** *The effect of duration of exposure on sulfuric acid-induced pulmonary function changes in asthmatic adolescent subjects: a dose-response study.* Toxicology and Industrial Health, 8:285-96, 1992;

29. **Koenig, J. Q., *et al.*** *Respiratory effects of inhaled sulfuric acid on senior asthmatics and nonasthmatics.* Archives of Environmental Health, 48:171-5, 1993;

30. **Koenig, J. Q., *et al.*** *Oxidant and acid aerosol exposure in healthy subjects and subjects with asthma. Part 1: effects of oxidants, combined with sulfuric or nitric acid, on the pulmonary function of adolescents with asthma.* Cambridge, MA; Health Effects Institute, Research Report No. 70, 36 pp., 1994;

31. **Kulle, T. J., *et al.*** *Pulmonary effects of sulfur dioxide and respirable carbon aerosol.* Environmental Research, 41:239-50, 1986;

32. **Laube, B. L., *et al.*** *Acute exposure to acid fog: effects on mucociliary clearance.* American Reviews of Respiratory Disease, 147:1,105-11, 1993;

33. **Lawther, P. J., R. E. Waller, and M. Henderson.** *Air pollution and exacerbations of bronchitis.* Thorax, 25:525-39, 1970;

34. **Linn, W. S., *et al.*** *Effect of droplet size on respiratory responses to inhaled sulfuric acid in normal and asthmatic volunteers.* American Reviews of Respiratory Disease, 140:161-6, 1989

35. **Meyer, M. B.** *Applications of continuous PM_{10} measurements.* Paper presented at the *Conference on the Role of Meteorology in Managing the Environment.* Scottsdale, Arizona; 12 pp., 26-28 January 1993;

36. **Meyer, M. B., E. Rupprecht, and H. Patashnick.** *Considerations for the sampling and measurement of ambient particle mass.* Paper presented at the U. S. EPA and Air & Waste Management Association *Conference on Particulate Matter: Health and Regulatory Issues.* Pittsburgh, Pennsylvania; 8 pp., 4-6 April 1995;

37. **Michaels, R. A.** Response to Chow (see citations 15, 16; above). In: J. G. Watson. *Measurement methods to determine compliance with ambient air quality standards for suspended particles.* Journal of the Air & Waste Management Association, 45:666-84, September 1995;

38. **Michaels, R. A.** *Health risks and particle monitoring: new technologies to meet emerging data needs. AAAR '95.* Pittsburgh, Pennsylvania; 14th Annual Meeting of the American Association for Aerosol Research, 9 - 13 October, 1995; Abstract, page 338, 1995;

39. **Miller, F. J., *et al.*** *Dosimetric issues relating to particulate toxicity.* In: R. F. Phalen and D. V. Bates (editors), *Proceedings of the Colloquium on Particulate Air Pollution and Human Mortality and Morbidity,* Part II; Irvine, California; Inhalation Toxicology, 7:615-32, 1995;

40. **Morrow, P. E., *et al.*** *Effects of near ambient levels of sulphuric acid aerosol on lung function in exercising subjects with asthma and chronic obstructive pulmonary disease.* Annals of Occupational Hygiene, 38(Supplement 1):933-8, 1994;

41. **Nearing, B. D., *et al.*** *Inhaled fly ash results in alteration in cardiac electrophysiologic function.* New Orleans, Louisiana; American Thoracic

Society 1996 International Conference, 11-15 May, abstract in press, 1996;

42. **Nearing, B. D., *et al.*** *Exposure to inhaled environmental air particles results in significant ST-segment elevation in dogs with normal coronary arteries.* American College of Cardiology 45th Annual Scientific Session, Abstract No. 075548, abstract in press, 1996;

43. **Patashnick, H., and E. G. Rupprecht.** *Continuous PM-10 measurements using the tapered element oscillating microbalance.* Journal of the Air & Waste Management Association, 41(8):1,079-83, August 1991;

44. **Pope, C. Arden, J. Schwartz, and M. R. Ransom.** *Daily mortality and PM_{10} pollution in Utah Valley.* Archives of Environmental Health, 47(3):211-7, May/June 1992;

45. **Pope C. Arden, and D. W. Dockery..** *Acute health effects of PM_{10} pollution on symptomatic and asymptomatic children.* American Reviews of Respiratory Disease, 145:1,123-8, 1992;

46. **RAM TRAC.** *Health Risks and Particle Monitoring: New Technologies To Meet Emerging Data Needs, Including A One-Hour Upper Mass Limit In the Next National Ambient Air Quality Standard.* Robert A. Michaels, PhD, CEP; Project Director. Schenectady, New York; RAM TRAC Corporation, 169 pp., 17 July 1995;

47. **R&P.** *TEOM® Series 1400A ambient particulate monitor.* Albany, New York; Rupprecht and Patashnick Co., product technical literature 4 pp. plus attachments, undated;

48. **R&P.** *Partisol Model 2000 air sampler.* Albany, New York; Rupprecht and Patashnick Co., product technical literature 4 pp. plus attachments, undated;

49. **R&P.** *Summary: Series 5400 ambient carbon particulate monitor.* Albany, New York; Rupprecht and Patashnick Company, product technical literature 11

pp. plus attachments, September 1994;

50. **Rupprecht, E., M. B. Meyer, and H. Patashnick.** *Performance characteristics of a near real-time ambient particulate mass monitor.* Paper presented at the U. S. EPA and Air & Waste Management Association *Conference on Particulate Matter: Health and Regulatory Issues.* Pittsburgh, Pennsylvania; 11 pp., 4-6 April 1995;

51. **Rupprecht, G., *et al.*** *A new automated monitor for the measurement of particulate carbon in the atmosphere.* Paper presented at the U. S. EPA and Air & Waste Management Association *Conference on Particulate Matter: Health and Regulatory Issues.* Pittsburgh; 11 pp., 4-6 April 1995;

52. **Rylander, R.** *Alterations of lung defense mechanisms against airborne bacteria.* Archives of Environmental Health, 18:551-5, April 1969;

53. **Schwartz, J.** *Environmental pollution and human health: an epidemiology perspective.* Chapter 11 in: C. R. Cothern and N. P. Ross (editors), *Environmental Statistics, Assessment, and Forecasting;* Boca Raton, Florida; Lewis, pp. 209-22, 1993;

54. **U. S. District Court.** *Judgment in a civil case: American Lung Association Vs. Carol Browner, U. S. EPA;* U. S. District Court, District of Arizona, Case No. CIV-93-643-TUC-ACM, 11 pp., 6 October 1994;

55. **U. S. EPA.** *Ambient Air Quality Standards for Particulate Matter; Final Rules.* Federal Register, 52(126):24,633-68, 1 July 1987;

56. **U. S. EPA.** *Interim Methods for Development of Inhalation Reference Doses.* Washington, DC; Office of Health and Environmental Assessment, EPA/600/8-88/066F, PB90-145 723, i. p., August 1989;

57. **U. S. EPA.** *Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical*

Information: OAQPS Staff Paper. Research Triangle Park, North Carolina; Office of Air Quality Planning and Standards (OAQPS), External Review Draft, i.p., November 1995;

58. **U. S. EPA.** *Air Quality Criteria for Particulate Matter, Review Draft.* Washington, DC; Office of Research and Development, EPA/600/AP-95/001a, Vol. 1 of 3 volumes, i. p., 5 December 1995;

59. **U. S. EPA.** *Air Quality Criteria for Particulate Matter, Review Draft.* Washington, DC; Office of Research and Development, EPA/600/AP-95/001b, Vol. 2 of 3 volumes, i. p., 5 December 1995;

60. **U. S. EPA.** *Air Quality Criteria for Particulate Matter, Review Draft.* Washington, DC; Office of Research and Development, EPA/600/AP-95/001c, Vol. 3 of 3 volumes, i. p., 5 December 1995;

61. **Utell, M. J., *et al.*** *Comparison of normal and asthmatic subjects' responses to sulphate pollutant aerosols.* In: W. H. Walton, Editor. *Inhaled Particles. V. Proceedings of an International Symposium* organized by the British Occupational Hygiene Society, Cardiff, Wales; September 1980. Annals of Occupational Hygiene, 26:691-7, 1982;

62. **Utell, M. J., *et al.*** *Effect of inhaled acid aerosols on respiratory function: the role of endogenous ammonia.* Journal of Aerosol Medicine, 2:141-7, 1989;

63. **Waller, R. E., and B. T. Commins.** *Episodes of high pollution in London, 1952-1966.* In: National Society for Clean Air, London, *Proceedings of the International Clean Air Congress, London, 1966,* Part I, p. 228, 1966;

64. **Yang, S.-C., and S.-P. Yang.** *Respiratory function changes from inhalation of polluted air.* Archives of Environmental Health, 49:182-7, 1994.

ACKNOWLEDGEMENT

This research was supported by Rupprecht & Patashnick, Inc.; Albany, New York.

Aerosol Time-of-Flight Mass Spectrometry: A New Method for Performing Real-Time Characterization of Aerosol Particles

Christopher A. Noble and Kimberly A. Prather*
Department of Chemistry, University of California, Riverside, California 92521

Abstract

Recently, our research group has developed aerosol time-of-flight mass spectrometry, an instrumental method for the real-time characterization of individual aerosol particles. Aerosol time-of-flight mass spectrometry couples two laser aerodynamic particle sizing with time-of-flight mass spectrometry to measure both the size and composition of single particles. One of the aims of this research is to provide more detailed measurements of atmospheric aerosol particles than are currently available for epidemiological studies. Current aerosol data mainly consist of particle mass concentration measurements which is employed to correlate particle concentration with effects on mortality and morbidity. Sample spectra of several different particle classifications are shown. Monitoring ambient aerosols over time demonstrates that significant changes in particle chemical composition can occur without correspondingly large changes in the total size distribution. Also, certain metal species (such as iron, lead, titanium and vanadium) are found to be associated with specific compounds, perhaps providing direct indication on particle sources. A larger, more complete database of ambient aerosol measurements based on single particle analysis will provide a thorough foundation for more detailed and extensive epidemiological studies. For example, single particle analysis provides the means for measuring not only sulfates in the fine particle mode, but it may also determine which species are associated with the sulfates in individual particles.

Key words

Real-time, environmental aerosols, single particle analysis, aerodynamic particle sizing, time-of-flight mass spectrometry.

Introduction

Numerous epidemiological studies have related ambient atmospheric conditions to specific health effects. One well reported source of sickness and premature death is ambient particle pollution.[1-6] While both accurate and reliable sampling methods exist for measurement of various ambient gas phase pollutants, there are no comparable sampling techniques which provide detailed information on ambient aerosol particles. Typically, particle measurements which are employed for epidemiological studies are somewhat limited, focusing mainly on particle mass concentration with some measurements of chemical speciation.

Currently, there are only a limited number of areas in which epidemiology may expand in regard to health effects of aerosol particles: (1) greater quantity of data, (2) better quality of analysis and (3) better quality of data. Using a greater quantity of data for epidemiological studies may include things such as a larger sample population and a broader range of cities and geographical/environmental.[6] Better data analysis models will likely be employed for epidemiology as they are developed. Providing a more detailed data set is an option which has recently become more practical due to recent advances in aerosol mass spectrometric analysis.

Several chemistry researchers are presently performing single particle mass spectral analysis in real-time,[7-16] which has the potential of providing a more detailed level of information than previously available with more standard aerosol measurement methods. Some of these researchers are attempting to measure corresponding size information for each particle, thus providing both size and chemical composition on a single particle basis. These two parameters of single particles are of considerable importance because size and composition determine the mobility and reactivity of each particle, respectively. Because these methods are real-time, compositional information can be broken up into both short and long time windows (from minutes to months) to fit the needs of the epidemiologist. This will allow the determination and study of relatively short-lived episodes. Until epidemiological studies have the opportunity to focus on single particle measurements, it likely cannot be determined with great certainty that particles of specific composition are more or less harmful to human health than the bulk aerosol sample.

As an example of the potential benefit of single particle analysis, consider a hypothetical, toxic compound X, which by bulk chemical analysis is found to be 10% of the accumulation mode particles by mass. Compound X likely exists in a very specific size range and is associated with specific chemical compounds based on its source and the processes it has undergone while in the atmosphere. More standard methods for aerosol characterization,[17,18] such as the tapered element oscillating microbalance (TEOM), which measure mass concentration cannot give any indication as to the compositional breakdown of the aerosol sample and could find no evidence of compound X in the sample. Chemical methods do provide necessary information regarding the composition of the bulk aerosol and would, therefore, determine the presence of X in the sample. However, these methods could not determine what chemicals are associated with

X on an individual particle basis. Knowing the specific compounds associated with X will allow the epidemiologist to actually search for certain particles types which may be acting as confounding factors and not necessarily be influencing human health. Also, with this additional information, potential synergistic and/or antagonistic effects may be discovered.

Methods

Aerosol time-of-flight mass spectrometry (ATOFMS) is a recently developed instrumental method which couples two laser aerodynamic particle sizing[19,20] with time-of-flight mass spectrometry[21] to measure both the size and composition of single aerosol particles. Detailed descriptions of the instrumental setup have been described previously,[14-16] as well as an initial application for ambient aerosol monitoring in Riverside, California.[16] Currently, our two laser aerodynamic sizing allows for precise size analysis of polydisperse aerosol samples over the size range from ~0.1-10 μm in diameter—both accumulation and coarse modes. Analysis of mass spectra for classification of particles by chemical composition is performed manually.

Particle analysis studies presented here are for ambient aerosols sampled directly into our ATOFMS instrument at the University of California, Riverside campus, during the months of April and May 1995.

Results

Particles are grouped into approximately ten chemically distinct categories based on their mass spectra. Particles are desorbed/ionized in flight from a single 266 nm pulse of a frequency quadrupled Nd:YAG laser (Continuum). The resulting spectrum, from a single laser pulse on an single particle, is then correlated with the aerodynamic diameter of the desorbed/ionized particle. Representative positive ion spectra of five of the ten categories are shown in Figures 1 and 2. ATOFMS is also capable of performing negative ion analysis, however, this paper will focus on the positive ion spectra.

Figure 1a demonstrates a spectrum of the most common type of organic particles analyzed during this sampling period. Sampling from day to day, the size range in which this particle type is found is ~0.4-2.0 μm. This simple organic class is typified by carbon peaks extending out to C_5^- or C_6^+, and also peaks due to NH_4^+ and NO^+ which indicate the presence of ammonium and nitrate in the original particle. This particle type is likely due to coagulation of nuclei mode particles formed by homogeneous nucleation of gas phase organic compounds produced in emission and combustion processes. The presence of ammonium and nitrate in this particle class is potentially due to heterogeneous reactions during which gas phase ammonia and nitric acid react with the particle. A pure organic particle class has also been identified which is very similar to the simple organic with two significant difference: (1) the pure organic does not contain peaks due to NH_4^+ and NO^+ and (2) the size range in which the pure organic type is found is smaller than the simple organic, ranging from ~0.1-1.0 μm. The source for these pure organic particles is thought

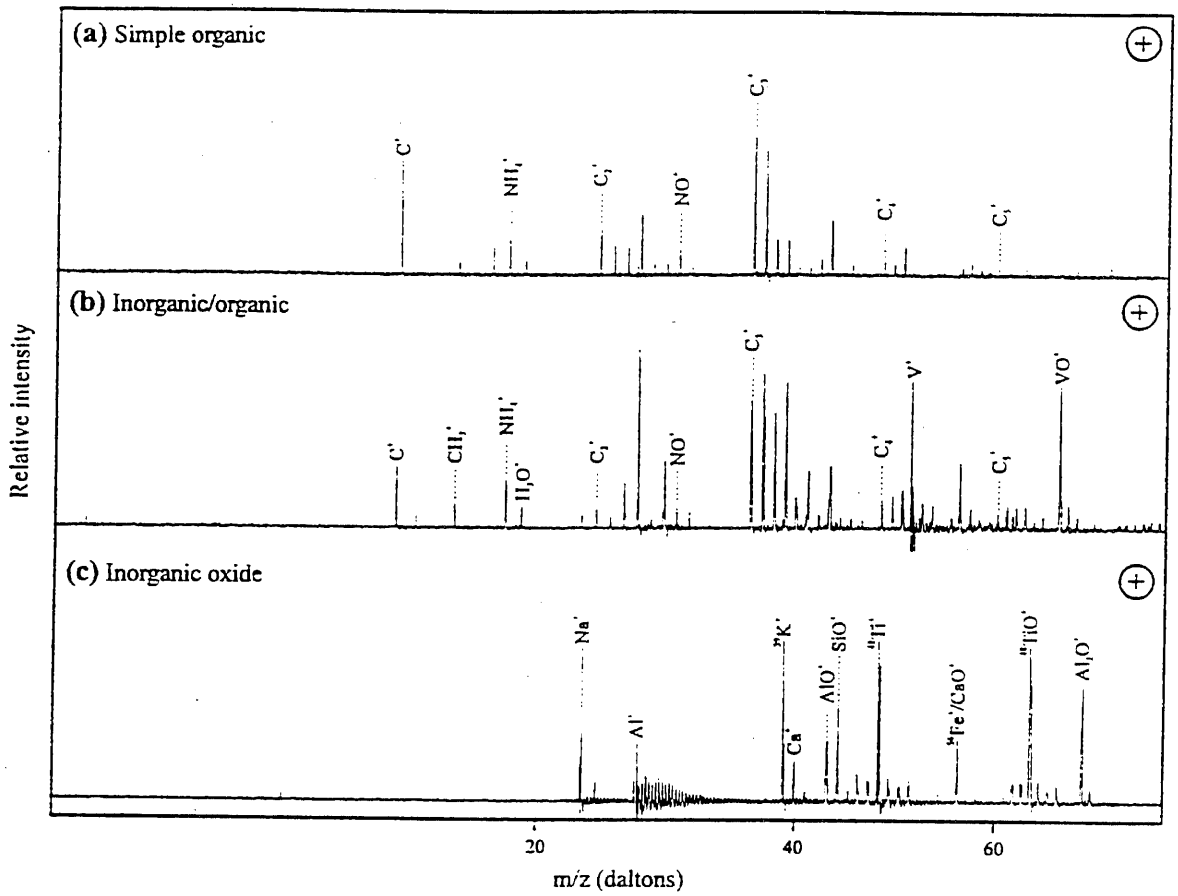


Figure 1: Laser desorption/ionization positive ion mass spectra of single ambient particles. (a) Simple organic particle mass spectrum. (b) Inorganic/organic particle mass spectrum. (c) Inorganic oxide particle mass spectrum.

to be combustion processes, similar or identical to the source of the simple organic type, without the heterogeneous reactions with gas phase ammonia or nitric acid.

An example spectrum of the inorganic/organic particle class is shown in Figure 1b. This particle type is commonly found to be in the size range from ~0.5-2.5 μm and has peaks due to both organic and inorganic components. Representative peaks which are found in this type include carbon peaks extending out to C_5^+ or C_6^+, peaks from C^+, CH_3^+, NH_4^+, H_3O^+, NO^+ and also peaks due to metal cations. Commonly seen metal ions include: Na^+, Mg^+, K^+, Ca^+, V^+, Cr^+, Mn^+, Fe^+, Co^+, Ni^+, Cu^+, Zn^+, Ge^+, Sr^+, Cd^+, Pt^+ and Pb^+. Iron and vanadium are the most common transition metals detected in this particle type. It is speculated that, similar to the simple organic particle type, this particle class is also the product of combustion or emission processes—likely a non-combustible metallic core which serves as the nucleus for heterogeneous nucleation of gas phase organic compounds. Similar to the simple organic particles, the peaks from ammonium and nitrate are possibly caused by heterogeneous reactions.

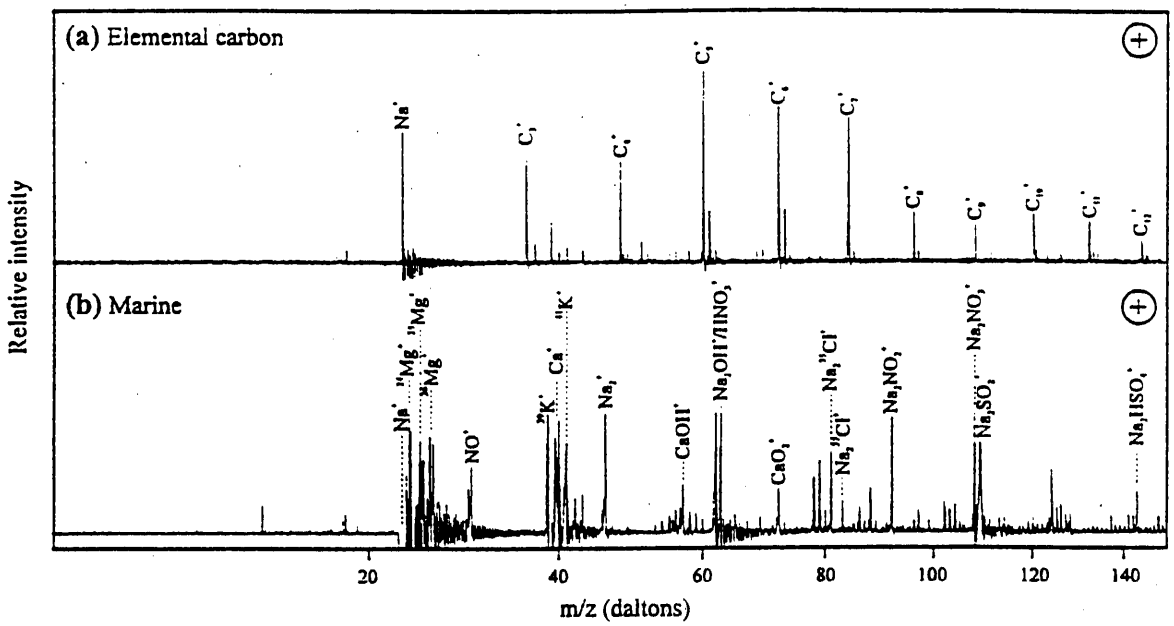


Figure 2: Laser desorption/ionization positive ion mass spectra of single ambient particles. (a) Elemental carbon particle mass spectrum. (b) Marine particle mass spectrum.

Shown in Figure 1c is an example spectrum of the inorganic oxide particle category, which commonly fall in the ~1.5-4.5 μm size range. Species associated with this particle type include metals and related oxides; frequently observed peaks are: Na^+, Mg^+, Al^+, Si^+, K^+, Ca^+, Ti^+ and Fe^+. Based on both particle composition and size, the source of this particle class is thought to be dust or soil which has been suspended in the atmosphere by wind.

A sample spectrum of the elemental carbon particle type is displayed in Figure 2a. This particle class is most commonly found in the size range from ~0.8-3.0 μm in diameter. This type of particle is distinguishable from the simple organic particles by the presence of carbon peaks extending out past C_{12}^+ without any hydrogen-attached peaks. Combustion of oil products and wood burning are thought to be the source of these specific types of particles. During this sampling period there was not a large amount of this type of particle detected.

Finally, Figure 2b shows a representative spectrum of a marine particle. These particles are typically slightly larger than the inorganic oxide particles, ranging from ~1.5-4.0 μm in diameter. Besides having components which are found in sea water, such as Na^+, Mg^+, K^+ and Ca^+, the presence of chlorine is also seen in complexes such as $NaCl^+$ and Na_2Cl^+.[22] In addition to these species, marine particles often, but not always, exhibit peaks due to sulfate and nitrate in the original particle. Figure 2b shows several of the sulfate and nitrate peaks which are sometimes observed: NO^+, HNO_3^+, $Na_2NO_2^+$, $Na_2NO_3^+$, $Na_2SO_2^+$ and $Na_2HSO_4^+$. These particles are suspected to be caused by small air

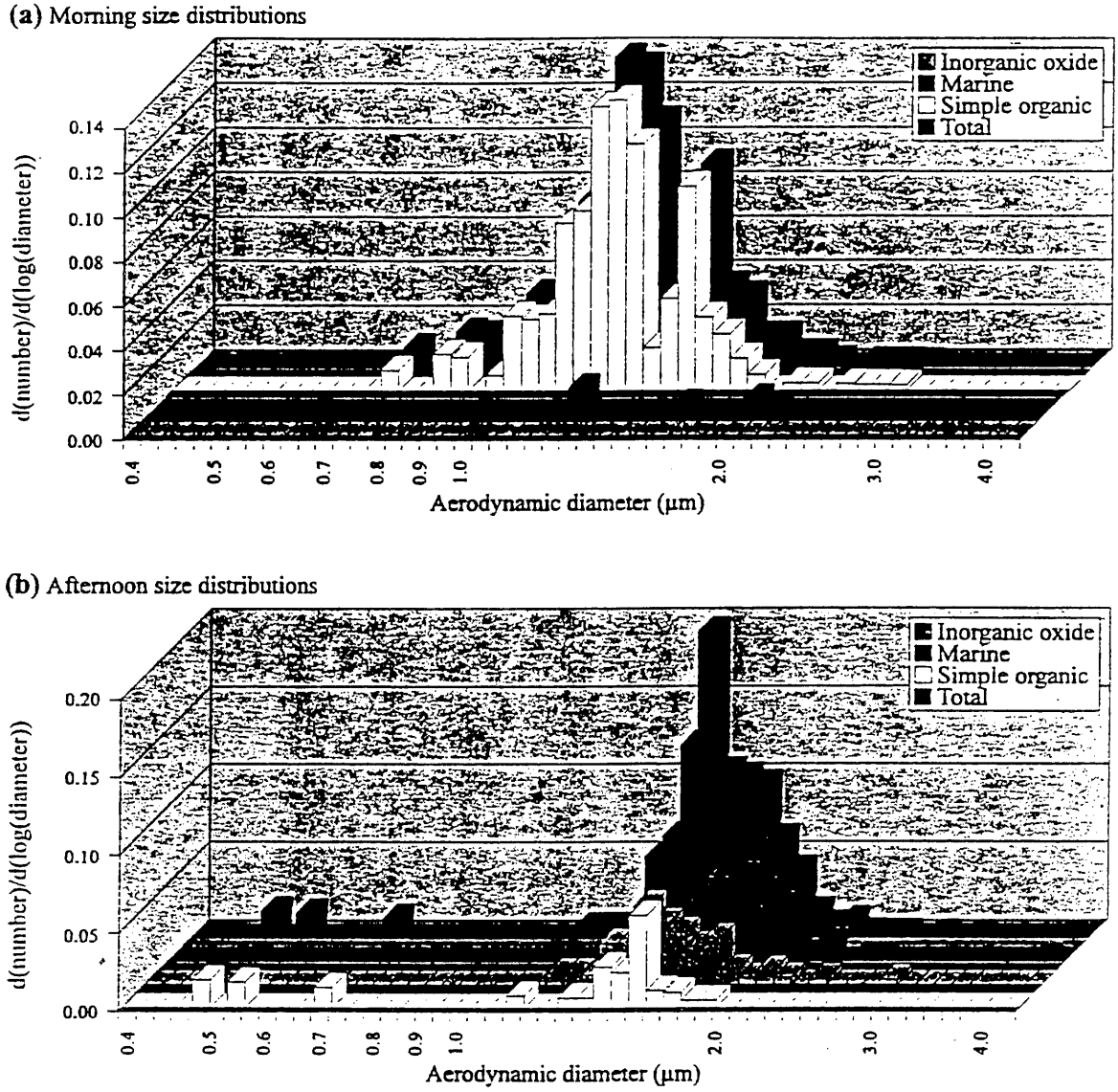


Figure 3: Compositionally-resolved particle size distribution. (a) Morning sample. (b) Afternoon sample from the same day.

bubbles bursting on the ocean surface which results in suspended particles of ocean water. These particles are likely dried shortly after introduction into the atmosphere depending on the ambient relative humidity and temperature. The presence of sulfates and nitrates in some of the marine particles is potentially the result of heterogeneous reactions with gas phase oxides of sulfur and nitrogen, occurring as the particle passes through the Los Angeles air basin located about 60 km west of Riverside.

Because the corresponding size of each particle is measured along with the chemical composition, size distributions of chemically specific classes may be plotted. Two examples of this are shown in Figure 3 for both morning (3a) and afternoon (3b)

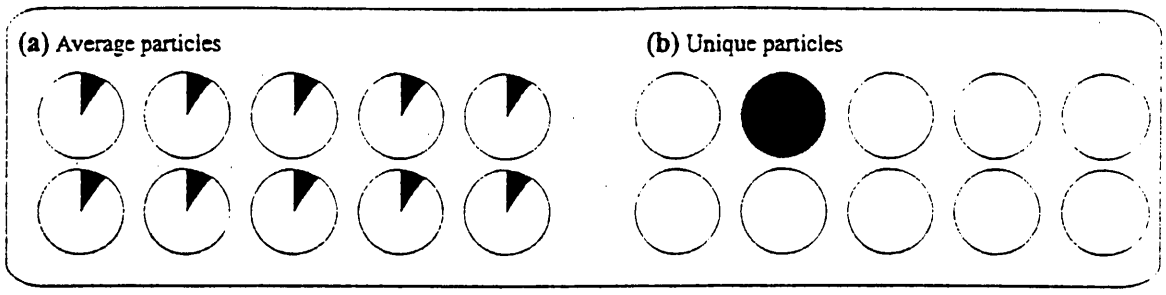


Figure 4: Possible scenarios for aerosol sample which is 10% compound X, by mass. Each circle represents a compositional pie chart for a single particle. Black shading indicates percentage of compound X; white area indicates other compounds. (a) Average particle case. (b) Unique particle case.

sampling periods. The purpose of these plots is to demonstrate that significant chemical differences occur over a relatively short time window with only a minor change in the total size distribution. This figure is not intended to demonstrate the size range of the ATOFMS instrumentation. During morning sampling, the total size distribution ranges from 0.7-2.6 μm with two discrete modes centered at 1.1 μm and 1.7 μm. In the afternoon, the full range of total particles is somewhat broader, extending from 0.5-4.0 μm in diameter. The mode centered at 1.1 μm has disappeared while the mode at 1.7 μm has approximately doubled in magnitude. Though these shifts in the size distribution are measurable, the changes are relatively minor—basically a shift in the primary mode from 1.1 μm to 1.7 μm. However, when the corresponding chemical compositions of these particles is also measured, significant changes are immediately obvious. In the morning sampling period, the vast majority of all particles sampled are of the simple organic type. In contrast, the afternoon aerosol sample is composed of approximately equal amounts of simple organic, marine and inorganic oxide particles.

Real-time data measurements of this nature— providing both size and chemical composition of single particles—can provide more complete information for epidemiological studies. This, in turn, may allow for the determination of higher correlation between chemically specific particle types and increases in both premature death and sickness than is currently available with present aerosol sampling data.

Discussion

Until the epidemiologist is provided with more thorough data than is presently available, the impact of chemically unique particle types on human health cannot be determined. Even provided with bulk chemical composition of the aerosol sample, such studies must still make an assumption of a chemically "average" particle rather than study the effects of chemically specific particles. Reconsider the case in which an aerosol sample is found to contain 10%, by mass, toxic compound X (expressed graphically in Figure 4). Standard methods cannot determine what the original aerosol sample was like. Figure 4 demonstrates the two extreme possibilities of the chemical breakdown of the

Table I: Size modes and some metal constituents

Compound	Accumulation mode	Coarse mode
Iron (Fe)	Present	Present
Lead (Pb)	Present	Present
Titanium (Ti)	Not present	Present
Vanadium (V)	Present	Not present

sample. In the first case (Figure 4a), the particles are assumed to be chemically "average" or identical. As a result, each particle is 10%, by mass, compound X. In contrast (Figure 4b), particles are shown to be unique with one in ten particles composed wholly of compound X. Though the true situation may actually be between these two extremes, only a single particle method, such as ATOFMS, can determine the single particle breakdown of an aerosol sample. A similar situation has been presented for laser microprobe mass spectrometry (LMMS).[23] In this study, the focus is to determine how quartz is distributed in coal mine dust samples on a single particle basis. Both ATOFMS and LMMS are single particle mass spectral methods. However, ATOFMS offers the advantage of characterizing particles in real-time while LMMS is an off-line method.

This situation is exemplified, for a real application, by the data presented in Figure 3. By measuring only the size distribution, it could not be determined that the aerosol sampled in the morning was chemically different from the afternoon sample. By performing chemical analysis on the bulk aerosol, it could be concluded that the chemical composition changed between morning and afternoon samples. However, it could not be determined that there are three chemically distinct particle types in the afternoon sample, only a single particle method can determine this. Data based on chemically distinct particle categories is the type of information our research group is striving to make more readily available.

While inorganic oxide particles (or any other particle class discussed in this paper) may not pose major threats on human health, they are presented as a demonstration of the single particle measurement capabilities of ATOFMS. More detailed chemical classifications will probably identify at hundreds of particle categories, which will then allow the epidemiologist to search for both synergistic and antagonistic effects of various particle types when related to human health.

Table I is presented as a preliminary example of the more detailed information which may be derived from single particle analysis. While iron and lead are found to be present in both accumulation and coarse mode particles, titanium and vanadium are evident only in specific size ranges and associated with certain compounds. Titanium is present in coarse mode particles and seems to be mainly associated with the inorganic oxide particle type. In comparison, vanadium is found in the accumulation mode in the inorganic/organic particle class and likely caused by combustion. As more detailed mass spectral analysis is performed, particle sources may be identified with more specificity and more detailed epidemiological studies may be performed.

Conclusions

Aerosol time-of-flight mass spectrometry is capable of real-time aerosol analysis—measuring both the size and composition of single particles. Particles can be separated into chemically distinct classes by mass spectral analysis. Because size and composition are measured for each particle, size distributions of chemically unique particle types may be plotted to provide an additional level of information which is currently unavailable through more standard sampling methods. Finally, significant chemical changes can occur within a short time period without large changes in the total particle size distribution.

Recommendations

Immediate objectives should involve the continued development and refinement of single particle methods. Specifically, two major improvements would be of significant benefit. First, a field portable, single particle instrument would allow for sampling at remote sites under a variety of atmospheric, meteorological and environmental situations. This will allow for a more geographically broad and complete data set. Second, more thorough chemical characterization of unique particle types will provide the necessary information for epidemiological studies to potentially expand into new areas.

Both of these issues are currently being addressed in our laboratory. A field portable ATOFMS system has been designed and is in the final stages of assembly and testing. Likewise, progress is also being made regarding computer automated mass spectral analysis and should be completed shortly after the portable ATOFMS system is ready for operation.

Acknowledgments

This work was supported by funding from the University of California/Los Alamos National Laboratory (Grant UC-94-5-A-218) and the National Science Foundation (Grant CHE-9457680). Thanks also goes to coworkers who provided technical assistance and advice throughout this work: Tas Dienes, David P. Fergenson, Eric E. Gard, Don-Yuan Liu, Bradley D. Morrical, Kimberly Salt and Philip J. Silva.

References

(1) Friedlander, S. K.; Lippman, M.: Revisiting the Particulate Ambient Air Quality Standard. Environ. Sci. Technol. 28 (3): 148A-150A (1994).

(2) Dockery, D. W.; Pope, C. A., III: Acute Respiratory Effects of Particulate Air Pollution. Ann. Rev. Public Health. 15 (1): 107-132 (1994).

(3) Dockery, D.W.; Pope, C.A., III; Xu, X.; et al.: An Association between Air Pollution and Mortality in Six U. S. Cities. New Engl. J. Med. 329 (24): 1753-1759 (1993).

(4) Schwartz, J.: Air Pollution and the Duration of Acute Respiratory Symptoms. Arch. Environ. Health 47 (2): 116-122 (1992).

(5) Pope, C.A., III: Respiratory Hospital Admissions Associated with PM10 pollution in Utah. Arch. Environ. Health 46 (2): 90-97 (1991).

(6) Pope, C. A., III; Thun, M. J.; Namboodiri, M. M.; et al.: Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U. S. Adults. Am. J. Respir. Crit. Care Med. 151 (3): 669-674 (1995).

(7) Neubauer, K. R.; Johnston, M. V.; Wexler, A. S.: Chromium Speciation in Aerosols by Rapid Single-Particle Mass Spectrometry. Int. J. Mass Spectrom. Ion Processes

(8) Johnston, M. V.; Wexler, A. S.: MS of Individual Aerosol Particles. Anal. Chem. 67 (23): 721A-726A (1995).

(9) Murphy, D. M.; Thomson, D. S.: Laser Ionization Mass Spectrometry of Single Aerosol Particles. Aerosol Sci. Technol. 22 (3): 237-249 (1995).

(10) Hinz, K.-P.; Kaufmann, R.; Spengler, B.: Laser-Induced Mass Analysis of Single Particles in the Airborne State. Anal. Chem. 66 (13): 2071-2076 (1994).

(11) Reents, W. D., Jr.; Downey, S. W.; Emerson, A. B.; et al.: Single Particle Characterization by Time-of-Flight Mass Spectrometry. Aerosol Sci. Technol. 23 (3) 263-270 (1995).

(12) Kievit O.; Marijnissen, J. C. M.; Verjeijen, P. J. T.; et al.: On-Line Measurement of Particle Size and Composition. J. Aerosol Sci. 23 (Suppl. 1): S301-S304 (1992).

(13) Yang, M.; Dale; J. M.; Whitten, W. B; et al.: Laser Desorption Tandem Mass Spectrometry of Individual Microparticles in an Ion Trap Mass Spectrometry. Anal. Chem. 67 (23): 4330-4334 (1995).

(14) Nordmeyer, T.; Prather, K. A.: Real-Time Measurement Capabilities Using Aerosol Time-of-Flight Mass Spectrometry. Anal. Chem. 66 (20): 3540-3542 (1994).

(15) Salt, K.; Noble, C. A.; Prather, K. A.: Aerodynamic Particle Sizing versus Light Scattering Intensity Measurement as Methods for Real-Time Particle Sizing Coupled with Time-of-Flight Mass Spectrometry. Anal. Chem. 68 (1): 230-234 (1996).

(16) Noble, C. A.; Prather, K. A.: Real-Time Measurement of Correlated Size and Composition Profiles of Individual Atmospheric Aerosol Particles. Environ. Sci. Technol. accepted for publication.

(17) Lehtimaki, M.; Willeke, K.: Measurement Methods. In: Aerosol Measurement: Principles, Techniques, and Applications, pp. 112-129, K. Willeke; P. A. Baron, Eds. Van Nostrand Reinhold, New York (1993).

(18) Hinds W. C.: Measurement of Concentration. In: Aerosol Technology, pp. 187-210, John Wiley and Sons, New York (1982).

(19) Dahneke, B.: Aerosol Beam Spectrometry. Nat. Phys. Sci. 244 (134) 54-55 (1973).

(20) Dahneke, B.: Aerosol Beams. In: Recent Developments in Aerosol Science., pp. 187-223, D. T. Shaw, Ed. John Wiley and Sons, New York (1978).

(21) Cotter, R. J.: Time-of-Flight Mass Spectrometry for the Structural Analysis of Biological Molecules. Anal. Chem. 64 (21): 1027A-1039A (1992).

(22) Bruynseels, F.; Storms, H.; Tavares, T.; et al.: Characterization of Individual Particle Types in Coastal Air by Laser Microprobe Mass Analysis. Int. J. Environ. Anal. Chem. 23 (1-2): 1-14 (1985).

(23) Tourmann, J. L.; Kaufmann, R.: Laser Microprobe Mass Spectrometry (LAMMS) of Coal Mine Dusts: Single Particle Analysis and Toxicity Correlation. Int. J. Environ. Anal. Chem. 52 (1-4): 215-227 (1993).

Particulate Matter and Asthma: A Quantitative Assessment of the Current Evidence

Bart D. Ostro, Michael J. Lipsett, and Rupali Das
Air Pollution Epidemiology Unit
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

ABSTRACT

Numerous reports document significant world-wide increases in asthma morbidity and mortality from the late 1970s to the early 1990s. Various social and environmental factors, including exposure to indoor and outdoor pollutants and allergens, have been postulated as partial explanations of increasing asthma trends. Although air pollution concentrations have not generally increased over this period, other factors, including increases in poverty and decreases in regular medical care, may render individuals more susceptible to effects from exposures. There is a substantial literature linking exposure to several gaseous air pollutants with respiratory effects in asthmatics. Since the chemical composition and size distribution of airborne particles vary markedly with time and location, the impact of these heterogeneous mixtures on asthmatics is difficult to ascertain in controlled exposure studies. Epidemiologic studies, however, have repeatedly demonstrated associations of particulate matter with exacerbations of asthma in ecological time-series analyses of emergency room visits and hospital admissions, as well as in panel studies examining associations with peak flow, medication use, and symptoms. In this paper we briefly review asthma pathophysiology and potential pathways through which inhaled particles may affect the respiratory status of asthmatics. Next, we review advantages and disadvantages of studying asthmatics in epidemiologic investigations of air pollution. Finally, we summarize the quantitative results from epidemiologic studies linking ambient particulate matter (PM) to several measures of asthma exacerbations. Our analysis indicates that mean levels of PM occurring in urban areas of North America and Europe may be associated with increases of 2 to 5 percent for hospital admissions for asthma, from 5 to 10 percent for emergency room visits, and up to 60 percent for asthmatic symptoms.

key words: asthma, particulate matter, PM10, sulfates, epidemiology, peak flow, hospital admissions, emergency room visits

I. Introduction

Asthma is a chronic respiratory condition characterized by airway inflammation and intermittent episodes of bronchospasm that can be provoked by a variety of stimuli, including air pollution. Numerous reports demonstrate marked increases in asthma prevalence, morbidity and mortality beginning in the late 1970s. [1] While some fraction of the increase is probably attributable to changes in coding and in physicians' diagnostic labeling of asthma versus other respiratory illnesses, these factors cannot explain the entire phenomenon.[2] Though estimates of asthma prevalence vary depending on the clinical definition used, this condition has been recently estimated to affect 12.4 million Americans, including 4.2 million children and adolescents.[3] Health-care costs related to asthma were estimated to amount to $6.2 billion in the U.S. in 1990 - - approximately one percent of all health-care expenditures.[1]

The fundamental pathology in asthma is chronic airway inflammation, which is associated with hyperresponsiveness, episodic airflow limitation and respiratory symptoms, including cough, wheeze, chest tightness, excess phlegm production, and dyspnea. Hyperresponsiveness refers to an enhanced tendency of the airways to constrict in response to a variety of chemical and physical stimuli, including respiratory irritants. Airway hyperresponsiveness with its attendant symptoms, and the major clinical impact of asthma make the collection of individuals with this condition an important sentinel subpopulation to study in relation to the health effects of air pollution.

Effects of the gaseous pollutants ozone, nitrogen dioxide, and sulfur dioxide on asthmatics have been extensively studied in controlled exposure settings. Although this experimental methodology has some advantages over epidemiologic studies in assessing acute exposures to pollutants, the complexity of real-world exposures to PM limits the utility of this investigatory tool, with the principal exception of studies of sulfuric acid particles. Thus, most recent reports of associations between PM exposures and exacerbations of asthma have been based on observational epidemiological studies, principally time-series analyses. In this paper, we provide a quantitative summary of these recent investigations, after reviewing briefly how asthma pathophysiology may predispose individuals with this condition to PM-related effects.

II. Asthma and Inflammation

When compared with normal subjects, bronchial biopsies even from subjects with mild asthma have consistently revealed disruption of the airway epithelium, deposition of collagen, edema and infiltration of the underlying tissue with inflammatory cells (eosinophils, lymphocytes and mast cells), and smooth muscle cells that are increased in number and size.[4-6] Results of bronchoalveolar (BAL) studies suggest an association between the extent of epithelial sloughing and airway hyperresponsiveness.[4]

The mechanisms underlying the induction of the chronic inflammatory state are partially understood at best. Epithelial damage is most likely the end-result of an intricate, multistep process in which external stimuli (which include exposure to aeroallergens, viruses and other microbial pathogens, and some respiratory irritants) repeatedly initiate an inflammatory cascade. The inflammation may have an allergic basis or may result from tissue damage, which itself may be amplified by the

inflammatory process. Activated cells migrating to an inflammatory focus may cause damage through the release of their contents. For example, major basic protein and eosinophil cationic protein (both released by activated eosinophils) may cause sloughing of epithelial cells, potentially facilitating access of bronchoconstricting agents to irritant nerves and smooth muscle in the underlying tissue.

Inflammation is a stereotyped response to injury, and in most situations undergoes resolution. For unknown reasons, resolution of inflammation of the asthmatic airway is incomplete, resulting in chronic alterations characteristic of this disease, such as physical disruption of the epithelium, an increase in the number of mucus-secreting cells, and functional changes, such as increased contractile responsiveness of airway smooth muscle. In addition to producing a less effective barrier against environmental agents, epithelial disruption may result in the loss of substances normally produced by the epithelium, such as neutral endopeptidase-1, an enzyme which breaks down endogenous bronchoconstrictors (e.g., substance P). Additionally, the irritant nerves of the nonadrenergic, noncholinergic system that produce substance P may be increased in asthmatics.[7]

III. Exacerbations of Asthma

Worsening of pre-existing asthma may involve augmentation of ongoing inflammation or transient episodes of bronchoconstriction (and possibly symptoms) that does not involve additional inflammation. Exposure to aeroallergens to which an asthmatic is sensitized may result in release of pro-inflammatory mediators from airway-associated mast cells (see below). Viral respiratory infections are also associated with inflammation and prolonged airway hyperresponsiveness.[8] Prospective studies have suggested that exacerbations of asthma are associated with respiratory virus infection in 20-50% of cases.[9,10] Many respiratory viruses, notably influenza and respiratory syncytial virus, cause sloughing of the airway epithelium, either through a direct toxic effect or through activation of an inflammatory response such as that outlined above.[11, 12] A variety of chemical and physical stimuli can trigger bronchoconstriction and airflow limitation in asthmatics, without inducing concomitant inflammation and increased airway hyperresponsiveness. These responses tend to be short-lived. Examples include exercise or voluntary hyperventilation, particularly in cold air at low relative humidity, which tends to cool and dry the airway mucosa, or exposure to the pharmacological spasmogen methacholine, which directly constricts airway smooth muscle.

The time course of asthmatic responses to environmental exposures has been most well characterized with respect to aeroallergens. Exposure to sufficient quantities of an aeroallergen to which an asthmatic has been sensitized may result in an immediate or early response (presumably due to the release of histamine and other bronchoconstricting agents in mast cells), which reaches a maximum within about a half-hour and resolves within one to three hours after the inhalation. About 50% of individuals with allergic asthma also experience a delayed or late asthmatic response (LAR), which is manifested by airway narrowing that persists or recurs after three to four hours, attaining maximum intensity within eight to twelve hours, and which may not resolve spontaneously even within 24 hours. The LAR is associated with both airway hyperresponsiveness and with

an influx of activated inflammatory cells into the airways.[13, 14] Many individuals experience dual reactions, with both early and late responses.

Although clearly not directly analogous to allergy-mediated responses, exposure to air pollutants may affect asthma exacerbations through a direct irritant effect, with transient bronchoconstriction, or through more indirect pathways involving induction of inflammation and increased airway hyperresponsiveness, or both direct and indirect mechanisms. For example, sulfur dioxide inhalation elicits an immediate response in many asthmatics, mediated in part by reflex bronchoconstriction. In controlled exposure settings, such events tend to resolve within minutes to hours (though some susceptible individuals have required rescue bronchodilator administration to relieve sulfur-dioxide induced symptoms).[15] Ozone exposure results in a longer time course of response, and can involve induction of airway inflammation and hyperresponsiveness.[16, 17] Effects of particulate air pollution on asthma may be either (or both) immediate and prolonged -- the latter would be more likely to be detected epidemiologically as a lagged association.

IV. Potential Role of Particles in Asthma Exacerbations

Particulate matter may exacerbate asthma through several potential mechanisms, which may not be mutually exclusive: 1) causing reflex bronchoconstriction via a nonspecific irritant effect; 2) causing direct toxicity to the airway epithelium and resident immune cells, augmenting preexisting inflammation and airway hyperresponsiveness; 3) stimulating an inflammatory immune response, either because the particles themselves are allergenic (e.g., fungal spores or latex particles) or by permitting access of other allergens to the underlying tissue.[18]

Widdecombe et al. reported that bronchoconstriction caused by inhalation of charcoal dust particulates could be blocked by administration of atropine, indicating that this response is mediated by a parasympathetic nervous system reflex.[19] Acidic aerosols may also exert nonspecific irritant effects on symptoms and lung function, either directly or via release of mediators during acid inhalation. Although studies have yielded conflicting results, some asthmatics may be especially sensitive to the effects of inhaled sulfuric acid, responding with immediate small decreases in airway conductance and small, transient decrements in forced expiratory flows.[20-23] Large acid droplets (>10 μm) appear to worsen upper airway symptoms in both normal and asthmatic subjects.[24, 25] Acid particles in the submicrometer range may have a deleterious effect on pulmonary function in some asthmatics, though results from different laboratories are not consistent.[20-25]

Particles deposited in the lower airways may cause injury, inflammation and possibly hyperresponsiveness either by themselves or via reactive substances transported on their surfaces. Though this evidence is indirect and speculative at this juncture, such effects could theoretically result in more prolonged deterioration of asthma in susceptible individuals. In nonasthmatic human subjects and in rabbits, acute exposure to sulfuric acid has been reported to be associated with increased airway hyperresponsiveness, although this is not clearly related to inflammation.[26, 27] However, several toxicologic studies provide evidence that particles, especially those in the fine and ultrafine modes, cause pulmonary inflammation.[28, 29] Particle composition can influence the extent of inflammatory effects. For example, pulmonary oxidant injury in rats (measured as

inflammatory mediators in BAL fluid and airway responsiveness) was reportedly increased by iron complexed on the surface of fly-ash particles compared to the particles alone.[30] Both animal and human studies also show that exposure to acid particles may also decrease the lung's defenses against environmental agents, e.g., through effects on mucociliary clearance and on the phagocytic capabilities of macrophages.[31, 32] To the extent that many asthmatics have pre-existing difficulty in effective mucociliary clearance resulting from epithelial cell damage and mucous cell proliferation, such effects could also potentially affect their clinical status.

IV. Quantitative Effects of Particulate Matter on Asthma Outcomes

Epidemiologic studies have reported quantitative associations between PM and several adverse health outcomes that reflect exacerbations of asthma, including hospital admissions for total respiratory disease and for asthma alone, emergency room visits, increases in asthma symptoms, and changes in peak flow. These studies are reviewed below, following a discussion of the utility of examining the impacts of air pollution on individuals with asthma.

There are advantages and disadvantages to studying asthmatics in air pollution epidemiology. . First, asthma exacerbations are of great concern from a public health perspective, since they may result in emergency room visits, hospital admissions, and even death. Second, as noted above, the chronic inflammation and airway hyperresponsiveness characteristic of this condition increase the likelihood that asthmatics may respond to ambient air pollution at lower concentrationsthan the general population. Third,in panel studies, where a cohort of individuals is followed over time, advantages include an increased ability to record health outcomes commonly associated with asthma (i.e., shortness of breath and wheeze) in addition to respiratory symptoms that are of more frequent occurrence in panel studies of nonasthmatics (i.e., cough or sore throat). Since the daily prevalence of asthma exacerbation is higher than that of respiratory symptoms in the general population, the power to detect an effect may be enhanced, reducing the sample size needed for a panel studyFinally, asthmatics (or, in the case of asthmatic children, their parents) are often motivated to learn about their asthma and may be more willing to participate in a panel study and provide accurate information over time. The principal disadvantages of studying asthmatics include the complicated use of medications, and the likelihood that some asthmatics may take steps to prevent symptoms. Since some asthmatics use both bronchodilators and anti-inflammatory medications prophylactically, it may be harder to detect an effect from exposure to air pollution. For instance, Peters et al. reported that medication may attenuate the immediate association between sulfates and asthma symptoms.[33] In addition, over time, asthmatics may deduce the factors that trigger their asthma and may undertake avertive behavior to avoid these stimuli. Therefore, they may stay inside more hours or reduce their activity during high air pollution days. For example, data from Ostro et al. indicate that adults with asthma were more likely to alter their behavior to reduce the possible effects of air pollution.[34] As a result, the true impact of air pollution may be underestimated.

Several different measures of particulate matter were used in these studies. Ideally, all results would be converted into PM10 equivalence for ease of comparison.

However, converting from the particle metric used in a given study to PM10 is not a simple task, but depends on three factors. First, one must take into account the correlation between the two pollutants in the study. If sulfates (for example) and PM10 are highly correlated on a daily basis, it is likely that the sulfate metric is a proxy for effects of other PM10 constituents as well. Second, the conversion depends on the ratio of sulfates to PM10 in the study area as well as the area to which the results are being extrapolated. Finally, the conversion depends on the toxicity of sulfates relative to all particles encompassed by PM10.

The analyses described below used either Poisson regression, logistic regression, or ordinary least squares. Once the mean ambient concentration of PM (P) was determined along with its estimated regression coefficient (β) the mean effect was determined as follows: for the Poisson and logistic regression model, the effect at the mean pollution effect was $[\exp(\beta \times P)-1] \times 100$; while for the ordinary least squares model, the mean effect was ($\beta \times P$) divided by the mean of the health outcome (e.g., emergency room visits per day).

A. Hospital Admissions

Recent evidence indicates an association between PM and respiratory hospital admissions (RHA). For example, associations between PM and RHA have been shown using data from the province of Ontario (Canada), Toronto, New York City, Buffalo, Montreal and for two valleys in Utah.[35-39] Based on these findings, we provide estimates for two different outcomes: asthma admissions associated with both acute and chronic exposure.

All of the studies relating hospital admissions to PM reviewed here use time-series regression models that control for meteorologic factors and seasonality. However, the model specification varies in each study. For example, different measures of particles were used (PM10, PM2.5, or sulfates), some included both particles and ozone in the regression specification as simultaneous covariates while others only considered one pollutant at a time, and some used data from only certain seasons. In addition, there were slight differences among the studies in the inclusion criteria for respiratory disease.

Burnett et al. studied the relationship between hospital admissions for respiratory disease and both sulfates and ozone from 1983 through 1988 in the province of Ontario, Canada.[35,36] Air pollution data were obtained from a large network of monitors throughout Ontario. Admissions data were collected from 168 acute-care hospitals in Ontario. After elective admissions were excluded, counts of daily admissions for all ages and for age-specific and disease-specific categories were created. A time-series regression model was used that removed the influences of day-of-week effects, slow-moving serial correlation due to seasonal patterns, and differences among hospitals. Burnett and colleagues estimated the relationships between air pollution and daily deviations in the expected number of admissions to each hospital. Regression models included temperature effects and were specified with ozone and sulfate considered alone and together as explanatory variables. In these models, one-day lags of both ozone and sulfates were associated with respiratory admissions. The sulfate effects were observed in both summer and winter quarters, males and females, and across all age groups. The studies indicates that the mean sulfate concentration (5.3 $\mu g/m^3$) was associated with a

1.4% increase in RHA when both sulfate and ozone (which itself accounted for an additional 4.5% increase in RHA) were included in the model. When only sulfate was included, the mean concentration was associated with a 3.5% increase in RHA.

Thurston et al. provide additional evidence of an association between RHA during summer months and either sulfate or ozone concentrations, or both.[37,38a] In one study, the relationship between daily RHA and air pollution was examined in Buffalo and New York City during summer 1988.[37] This study included unscheduled hospital admissions with a primary respiratory-related diagnosis. Data were pre-filtered to reduce the impacts of long-wave autocorrelation and the analysis also controlled for day-of-week effects. Daily maximum temperature was included in all model specifications. Because of the high correlation between ozone and sulfates, models were run for each pollutant separately. However, the high correlation between these pollutants ($r \approx 0.7$) during the study period suggests that the reported coefficients might also reflect effects of the other pollutant. One-day lags of both sulfates and ozone were associated with RHA and asthma-specific admissions. Specifically, this study reported that the mean concentration of sulfate was associated with increases in hospital admissions for asthma in New York City and Buffalo of 7.3% and 7.0%, respectively. These results do not include ozone in the regression model and therefore probably overestimate the magnitude of the association between sulfates and asthma admissions.

Thurston et al. also reported that the summertime mean concentrations of sulfate in Toronto from 1986 through 1988 were associated with a 5.7% increase in hospital admissions for asthma, with a 13% increase in the summer of 1988 alone.[38a] Again, these results to do not account for the effect of ozone. Additional analysis of the data suggested that when ozone is included as a covariate, the sulfate effect on hospital admissions for asthma in Toronto was 2.3% for 1986 through 1988. These estimates are based on summer-only analyses and the effects of summer versus winter effects of particles and sulfates must be considered. Evidence from Burnett suggests that seasonal effects are relatively similar.[35] Sulfate levels may be lower in the winter, but the population may be more susceptible due to increases in respiratory infections. Therefore, 2.3% may be a reasonable estimate of the annual effects. A additional estimate can be obtained from the results for a single year in the analysis by Thurston et al.[38a] Using a single pollutant model for 1988 indicates that the sulfate contribution to hospital admissions fro asthma was 13%. If there were no independent effect of ozone, this serves as the highest daily effect of particles.

An additional study examined the relationship between PM10 and daily urgent hospital admissions for respiratory illness in Montreal, Canada.[38b] This analysis reported an association between PM10 from May to October and asthma admissions. At the mean PM10 concentration of 30 $\mu g/m^3$, a 6% increase in admissions would be predicted. During this period ozone was not associated with asthma admissions.

Monthly counts of RHA and monthly PM10 concentrations for 1985 through 1989 were analyzed for two Utah valleys, controlling for temperature and autocorrelation.[39] The sample included RHA for individuals of all ages. Ozone concentrations were low during the winter season when RHA and PM10 were elevated, so that, unlike the eastern North American studies, there is little problem with covarying ozone concentrations. The results of this study may provide an upper estimate for quantifying the effects of PM10 on

RHA, since the cold temperatures and low relative humidity of Utah winters also contribute to exacerbation of asthma. In addition, the results of this study indicate the effects of more chronic exposure to PM10 since two months of previous exposure are used as predictor variables. Mean PM10 averaged approximately 55 $\mu g/m^3$ over the year, with distinct peaks during the winter. The results for the two valleys indicated a statistically significant association between monthly RHA and PM10 measured the same month and PM10 measured the prior month. The results imply that the mean concentrations of PM10 in the same and prior months were associated with 16% and 26% increases, respectively in monthly RHA in the two valleys.

Each of the above studies has advantages and disadvantages in attempting to determine the impact of PM10 on asthma. For example, in the study of Utah Valleys, Pope used monthly, not daily, data and therefore would have had greater exposure measurement error. However, it used PM10 as the particle metric, and potential pollutant confounders such as ozone and sulfur dioxide are believed to be very low during Utah winters. Since contemporaneous and one-month lags are used the regression model, the exposure metric represents more of a chronic than an acute measure. Therefore, it is more difficult to compare it to the daily averaging time used in the other papers. The Burnett et al. studies used sulfates, [35,36] not PM10, so it is not clear whether all the particle effects are accounted for. In addition, rather than asthma-specific admissions, all respiratory admissions are used. Regarding the Thurston studies, some examine both PM10 and sulfates, and asthma admissions are used as the health endpoint.[37,38a] However, only summer data are used. In addition, since ozone and sulfates are highly correlated ($r = 0.66$), it is difficult to disentangle the sulfate effects from those of ozone, even if both are included in the same regression model.

Table 1 summarizes the quantitative implications of the studies reviewed above. The Burnett et al. results indicate that mean sulfate is associated with a 1.4% increase in RHA.[35,36] As described earlier, converting the sulfate-specific effects to a PM10 equivalent depends on several factors. Thurston et al. report a correlation of 0.80 between sulfates and PM10 for Toronto, [38a] which is quite high but may not represent all of Ontario. Nevertheless, the sulfate estimates are likely to include some effects of nonsulfate PM10. To the extent that nonsulfate particles may also have some toxicity, the effects of PM10 at the mean concentration may be somewhat higher than the 1.4%. The evidence provided by Thurston et al. indicates that the effects of sulfates on asthma hospital admissions are approximately equal to or greater than the effects of sulfates on nonasthma RHA.[37,38a] For example, in New York City, the mean sulfate effect of was 7.3% for asthma-specific and 3.5% for all respiratory admissions. In Buffalo, the sulfate impacts on asthma and on all respiratory admissions were 7.0% and 8.0%, respectively. Therefore, the effects on asthma may be somewhat higher than the 1.4% estimated for all RHA by Burnett et al. Taken as a whole, these studies appear to indicate that at the mean concentration of PM10 in these study areas, acute exposure to ambient PM may account for a 2 to 3% increase in hospital admissions for asthma.

B. Emergency Room Visits:

The mean effects of PM on emergency room visits (ERV) are summarized in Table 2. Samet et al. analyzed the relationship between ERV and air pollution levels in

Steubenville, Ohio, during the months of March, April, October, and November of 1974 through 1977.[40] Air pollution measures were TSP, SO_2, and NO_2. Daily ERV for individuals of all ages for all causes and for respiratory symptoms alone were regressed separately on daily temperature and the air pollution measures. TSP and SO_2 were statistically significant for both ERV measures in separate regressions, but these pollution measures were highly correlated during the study period. The TSP coefficient for all-cause ERV was selected for use in this analysis. When applied to the mean concentration, it suggests an approximately 7% increase in emergency room visits for all respiratory causes, though this estimate may incorporate effects related to SO_2.

Schwartz et al. provide supporting evidence of a relationship between ERV and PM concentrations.[41] This study examined daily ERV for asthma and daily PM10 concentrations in Seattle during 1987 for people under age 65. The Poisson model adjusted for minimum temperature, season, hospital, day of week, age group, overdispersion and serial correlation. A statistically significant association was reported which appeared robust to specification and seasonality. A relative risk of 1.12 for a 30 $\mu g/m^3$ increase in daily PM10 was reported. At the mean concentration of PM10 (30 $\mu g/m^3$), this would result in a 12% increase in ERV for asthma.

Castellsague et al. also provide evidence of a association between daily ERV for asthma and particulate matter in Barcelona, Spain.[42] This study examined daily emergency room visits for asthma in Barcelona, Spain. A Poisson regression was used that controlled for minimum temperature, relative humidity, month, day of week, and dates of soybean unloading. Separate estimates were provided for winter and summer. The results suggested an association between Black Smoke, a surrogate measure of particulate matter based on light scattering, and ERV for asthma in the summer. At the mean concentration of Black Smoke, a 5.6% increase in asthma-specific ERV was predicted.

An unpublished paper by Murphy et al. examined the association between air pollution and ERV for respiratory illnesses in Montreal.[43] Seasonal and day of week trends, autocorrelation, temperature and humidity were controlled for using time-series regression analysis. The results indicated a statistically significant association between ERV and both ozone and PM10. A10 $\mu g/m^3$ increase in PM10 was associated with a 5.8% increase in ERV for patients aged 2 to 34.

An unpublished paper by Medina et al., reported an association between PM (measured as PM13) and ERV for asthma.[44] Studying hospital records for Paris between 1987 and 1992, a statistically significant relationship was found between ambient PM and pediatric ERV. At the median concentration (the mean was not reported) of PM13 of 46 $\mu g/m^3$, a 100% increase was reported.

C. Exacerbation of Asthma Symptoms

Several studies have related air pollutant concentrations to exacerbations of asthma symptoms in individuals with diagnosed asthma (Table 3).[34,45,46] These studies provide dose-response information that allow for quantitative estimates of the impact of PM on the frequency of elevated asthma symptoms. Two studies were undertaken in Los Angeles and examined the effects of both particles and ozone,[34,45] while the third was undertaken during the winter of 1987-88 in Denver when ozone levels were close to

background.[46] All three studies involved cohorts or panels of asthmatics recording daily respiratory symptoms for a period of at least 90. Other studies have attempted to minimize the potentially confounding effects of asthma medication usage by recruiting subjects who had been told by a physician that they had asthma but who were not currently taking medication.[47,48]

In these panel studies, daily PM levels were examined for correlations with day-to-day fluctuations in asthma symptom frequency, controlling for other factors such as weather, day of the study, and co-pollutants. Whittemore and Korn studied asthmatics (adults and children) living in six different communities in the Los Angeles area.[45] Each subject reported asthma symptoms during one or more 34-week periods between 1972 and 1975. A total of 443 subject-periods of data were obtained (some subjects provided data for more than one period). Using a logistic model with both PM and ozone included, and controlling for asthma attacks on the previous day, temperature, humidity and day of study, a statistically significant association between TSP and asthma was reported. Ozone was also found to be statistically significant. Based on these regression results, the mean concentration of TSP was associated with a 1.2% increase in asthma attacks.

In a pilot study of African-American children with asthma living in Los Angeles, Ostro et al. examined the effects of daily exposures to particles and ozone. A sample of 83 children ages 7 through 12 was recruited and followed for 90 days.[45] Of the sample, 30% rated their asthma as mild, 53% as moderate, and 18% as severe. A multiple logistic model was used to control for the independent effects of temperature, extremes in temperature and daily mold counts, pre-existing respiratory infections, and day of study. The analysis indicated that PM10 had a statistically significant association with daily shortness of breath. The mean concentration of PM10 (55.9 $\mu g/m^3$) corresponded to a 60% increase in asthma symptoms, measured as shortness of breath. After this pilot study, a full epidemiologic study was undertaken using a sample of 135 African-American children living in Los Angeles and Pasadena. Recruiting and analytical techniques generally similar to those employed in the pilot study were used. Preliminary results indicate that the mean PM10 concentration of 49 $\mu g/m^3$ corresponds to a 42% increase in the probability of shortness of breath.

Ostro et al. examined associations among several different air pollutants, including sulfates, PM2.5, and acidic aerosols, and exacerbations of asthma among adults during winter months in Denver.[34] A significant association was found between the probability of moderate or severe shortness of breath and sulfates, after controlling for temperature, day of week, previous-day illness, and use of a gas stove. Ozone levels were very low, near background levels, and did not confound the particle-asthma association. The mean daily proportion of the sample reporting moderate or severe shortness of breath was 6.5%. The study results suggest that at the mean concentration of sulfates (2.11 $\mu g/m^3$) there would be an 11% increase in reported moderate to-severe shortness of breath.

Pope et al. studied 34 fourth and fifth grade children in the Utah Valley who had chronic wheeze or physician-diagnosed asthma, and 21 physician-referred asthmatics receiving medical treatment.[47] A statistically significant association was reported between PM10 and lower respiratory symptoms for the school-based study. At the mean concentration of 46 $\mu g/m^3$, a 68% increase in symptoms was reported. Pope and Dockery

provide additional evidence from a slightly different population that included asthmatics.[48] They studied 32 symptomatic (chronic cough , wheeze, physician-diagnosed asthma) fourth and fifth grade children in Utah not currently taking asthma medication. Among this population, they found that at the average concentration of PM10 of 70 $\mu g/m^3$, there was an increase in reported lower respiratory symptoms of 60%, based on a model that used a five-day moving average of pollution.

Roemer et al. (1993) examined a panel of 73 children in the Netherlands who reported either chronic shortness of breath, cough, or asthma.[49] The regression models controlled for temperature and autocorrelation in the data. A statistically significant association was reported between PM10 and several symptoms, including wheeze. The mean one week average PM10 concentration of approximately 65 $\mu g/m^3$ corresponds to a 27% increase in wheeze.

Romieu et al. studied the effects of PM among a panel of 54 mildly asthmatic children living in Mexico City.[50] Children exposed to high particulate levels showed increases in respiratory symptoms, including cough, phlegm, and difficulty breathing, and decreases in evening peak flow. A 10 $\mu g/m^3$ increase in PM10 was associated with a 4% increase in an index of lower respiratory symptoms.

Forsberg et al. examined the association between air pollution and asthma exacerbations among a panel of 31 asthmatic patients of all ages living in northern Sweden. The researchers further stratified the sample to examine the impacts of the subgroup that ever reported severe shortness of breath (n=28).[51] Among this subgroup, a association was reported between Black Smoke and the probability of incident episodes of severe shortness of breath. The mean concentration of Black Smoke of 55 $\mu g/m^3$ corresponded to an 80% increase in these incident episodes.

The wide range in quantitative results is likely a result of the differences in the severity of the health outcomes analyzed and in the baseline asthma status of the study sample, as well as variability in the pollutant exposures in the different study sites. For example, the studies of Whittemore and Korn in Los Angeles and Ostro et al. in Denver involve relatively severe outcomes: either an asthma attack or a day with moderate or severe shortness of breath.[45,34] However, the Whittemore and Korn study combines children and adults, so the sample is less well characterized, while the Ostro et al. study reported relatively low levels of particles. These two studies generate mean effect estimates of around 9%. Three of the studies utilize relatively mild outcomes (i.e., respiratory symptom) as the endpoint and observe mean effect of 60 to 70%.[46,47,50] Forsberg et al. examined a very severe population (children who had at least one severe shortness of breath episode during the study period) and found a correspondingly higher effect of 80%.[51]

One additional study examines the effects of long-term exposure to fine particles (PM2.5) and PM10 on the severity of symptoms related to asthma.[52] This study used a cohort of Seventh Day Adventists and developed a severity score to determine whether the pre-existing chronic disease was worsened by exposure to pollution. The results suggest that higher long-term exposure to PM10 and PM2.5, the latter estimated from airport visibility, was associated with a worsening in general asthma status. Unfortunately, specific quantitative effects can not be derived from these data.

D. Medication Use

The Pope and Dockery study cited above also provided evidence for a statistically significant association between exposure to PM and increased asthma medication use.[48] This study, examining school children with a history of wheeze, chronic cough or asthma, found that the mean concentration of PM10 was associated with a 63% increase in medication use. The study also reported a 68% increase in medication use at the mean concentration of PM10 among the sample of asthma patients also included in the panel study.

Roemer et al. examined a panel of 73 children in the Netherlands who reported either chronic shortness of breath, cough, or asthma.[49] At the mean PM10 concentration , the average 7-day exposure to PM10 was associated with a 22% increase in bronchodilator use. These results are summarized in Table 4.

E. Peak Flow Changes

Several panel studies have been conducted to examine the association between changes in peak flow and PM among asthmatics (Table 5). Typically, these studies follow a cohort of asthmatics over a period of several months during which the subjects are asked to record three peak flow maneuvers in the morning upon awakening (prior to taking any asthma medication) and/or before retiring for bed in the evening. Analyses of these data usually control for meteorologic and other time-varying parameters factors. Pope et al. studied 34 fourth and fifth grade children in the Utah Valley who had chronic wheeze or physician-diagnosed asthma (12% used asthma medication) and 21 physician-referred asthmatics receiving medical treatment (67% used asthma medication).[47] A statistically significant association was reported between PM10 and evening peak flow for both groups. For the school-based sample, the analysis of peak flow indicated a reduction of 0.066 liters/min per $\mu g/m^3$ of PM10. At the mean level of PM10, this would amount to a 1.2% decline. For the asthma patient sample, the mean level of PM10 was associated with a 0.7% reduction in peak flow. The peak flow effect may be lower in this group because of the potentially confounding effect of asthma medication.

In a subsequent study in Utah, Pope and Dockery studied 33 symptomatic fourth and fifth grade children and 32 symptomatic (chronic cough , wheeze, physician-diagnosed asthma) fourth and fifth grade children not currently taking asthma medication.[48] Among the healthy sample, the results at the mean PM10 concentration corresponded to a 0.9% reduction in peak flow. Among the symptomatic group, a 0.6% reduction in peak flow was observed at the mean concentration of PM10.

As described above, Roemer et al. examined a panel of 73 children in the Netherlands who reported either chronic shortness of breath, cough, or asthma.[49] A statistically significant association was reported between PM10 (same day, one-day lag, or one-week average) and morning peak flow. Specifically, at the mean PM10 concentration (approximately 65 $\mu g/m^3$), a 0.9% decrease in peak flow would be predicted. Hoek and Brunekreef studied 1000 children aged 7 to 11 in the Netherlands,[53] of whom 27 reported physician-diagnosed asthma. Among this subgroup, the analysis indicated a (nonstatistically significant) reduction in peak flow of 1.4% at the mean concentration of PM10.

Preliminary results are available from additional analysis of a follow-up study of Africa-American children with asthma living in Los Angeles.[46] This study recorded daily and evening peak flow for approximately 90 days in the late summer and early fall of 1993. Regression results also suggest that at the mean concentration of PM10 (approximately 55 $\mu g/m^3$), a 1% reduction in peak flow, on average, would result. Among children currently using anti-inflammatory medication, the average reduction at the mean was about 2%.

IV. Conclusion

Air pollution may be a significant contributor to several adverse outcomes associated asthma. Although the mechanisms by which particulate matter may result in exacerbation of asthma are currently unclear, several possibilities may be hypothesized. Epidemiologic studies may be useful in determining the full range of air pollution effects since real-world exposures and a broad spectrum of asthma conditions and behaviors can be included in such studies. The epidemiologic data provide strong evidence for a significant effect of particulate matter, measured as PM10, TSP, sulfate or Black Smoke, on a wide range of outcomes, including hospital admissions, emergency room visits, asthma symptoms, medication use, and lung function.

VI. References

1. CDC (U.S. Centers for Disease Control) Asthma -- United States, 1980-1990. Morbidity and Mortality Weekly Report 41:733-735 (1992).

2. Gergen, P.J.; Weiss, K.B.: The Increasing Problem of Asthma in the United States. Am. Rev. Respir. Dis. 148:823-824 (1992).

3. American Lung Association: Estimated Prevalence & Incidence of Lung Disease by Lung Association Territory. New York, NY (May 1995).

4. Arm, J. P.; Lee, T. H.: The Pathobiology of Bronchial Asthma. Advances In Immunology. 51:323-382 (1992).

5. Boushey, H.A.; Fahy, J.V.: Basic Mechanisms of Asthma. Environmental Health Perspectives. 103(Suppl 6):229-233 (1995).

6. Hogg, J.C.: Bronchiolitis in Asthma and Chronic Obstructive Pulmonary Disease. Clinics In Chest Medicine 14(4):711-740 (1993).

7. Ollerenshaw, S.; Jarvis, D.; Sullivan, C.; et al.: Substance P Immunoreactive Nerves in Airways From Asthmatics and Nonasthmatics. Eur. Resp. J. 4:673-682 (1991).

8. Cheung, D.; Dick, E.C.; Timmers, M.C.; de Klerk, E.P.A.; Spaan, W.J.M.; Sterk P.: Rhinovirus Inhalation Causes Long-Lasting Excessive Airway Narrowing in Response to Methacholine in Asthmatic Subjects In Vivo, Am. J. Respir. Crit. Care. Med. 152:1490-96 1995.

9. Minor, T.E.; Dick, E.C.; Baker, J.W.; et al.: Rhinovirus and Influenza Type A Infections as Precipitants of Asthma. Am. Rev. Respir. Dis. 113:149-153 (1976).

10. Horn, M.E.; Reed, S.E.; Taylor, R.: Role of Viruses and Bacteria in Acute Wheezy Bronchitis in Childhood: A Study of Sputum. Arch. Dis. Child. 54:587-592 (1979).

11. Nadel, J.A.: Cell to Cell Communication: Some Epithelial Metabilic Factors Affecting Airway Smooth Muscle. Am. Rev. Respir. Dis. 138:22-23 (1988).

12. Bardin, P.G.; Johnston, S.L.; Pattemore, P.K.: Viruses as Precipitants of Asthma Symptoms II. Physiology and Mechanisms. Clinical and Experimental Allergy 22:809-822 (1992).

13. O'Byrne, P.M.; Dolovich, J.; Hargreave, F.E,: State of the Art: Late Asthmatic Responses. Am Rev Respir Dis. 136:74-751 (1987).

14. Pin, I.; Freitag, A.P.; O'Byrne, P.M.; et al.: Changes in the Cellular Profile of Induced-Sputum After Allergen-Induced Asthmatic Responses. Am. Rev. Resp. Dis.

15. Balmes, J.R.; Fine, J,M,; Sheppard, D.: Symptomatic Bronchoconstriction After Short-term Inhalation of Sulfur Dioxide. Am. Rev. Respir. Dis. 136:1117-1121 (1987).

16. Devlin, R.B; McDonnell, W.F.; Mann, R.; et al.: Exposure of Humans to Ambient Levels of Ozone for 6.6 hours Causes Cellular and Biochemical Changes in the Lung. Am. J. Respir. Cell.Mol. Biol. 4:72-81 (1991).

17. Selzer, J.; Bigby, B.G.; Stulbarg, M.; et al.: Ozone-Induced Change in Bronchial Reactivity to Methacholine and Airway Inflammation in Humans. J. Appl. Physiol. 60:1321-1326 (1986).

18. Hegele, R.G.; Hayashi, S.; Hogg, J.C.; et al.: Mechanisms of Airway Narrowing and Hyperresponsiveness in Viral Respiratory Tract Infections. Am. J. Respir. Crit. Care. Med. 151:1659-1665 (1995).

19. Widdecombe, J.G.; Kent, D.C.; Nadel, J.A.: Mechanism of Bronchoconstriction During Inhalation of Dust. J. Appl. Physiol. 17:613-616 (1962).

20. Utell, M.J.; Morrow, P.E.; Hyde, R.W.: Airway Reactivity to Sulfate and Sulfuric Acid Aerosols in Normal and Asthmatic Subjects. J. Air Pollution Control Assoc. 34:931-935 (1984).

21. Koenig, J.Q.; Covert, D.S.; Pierson, W.E.: Effects of Inhalation of Acidic Compounds on Pulmonary Function in Allergic Adolescent Subjects. Environmental Health Perspectives. 79:173-178 (1989).

22. Koenig, J.Q.; Covert, D.S.; Larson, T.V.; et al.: The Effect of Duration of Exposure on Sulfuric Acid-Induced Pulmonary Function Changes in Asthmatic Adolescent Subjects: A Dose-Response Study. Toxicology and Industrial Health 8:285-296 (1992).

23. Aris, R.; Christian, D.; Sheppard, D.; Balmes, J.R.: Lack of Bronchoconstrictor Response to Sulfuric Acid Aerosols and Fogs. Am. Rev. Respir. Dis. 143:744-750 (1991).

24. Linn, W.S.; Avol, E.L.; Anderson, K.R.; et al.: Effect of Droplet Size on Respiratory Responses to Inhaled Sulfuric Acid in Normal and Asthmatic Volunteers. American Review of Respiratory Disease 140:161-166 (1989).

25. Hackney, J.D.; Linn, W.S.; Avol, E.L.: Acid Fog:Effects on Respiratory Function and Symptoms in Healthy and Asthmatic Volunteers. Environmental Health Perspectives 79:159-162 (1989).

26. Utell, M.J.; Morrow, P.E.; Hyde, R.W.: Latent Development of Airway Hyperreactivity in Human Subjects After Sulfuric Acid Aerosol Exposure. Journal of Aerosol Science 14:202-205 (1983).

27. El-Fawal, H.A.N.; Schlesinger, R.B.; Nonspecific Airway Hyperreponsiveness Induced by Inhalation Exposure to Sulfuric Acid Aerosol: an In Vitro Assessment. Toxicol Appl Pharmacol 125:70-76 (1994).

28. Warheit, D.B.; Seidel, W.C.; Carakostas, M.C.; et al.: Attenuation of Perfluoropolymer Fume Pulmonary Toxicity: Effects of Filters, Combustion Method and Aerosol Age. Experimental and Molecular Pathology 52:309-329 (1990).

29. Ferin, J.; Oberdorster, G.; Penney, D.P.; et al.: Increased Pulmonary Toxicity of Ultrafine Particles? I. Particle Clearance, Translocation, Morphology. Journal of Aerosol Science 21:381-384 (1990).

30. Tepper, J.S.; Lehmann, J.R.; Winsett, D.W.; et al.: The Role of Surface-Complexed Iron in the Development of Acute Lung Inflammation and Airway Hyperresponsiveness. American Journal of Respiratory and Critical Care.

31. Chen, L.C.; Fine, J.M.; Qu, Q.-S.; et al.: Effects of Fine and Ultrafine Sulfuric Acid Aerosols in Guinea Pigs: Alterations in Alveolar Macrophage Function and Intracellular pH. Toxicology and Applied Pharmacology 113:109-117 (1992).

32. Spektor DM, Yen BM, Lippmann M. Effect of concentration and cumulative eposure of inhaled sulfuric acid on tracheobronchial particle clearance in healthy humans. Environ Health Perspect 1989;79:167-172.

33. Peters A.; Dockery D.W.; Heinrich J.; Wichmann H.E.: Medication use modifies responses to acid aerosols. American Thoracic Society Annual Meeting A360 (1995).

34. Ostro B.D.; Lipsett M.L.; Wiener M.B.; Selner J.C.: Asthmatic response to airborne acid aerosols. Amer. J. Pub. Health. 81:694-702 (1991).

35. Burnett R.T.; Dales R.E.; Raizenne M.E.; et al.: Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. Environ Res 65: 72-194 (1994).

36. Burnett, R.T.; Dales R.E.; Krewski D; et al.: Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am .J. Epidemiol. 142:15-22 (1995).

37. Thurston G.P.; Ito K.; Kinney P.; Lippmann M.: A multi-year study of air pollution and respiratory hospital admissions in three New York State metropolitan areas: Results for 1988 and 1989 summer. J. Exp. Anal .Environ. Epidemiol. 2:429-450 (1992).

38a. Thurston G.D.; Ito K.; Hayes C.G.; et al.: Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: Considerations of the role of acid aerosols. Environ. Res. 65:271-290 (1994).

38b. Delfino R.J.; Becklake M.R.; Hanley J.: The relationship of urgent hospital admissions for respiratory illnesses to photochemical air pollution levels in Montreal. Environ. Res. 67:1-19 (1994).

39. Pope C.A. III. Respiratory hospital admissions associated with PM10 pollution in Utah, Salt Lake and Cache Valleys. Arch. Environ. Health. 46:90-97 (1991).

40. Samet J.M.; Bishop Y.; Speizer F.E.; et al.: The relationship between air pollution and emergency room visits in an industrial community. J. Air. Pollut. Cont. Assoc. 31:236-40 (1981).

41. Schwartz J.; Slater D.; Larson T.; et al.: Particulate air pollution and hospital emergency room visits for asthma in Seattle. Am. Rev. Respir. Dis. 147:826-831 (1993).

42. Castellsague J.; Sunyer J.; Sáez M.; Anto J.M.: Short-term association between air pollution and emergency room visits for asthma in Barcelona. Thorax 50:1051-1056 (1995).

43. Murphy A.M.; Delfino R.J.; Becklake M.R.: Air pollution and emergency room visits for respiratory illnesses in Montreal: A daily time series analysis. American Thoracic Society Annual Meeting. A359 (1995).

44. Medina S.; Quenel P.; Le Tertre A.: et al.: Short term effects of air pollution in Paris Region (1987 - 1992). Presented at the International Society of Environmental Epidemiology, 1995.

45. Whittemore A.;. Korn E.: Asthma and air pollution in the Los Angeles area. Am. J. Pub. Health. 180:687-696 (1980).

46. Ostro B.D.; Lipsett M.J.; Mann J.K.; et al.: Air pollution and asthma exacerbations among African-American children in Los Angeles. Inhal. Toxicol. 7:711-722 (1995).

47. Pope C.A. III; Dockery D.W.; Spengler J.D.; Razienne M.E.: Respiratory health and PM_{10} pollution: A daily time series analysis. Am.Rev. Respir. Dis. 144:688-674 (1991).

48. Pope C.A. III; Dockery D.: Acute health effects of PM10 pollution on symptomatic and asymptomatic children. Am. Rev. Respir. Dis. 145:1123-1128 (1992).

49. Roemer W.; Hoek G.; Brunekreef B.: Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. Am. Rev. Respir. Dis. 147:118-124 (1993).

50. Romieu I.; Meneses F.; Ruiz S.; et al.: Effects of fine particulates on the respiratory health of children with asthma. American Thoracic Society Annual Meeting A361 (1995).

51. Forsberg B.; Stjernberg N.; Falk M.; et al.: Air pollution levels, meteorological conditions and asthma symptoms. Eur. Respir. J. 6:1109-1115 (1993).

52. Abbey D.E.; Ostro B.D.; Fraser G. et al: Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter (PM2.5) and other air pollutants. J.Exp. Anal. Environ. Epidemiol. 5:137-159 (1995).

53. Hoek G.; Brunekreef B.: Effects of low-level air pollution concentrations on respiratory health of Dutch children. Environ. Res. 64:136-150 (1994).

Table 1. Particulate Matter Associations with Respiratory Hospital Admissions, Including Asthma

Study	Pollutant (mean)	Endpoint/ Population	Mean Effect (%)
Burnett et al. [35]	Sulfate (5.3) (& ozone)	Respiratory: Ontario	1.4
Burnett et al. [36]	Sulfate (5.3)	Respiratory: Ontario	3.5
Thurston et al. [37]	Sulfate (9)	Asthma: NYC asthma: Buffalo	7.0 7.3
Thurston et al. [38a]	Sulfate (8) (& ozone)	Asthma: Toronto 1986-1988	2.3
Thurston et al. [38a]	Sulfate (12)	Asthma: Toronto, 1988	13
Delfino et al. [38b]	PM10 (29.6)	Asthma: Montreal summers	6.2
Pope et al. [39]	chronic PM10 (54)	Respiratory: Utah	21

Table 2. Particulate Matter Associations with Emergency Room Visits.

Study	Pollutant (mean)	Endpoint/ Population	Mean Effect (%)
Samet [40]	TSP (156)	All respiratory: Steubenville	7.0
Schwartz et al. [41]	PM10 (30)	Asthma: Age < 65, Seattle	12.0
Castellsague et al.[42]	BS (48)	Asthma: Barcelona summer	5.6
Murphy et al.[43]	PM10	All respiratory: Montreal, ages 2-34	5.8
Medina et al.[44]	PM13 (46)*	Pediatric asthma: Paris	100.0

* median concentration

Table 3. Particulate Matter Associations with Asthma Symptoms.

Study	Pollutant (mean)	Endpoint/ Population	Mean Effect (%)
Whittemore & Korn [45]	TSP (83)	Asthma attacks: Los Angeles basin	6.8
Ostro et al.[46]	Sulfate (2)	Moderate or severe asthma: Denver adults	11.0
Pope & Dockery[48]	PM10 (76)	LRS: symptomatic Utah children	26.0
Pope & Dockery [48]	PM10 (76)	LRS: symptomatic Utah children	58.5
Roemer et al. [49]	PM10 (65)	LRS: Symptomatic Dutch children	27.0
Ostro et al.[46]	PM10 (56)	Shortness of breath: L.A. children	60.0
Romieu et al.[50]	PM10	LRS: Mexican children	67.0
Forsberg et al.[51]	BS (55)	Shortness of breath: Severe Norwegian children	80.0

LRS = Lower respiratory symptoms; BS = Black Smoke

Table 4. Particulate Matter Associations with Asthma Medication.

Study	Pollutant (mean)	Endpoint/ Population	Mean Effect (%)
Pope & Dockery[48]	PM10 (76)	Symptomatic Utah children	63.0
Pope & Dockery[48]	PM10 (76)	Asthma patients in Utah	68.0
Roemer et al.[49]	PM10 (65)	Symptomatic Dutch children	22.0

Table 5. Particulate Matter Effects on Peak Flow Decrements in Asthmatics.

Study	Pollutant (mean)	Population	Mean Effect (%)
Pope et al.[47]	PM10 (76)	Symptomatic Utah children	0.7
Pope and Dockery [48]	PM10 (76)	Symptomatic Utah children	0.6
Roemer et al.[49]	PM10 (45)	Symptomatic Dutch children	0.9
Hoek and Brunekreef [53]	PM10 (45)	Dutch children with asthma	1.4
Ostro et al. (unpublished)	PM10 (47)	Los Angeles children with asthma	1.0-2.0

Hazard Identification and Risk Assessment of Pyrethroids in the Indoor Environment

J. Pauluhn, Institute of Toxicology, Bayer AG, D-42096 Wuppertal, Germany

Address:

Dr. Jürgen Pauluhn
Bayer AG, Institut für Toxikologie, Build. no. 514
D-42096 Wuppertal
GERMANY

Tel.: 0202 368909
Fax: 0202 364589

Hazard Identification and Risk Assessment of Pyrethroids in the Indoor Environment

ABSTRACT

Pyrethroids often have greatly varying activities, depending on the route of administration (oral, dermal, inhalational). Particularly the α-cyano-pyrethroids have additional specific features, for example the upper respiratory tract sensory irritation potential. This mode of action can be quantified by inhalation testing only. Thus quantification of sensory irritation is considered to be one of the most important endpoints for risk assessment of α-cyano-pyrethroids in the indoor environment. Measurements were taken during acute and repeated exposure of rats to evaluate whether this endpoint is threshold concentration-dependent or cumulative. To reproduce exposure scenarios resulting from *worst-case* pest control measures on carpets, the dislodgement of pyrethroid laden dust particles was studied on a small-scale test model. Findings support the conclusion that α-cyano-pyrethroids may be potent sensory irritants. However, concomitant respiratory tract inflammation and ensuing changes in susceptibility - a common finding in chemical sensory irritants - was not found even after repeated high level exposures. Consequently, the activity of α-cyano-pyrethroids in "equitoxic doses" may differ considerably after inhalational and oral administration. The carpet study showed that there was no specific enrichment of pyrethroids in the total dust fraction, even after sustained, extreme mechanical loading (continuous brushing for 18 hours). The lack of correlation between absolute (mg pyrethroid/m^3 air) and relative (mg pyrethroid/kg dust)

concentrations of airborne pyrethroids as well as the low rate of dislodgement of pyrethroids from carpets showed that sedimented house dust is not a suitable matrix for risk assessment of pyrethroids in such an environment and therefore pyrethroid determinations in sedimented house dust (vacuum cleaner bag analyses) are considered a poor indicator for the assessment of potential, inhalation exposure.

INTRODUCTION

Pyrethroids are potent insecticides that act on the nervous system. Their preferred target is the axonal sodium channel (1-3). One notable form of acute *in vivo* exposure is frequently associated with cutaneous paresthesia (3-6). This strong excitatory action on the sensory organs in the skin of vertebrates and the upper respiratory tract is characteristic for synthetic pyrethroids. The cyano pyrethroids evoke more intense neuroexcitatory activities than the non-cyano pyrethroids (3, 7, 8). Facial sensations and irritative symptoms appear to be produced by direct stimulation of peripheral sensory nerve endings rather than by inflammatory mechanisms.

Pyrethroids (permethrin), are commonly used as moth repellents in wool carpets. The favorable properties have promoted the widespread application of pyrethroids in virtually all sectors of pest control. The world-wide tendency is to use pyrethroids for the public health control of vectors. Recent press reports have highlighted the emerging issue of pyrethroid on indoor air quality. In the light of this, doubt has been were raised as to whether indoor-use of pesticides in general and pyrethroids in particular pose health risks to the public. In the context, the public may be subjected to pyrethroids via prolonged skin contact with textiles, including carpets. Exposure is also possible via airborne dust. Because of their often very low vapor pressure,

exposure of adult humans to pyrethroids in the indoor environment is thought to occur via airborne housedust. However, in most instances, the concentration of pyrethroids in indoor air was found to be very low (9, 10). This prompted studies on sedimented house using dust samples collected by vacuum cleaner. Despite the fact that no standard protocol for house dust sampling is as yet available, the contents of pyrethroids in sedimented dust taken from vaccum cleaner bags is used for risk assessment. The major flaw in the vacuum cleaner sampling technique is that it may not necessarily reflect those concentrations likely to occur under actual exposure conditions.

The objective of the this study is to present a bioassay for the quantitative assessment of pyrethroid contaminated carpet-dust with particular attention being paid to subtoxic, i.e., paresthesia-like effects. Additionally, an assessment is also made to establish to what extent dust particles containing pyrethroids can be dislodged from carpets using a dynamic small-scale chamber technology. Due to its greater potency to elicit sensory irritation the α-cyano pyrethroid cyfluthrin was selected for analysis. As previous studies demonstrated that rats are more sensitive than mice (11), the rat was selected as the animal species of choice.

MATERIAL AND METHODS

Test material. Cyfluthrin, 3-[2,2-Dichlorethenyl]-2,2-dimethyl-cyclo-propane-carbonic acid-[cyano-(4-fluoro-3-phenoxyphenyl)methyl]-ester; Cyfluthrin WP (10 % cyfluthrin dust formulation, and Cyfluthrin EW (5 % cyfluthrin liquid formulation). All are proprietary products of BAYER AG, Leverkusen, Germany. Kaolin (Bole white powder) was from Merck,

Darmstadt, Germany. The moth-resistant carpet was from Vorwerk, Germany, 1120 g/m² sheep wool, 150 mg permethrin/kg wool (150 ppm).

Study design. The degree of respiratory tract sensory irritation of the aerosolized active ingredient (a.i.) cyfluthrin was evaluated in acute and subacute exposure on rats. The findings are compared with available inhalation toxicity data from an earlier 13-week inhalation study. In the carpet dust study, a "mothproof" carpet was examined for the amount of permethrin mechanically brushed off. In addition, the ability of the permethrin to migrate from the carpet fibers to the house dust substitute kaolin was assessed (carpet dusted with approximately 3 g kaolin/m^2, examination of rubbed off dust after 1 day or 6 weeks of contact time). The *worst-case* simulation of a pest control measure was determined on a carpet made insect resistant with permethrin as well as cyfluthrin as powder (WP: about 3250 mg dust/m^2 placebo formulation or about 3600 mg dust/m^2) or liquid formulation (EW: application of an aqueous aerosol formulation to achieve 20-40 mg a.i./m^2). The carpet size used throughout the study was 1 m^2.

Animals. Specified, young adult pathogen-free Wistar rats (Hsd Win:WU SPF-Cpb) were supplied by Harlan-Winkelmann (Borchen, Germany). Animals were provided with Altromin® 1324 chow and water *ad libitum*. The light cycle was automatically controlled in the animal holding room to provide 12 hr of fluorescent light and 12 hr of darkness each 24 hr.

Assessment of respiratory tract sensory irritation. Tests with the active ingredient alone were performed on spontaneously breathing, conscious rats using modified nose-only plethysmographs (exposure 45-min to 1 hour) as already published (11-13).

Carpets containing or treated with pyrethroids were tested so as shown in Fig. 1. The carpet (1 x 1 m) was fitted onto a revolving cylinder within the dust generation chamber shown in Fig. 1. The air exchange volume in the chamber was approximately 40 liters (0.5 m^3 air x m^{-2} carpet x h^{-1}). The length of the rotating brush matched the width of the carpet. During the study, the brush and carpet rotated countercurrently. The thus generated dust atmosphere was drawn from the generation chamber using a flow-rate of approximately 8 liters/min via a perforated duct in the top of the chamber thus assuring that the material extrated from the chamber fulfilled the criterion 'airborne'. The temporal stability of the dust atmosphere was monitored continuously using a *real-time* RAM-1 aerosol photometer (MIE, Bedford, MA, USA). As Fig. 2 shows, maximum concentrations occurred after onset of brushing. Analytical air samples were taken throughout exposure. Continuous sampling was devided into two periods, period I during the first two hours, period II: during the remaining 16 hours. Through each of the whole-body bias-flow plethysmographs (volume of ca. 11 liters) a constant air-flow rate of 1.5 liters/min per chamber was maintained. Conditioned room air was used throughout the experiments (relative humidity ca. 45-55% and 23-25 °C). Before feeding the atmosphere into the exposure chambers, samples of the dust atmosphere were taken. For its analytical characterization an in-line combination of Teflon® filter (1) and Florisil® adsorption tube (2) was used allow differentiation of pyrethroid associated to particles and present as vapor. The test atmosphere then passed through four whole-body bias-flow plethysmographs, one male rat/chamber. Exposure and data collection were during the night, i.e. during maximum activity of rats. Data were recorded *on-line* using a PC. Throughout the studies the mass median aerodynamic diameter of dust was 1.5-2 µm (geometric standard deviation ca. 1.5).

Respiratory and behavioral activity during exposure to carpet dust. Measurements of respiratory rate were performed using a Respiration Monitor Model RM-80, total and ambulatory activities were measured and recorded by an Opto-Varimex Mini infrared system (Columbus Instruments, Columbus, Ohio, USA). The ambulatory option allows the automatical differentiation between actual ambulatory movements and stereotypic movements such as scratching, grooming, and digging. Stereotypic movements usually involve a single light beam. The ambulatory option filters out such movements by counting the first interruption, but ignoring further interruptions unless other beams are restored or interrupted in the same time period. During the exposure period of approximately 18 hours (start at approximately 2 p.m.) feed and water was available *ad libitum*. No bedding material was provided. Before exposure to the carpet dust, rats were acclimatized in the chamber for 3 days. During the acclimatization period, all exposure conditions were set so as to duplicate those occurring during the actual exposure period. Thereafter, rats were exposed to room air and to atmospheres from non-dusted and dusted carpets on days 1 and 2, respectively. Respiratory rate, ambulatory and total activity were averaged and recorded over data collection-periods each of 30 minutes.

RESULTS

The concentration of cyfluthrin evoking fifty percent decrease in respiratory rate (RD_{50}) was ≈ 47 mg/m³ air. The respective extrapolated non-irritant threshold concentration (RD_0) obtained by linear extrapolation was 0.2-0.4 mg/m³ air. In a subacute inhalation study rats were repeatedly nose-only exposed to actual concentrations of 0 (air), 0 (vehicle), 0.44, 6 or 47 mg cyfluthrin/m³ air {exposure 6 h/day, 5 days/week for four weeks}. Breathing patterns showed a

concentration-dependent decrease in the respiratory rate after exposure to 6 and 47 mg/m³ air as observed after acute exposure. As summarized in Fig. 3, the repeatedly performed measurements did not indicate any tachyphylaxis or exacerbation of response, i.e., both the acute and the 4-week RD_{50}'s as well as the irritant threshold concentrations were virtually identical. Changes in respiratory rate following single exposure to cyfluthrin containing dust (≈ 6 mg a.i./m³ air or 76 mg WP10%/m³ air) was indistinguishable from rats exposed the same concentration of liquid aerosol (Fig. 3).

The carpet was subjected to continuous brushing for approximately 18 hours to assess whether toxicologically significant concentrations of permethrin-laden dust particles could be rubbed off mechanically in the absence or presence of kaolin as house dust substitute. Data depicted in Fig. 4 demonstrate that the relative concentrations of permethrin in airborne dust corresponded roughly to that of the starting material. The slightly higher relative contents in airborne dust following kaolin administration could have been caused by an additional grinding effect (dusting the carpet with about 3 g kaolin/m^2), since the different resting periods did not change the outcome of test.

Following treatment of carpet with an aqueous (EW) or dry powder formulation (WP), the same series of measurements was performed. Again, the analytical characterization of exposure atmospheres revealed that airborne pyrethroids were solely associated with the dust. As summarized in Fig. 5, the dust concentrations were highest directly after onset of brushing (during approximately the first 2 hours, see also Fig. 2) and were dependent on the intensity of brushing. The ratio of cyfluthrin applied to the carpet in relation to the cumulative mass brushed off the carpet during the 18-hour testing period was used to calculate the dislodgement

factor for each type of test and was compared to the time-weighted average (TWA) of airborne cyfluthrin (Fig. 6).

Pyrethroid-specific neuroexcitatory effects, quantified as change in respiratory rate, total and ambulatory activity, were detected only after high-level treatment during the first phase of exposure to cyfluthrin (Figs. 7, 8), i.e., concentrations temporarily exceeding the RD_0-concentration. Despite of comparable total dust concentrations, rats behaved distinctly differently when exposed to cyfluthrin-laden particles and placebo dust. From Figs. 7 and 8 it can be seen that peak-exposure concentrations (Fig. 2) coincide with hyperactivity and mild decrease in respiratory rate, whereas pyrethroid-free dust did not change the ambulatory activity but increased the respiratory rate. In quantitative terms, changes in ambulatory activity were more pronounced than those of respiratory rate.

DISCUSSION

For the α-cyano-pyrethroid cyfluthrin the RD_{50} is about 47 mg/m^3 air and the acute respiratory tract sensory irritation threshold concentration in the most sensitive species, *viz.* the rat (14), is 0.2-0.4 mg/m^3 air. It would appear, that the NO(A)EL of the subacute inhalation study is dependent on this endpoint (Fig. 3) rather than the systemic toxicity. In a conventional subchronic inhalation study - nose-only exposure of rats, 6 h/day, 5 times a week for 3 months; no information on the relevance of sensory irritation was available when the study was carried out - the NO(A)EL was 0.09 mg/m^3 air and the rats exposed to the next higher concentration (0.71 mg/m^3 air) showed mild effects on body weights (14). The experimental evidence suggests that the respiratory tract sensory irritation threshold concentration appears to be

decisive for the inhalation NO(A)EL's, irrespective of the duration of exposure. The findings gained with the active ingredient (liquid aerosol) have been confirmed by the carpet-dust studies. However, it would appear, that the transient increase in total and ambulatory activity is associated with increased preening activities as a result of upper respiratory tract and mucous membrane sensory irritation.

The agreement of the results of the acute and subacute studies supports the conclusion that cyfluthrin-induced effects are adaptive and are related to reflexively induced, transient effects. This is further substantiated by the histopathological examinations of the respiratory tract performed in the subchronic inhalation studies. There were no findings characteristic of (neurogenic) inflammatory responses or (neurogenic) vasodilatation (values not shown). An additional feature of this portal-of-entry specific sensory effect is that species-specific biotransformational or toxicokinetic processes are not likely to play an important role. Haber's law (effect = concentration x time) does not apply for this type of respiratory tract sensory irritant, since sensory irritation is triggered as a direct result of the concentration rather than of the time-dependent exposure dose. With increasing duration of exposure, after the maximum effect has been achieved, the effect remains constant despite increase of exposure dose.

Taking this into account, the R_fC calculation is based on the results of the 3-month subchronic rat study (nose-only exposure 6 hours/day; 5 x/week; MMAD = 2.5 µm, GSD 1.8; NO(A)EL = 0.09 mg/m^3 air). For the concentration-dependent sensory irritation in the extrathoracic and tracheobronchial airways a relative deposited dose ratio (RDDR) = 1.043 was used (RDDR value taken from 15). Sensory irritation is concentration-dependent, i.e., owing to the inapplicability of Haber's law, no dosimetric adjustment was carried out: $NO(A)EL_{HEC}$ =

$NO(A)EL \times RDDR_{ET+TB} = 0.094$ mg/m^3 air, $R_fC = NO(A)EL_{HEC}/UF = 0.094/10 \approx 9$ µg/m^3 air whereas hypersensitive subpopulations are taken into account by an uncertainty factor (UF) = 10 and the interspecies extrapolation is based on an UF = 1, since a dosimetric/morphometric species adjustment has already taken into consideration through the RDDR. This type of sensory irritation is triggered by peripheral or local, reversible effects, i.e. toxicokinetic species-differences may play a negligible role (approximation: target-organ concentration ≈ exposure concentration). In none of the studies did the performed histopathological investigations reveal any mophological changes indicative of airway inflammation.

All studies carried out to elucidate the relevant mechanism of inhaled cyfluthrin aerosol demonstrate that in the most sensitive species (rat), 0.2-0.4 mg/m^3 air may be considered the irritation threshold concentration, after both single and repeated exposure. If the R_fC is related to the potential human exposure dose (≈ 90 µg/m^3 x 20 m^3/24 h x 1/70 kg = 2.6 µg/kg per day), this α-cyano pyrethroid appears to be more potent via the inhalation route when compared to the dietary intake (acceptable daily intake (ADI) = 20 µg/kg per day) (17). This result is to be expected, since the most sensitive toxicological endpoint, i.e., the reflexively induced respiratory tract sensory irritation, becomes biologically important only when exposure is via inhalation. The inhalation route appears to be the most important for potentially sensory irritant pyrethroids as this is further confirmed by human evidence (7).

It may be summarized, that the present study as well the risk analysis support the worldwide-experience with this class of substances, which uniformly confirms that for passively exposed populations, the indoor use of pyrethroids poses no specific health risk. Furthermore, published

evidence goes as far to suggest (9,10) that in relation to other pesticides potentially present in the indoor environment the magnitude of exposure to pyrethroids is smallest due to their low volatility. This bioassay confirms existing human evidence that improper occupational use may lead to transient paresthesia-like effects (4,5,7,16), i.e., effects associated mainly with the clear warning action of pyrethroids (3), e.g. sensory irritation of the facial skin and upper respiratory tract. Considering the total mass of cyfluthrin applied to the carpet and that brushed off within 18 hours, only a small fraction of the applied pyrethroid can be seen as potentially bioavailable by inhalation. In the indoor environment a concentration of approximately 0.2 mg/m^3 air is considered to be a heavy dust load. To achieve a comparable concentration in this small-scale model, 5.1-9.4 x 10^{-4} % of the amount of pyrethroid applied nominally to the carpet has to be brushed off. This demonstrates that only a very small fraction of the total carpet dust pool is readily available for uptake by inhalation. Therefore, assessment of health hazards in the indoor environment based solely on 'vacuum cleaner' sampling, rather than examination of the actual airborne concentration, including other relevant airborne materials, is prone to tremendous errors and misjudgments.

REFERENCES

1. Aldridge W.N.: An Assessment of The Toxicological Properties of Pyrethroids and Their Neurotoxicity. Critical Reviews in Toxicology 21:89-104 (1990).

2. Ecobichon D.J.: Toxic Effects of Pesticides. In Casarett and Doull's Toxicology. In: The Basic Science of Poisons, 4th ed., M.O.Amdur, J. Doull, C.D.Klaassen, pp. 565-622. Pergamon Press (1991).

3. Vijverberg H.P.M.; van den Bercken J.: Neurotoxicological Effects and the Mode of Action of Pyrethroid Insecticides. Critical Reviews in Toxicology 21:105-126 (1990).

4. Flannigan S.A.; Tucker S.B.: Variation in cutaneous sensation between synthetic pyrethroid insecticides. Contact Dermatitis 13:140-147 (1985).

5. Flannigan S.A.; Tucker S.B., Key M.M.: et al.: Synthetic pyrethroid insecticides: a dermatological evaluation. British J. Indust. Med. 42:363-372 (1985).

6. Tucker S.B.; Flannigan S.A.: Cutaneous effects from occupational exposure to fenvalerate. Arch. Toxicol. 54:195-202 (1983).

7. Moretto A.: Indoor spraying with the pyrethroid insecticide lambda-cyhalothrin: effects on spraymen and inhabitants of sprayed houses. Bull. WHO 69:591-594 (1991).

8. Kolmodin-Hedman B., Swensson Å., Akerblom Å.: Occupational exposure to some synthetic pyrethroids (permethrin and fenvalerate). Arch. Toxicol. 50:27-33 (1982).

9. Immerman F.W.; Schaum J.L.: Non-occupational pesticide exposure study (NOPES), Project Summary, United States Environmental Agency, EPA/600/S3-90/003 April

1990.

10. Whitmore R.W., Immerman F.W., Camann D.E.; et al.: Non-Occupational exposure to pesticides for residents of two U.S.Cities. Arch. Environ. Contam. Toxicol. 26:47-59 (1994).

11. Pauluhn J.: Animal Model for the Quantitative Assessment of α-cyano-pyrethroid induced sensory irritation. The International Toxicologist, Abstract 20-P-21 of the VII International Congress of Toxicology, 7: (1995).

12. Pauluhn J.: Test methods for respiratory sensitisation. In: Use of mechanistic information in risk assessment, H.M. Bolt, B. Hellman and L. Dencker (eds), EUROTOX proceedings, Arch. Toxicol. Suppl. 16: 77-86 (1991).

13. Pauluhn J.; Eben A.: Validation of a non-invasive technique to assess immediate or delayed onset airway hyperreactivity in guinea-pigs. J. Appl. Toxicol. 11:423-431 (1991).

14. WHO Evaluations. Pesticide residues in food - 1987, Sponsored jointly by FAO and WHO, Part II-Toxicology (1994).

15. US-EPA: Interim Methods for Development of Inhalation Reference Concentrations, Review Draft EPA 600-8-90 066A, August 1990.

16. He F., Wang S., Liu L.;et al.: Clinical manifestations and diagnosis of acute pyrethroid poisoning. Arch Toxicol. 63:54-58 (1989).

17. Lu F.C.: A review of the acceptable daily intakes of pesticides assessed by WHO. Regulatory Toxicology and Pharmacology 21: 352-364 (1995).

LEGENDS TO FIGURES

Fig. 1: Small-scale apparatus for evaluation of airborne carpet dust. 1. Rotating brush. 2. Motor for rotation of the carpet fitted to a revolving cyclinder. 3. Carpet (1 m^2). 4. Cover for hermetic sealing of the test chamber. 5. HEPA absolute filter for the air pulled into the chamber (distribution through a perforated entry tube). 6. Air pulled from the chamber through a perforated tube. 7. Ducting system to whole body bias-flow plethysmographs, filter samplers and *real-time* aerosol monitor. All measures in mm.

Fig. 2: *Real-time* aerosol monitoring (RAM-1 *real-time* aerosol photometer) of dislodged carpet dust during the course of 18 hours. Two samples for analytical characterization of atmospheres were taken: (1) continuously during the first 2 hours and (2) continuously during the remaining 16 hours.

Fig. 3: Subacute nose-only exposure of rats to concentrations of aerosolized cyfluthrin: 0 (air), 0 (vehicle), 0.44, 6, or 47 mg /m^3 air (exposure for 6 h/day, 5 days/week for 4 weeks; vehicle: mixture of polyethylene glycol 400 and ethanol). Respiration rate (RR) was evaluated during weeks 2, 3, and 4 in four rats/group simultaneously. Relative changes were calculated on the basis of respective baseline data collected during a 15-min air pre-exposure period. The decrease in respiratory rate as a result of exposure to the vehicle was taken into account for the calculation of the sensory irritant threshold concentration (RD_0). Comparison was made with rats after single acute exposure to cyfluthrin dust (WP10%). Acute exposure was for 45-min to 5.63 mg cyfluthrin/m^3 air. The respective total dust concentration was 76 mg/m^3 air.

Fig. 4: Dislodgement of permethrin from moth-resistant carpet containing 150 mg permethrin/kg wool (150 ppm) by continuous brushing of carpet for 18 hours. To enhance migration of permethrin from the carpet fiber to the house dust substitute (kaolin) the contact time either 1 day or 6 weeks.

Fig. 5: Dislodgement of permethrin containing dust from moth-resistant carpet, and carpets additionally treated with cyfluthrin as aqueous (EW) or powder formulation (WP10%). TSP: total suspended particulate matter recovered by filter analyses.

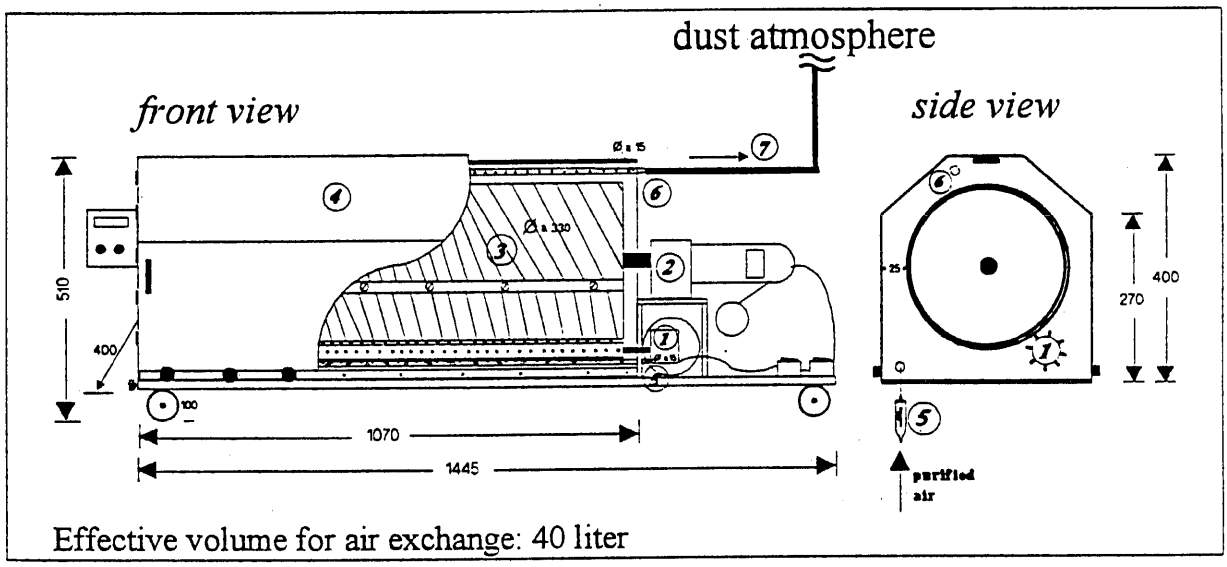
Fig. 6: Association of relative recoveries of cyfluthrin-containing airborne carpet dust dislodged from 1x1 m^2 carpets during a brushing period of 18 hours.

Fig. 7: Mean ambulatory activity of rats (n = 4) in bias-flow plethysmographs during exposure to air (carpet), cyfluthrin-free carpet dust substitute (kaolin), and cyfluthrin-containing dust for about 18 hours. Administration of 3 gram of kaolin powder/m^2 carpet. To compensate for circadian changes in activity data were calculated relative measurements taken from control rats exposed to air only.

Fig. 8: Mean respiratory rate of rats (n = 4) in bias-flow plethysmographs during exposure to air (carpet), cyfluthrin-free carpet dust substitute (kaolin), and cyfluthrin-containing dust for about 18 hours. Administration of 3 gram of kaolin powder/m^2 carpet.

Figure 1

Dislodgement of Carpet Dust



Effective volume for air exchange: 40 liter

Air flow rate: 8 l/min

Figure 2:

Dislodgement of Carpet Dust

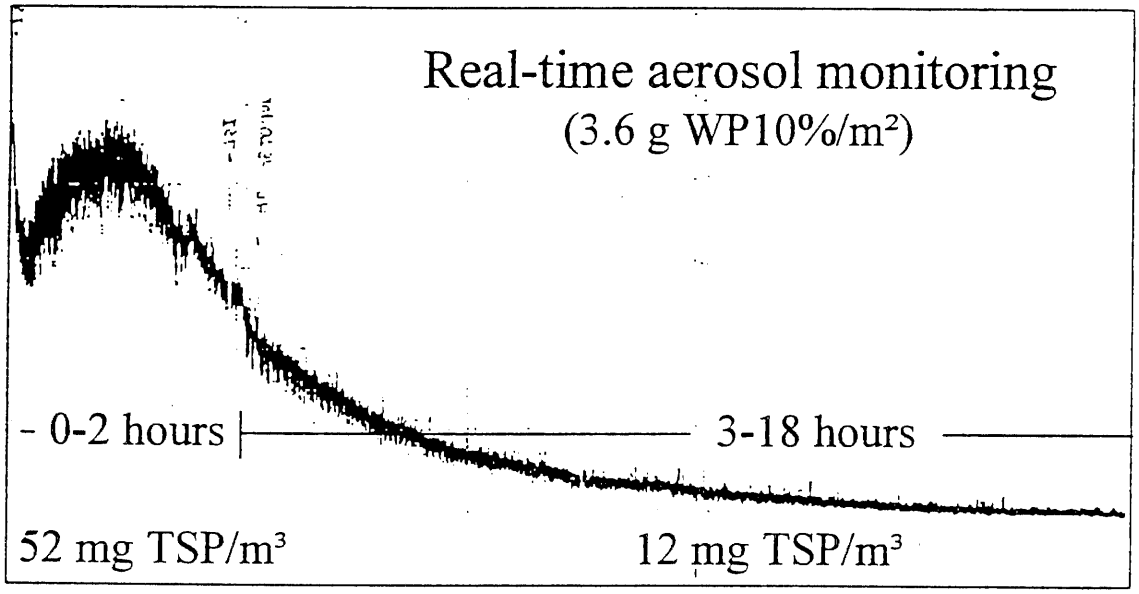
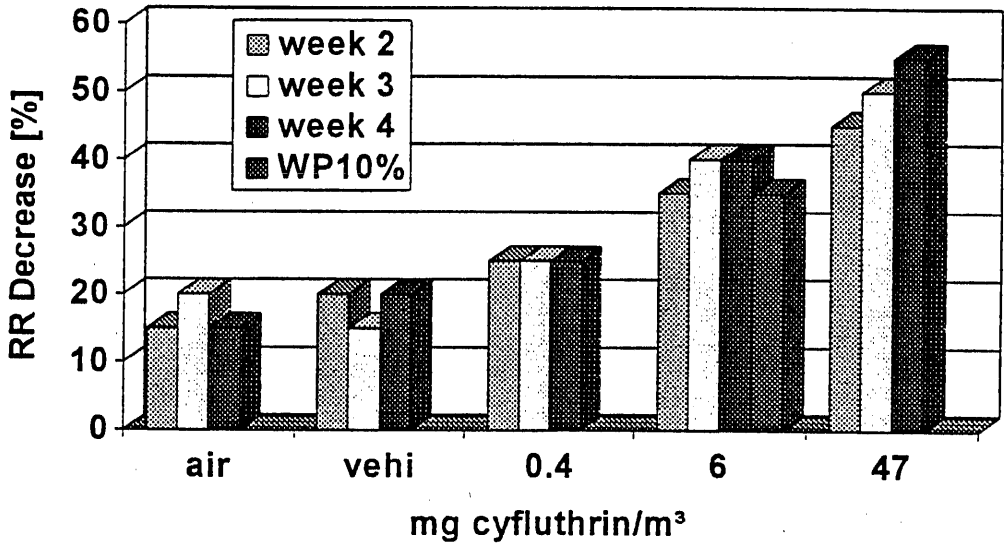


Figure 3:

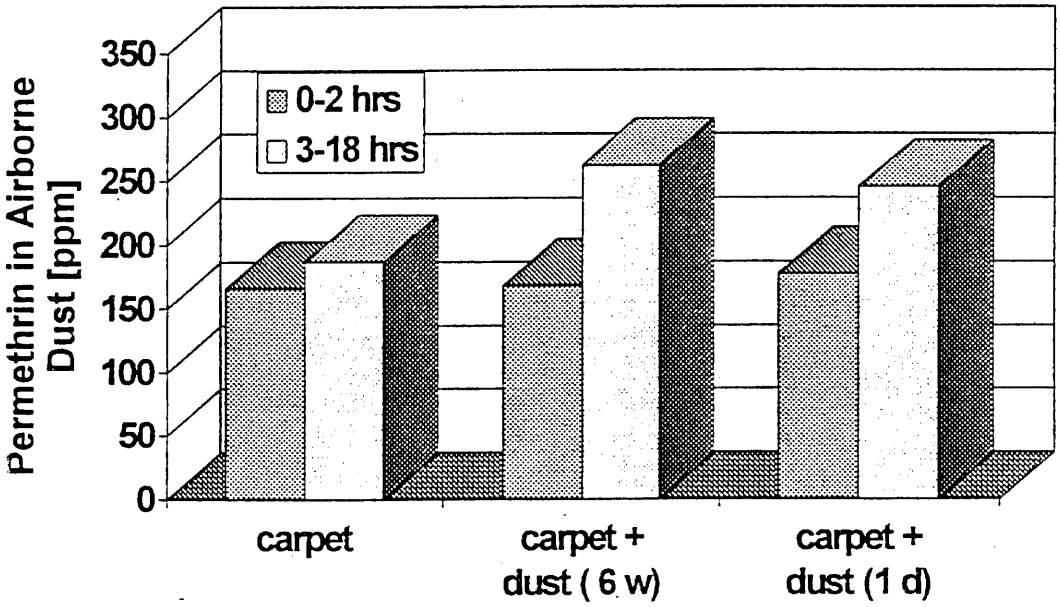
Sensory Irritation in Rats
(Acute or subacute exposure to cyfluthrin)



Exposure: 6 hours/day, 5 times/week for 4 weeks; WP10%: 1 x 1 hour

Figure 4:

Dislodgement of Permethrin from Moth-Resistant Carpets



dust: ca. 3 g kaolin/m²; specification of carpet: 150 ppm

Figure 5:

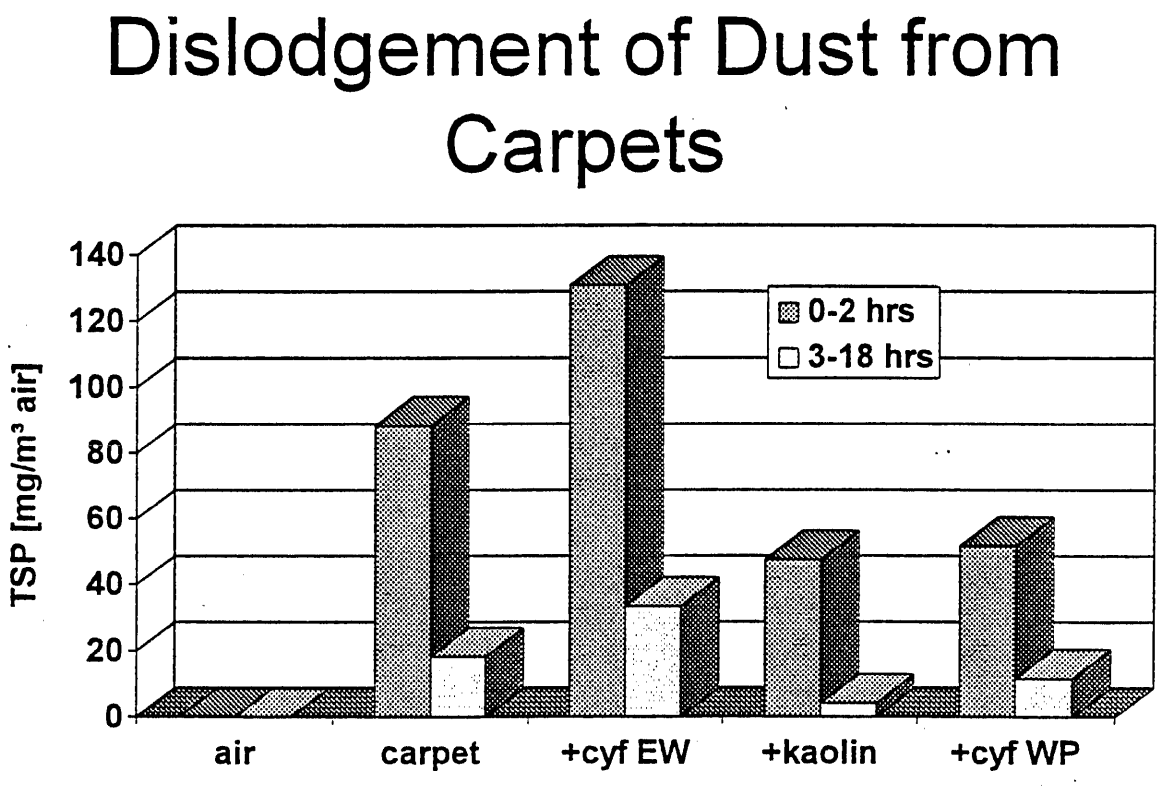
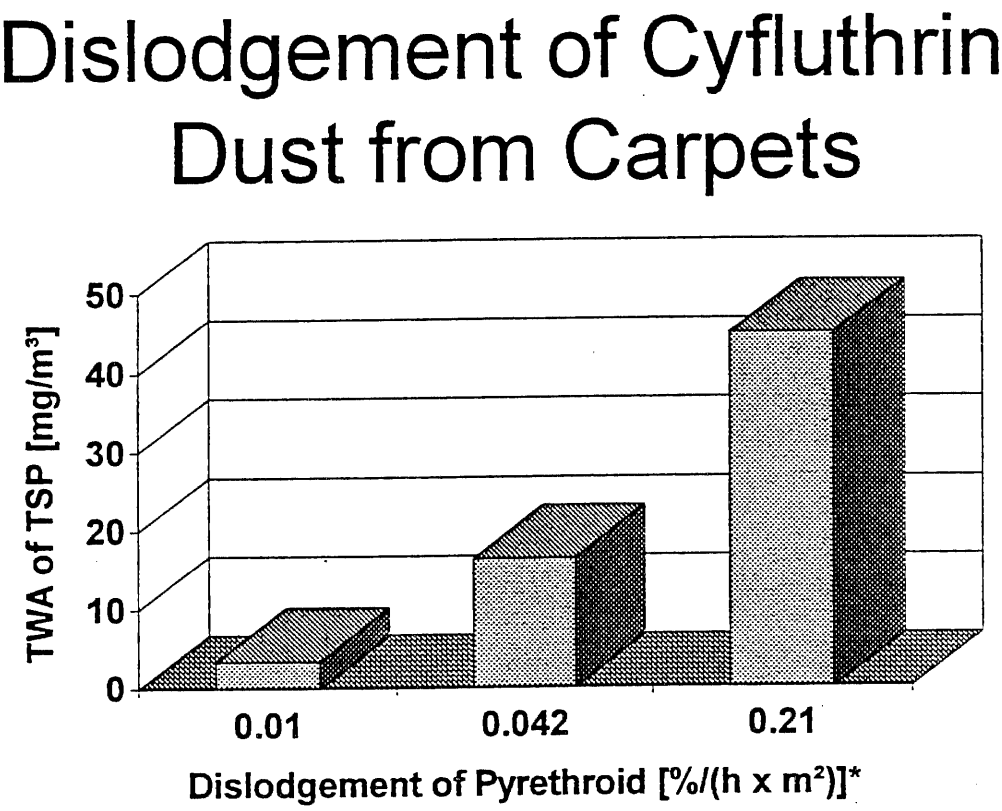

Dislodgement of Dust from Carpets
TSP [mg/m³ air]
140
120
100
80
60
40
20
0
0-2 hrs
3-18 hrs
air
carpet
+cyf EW
+kaolin
+cyf WP

Figure 6:



*) %: relative to nominal mass/m² carpet

Figure 7:

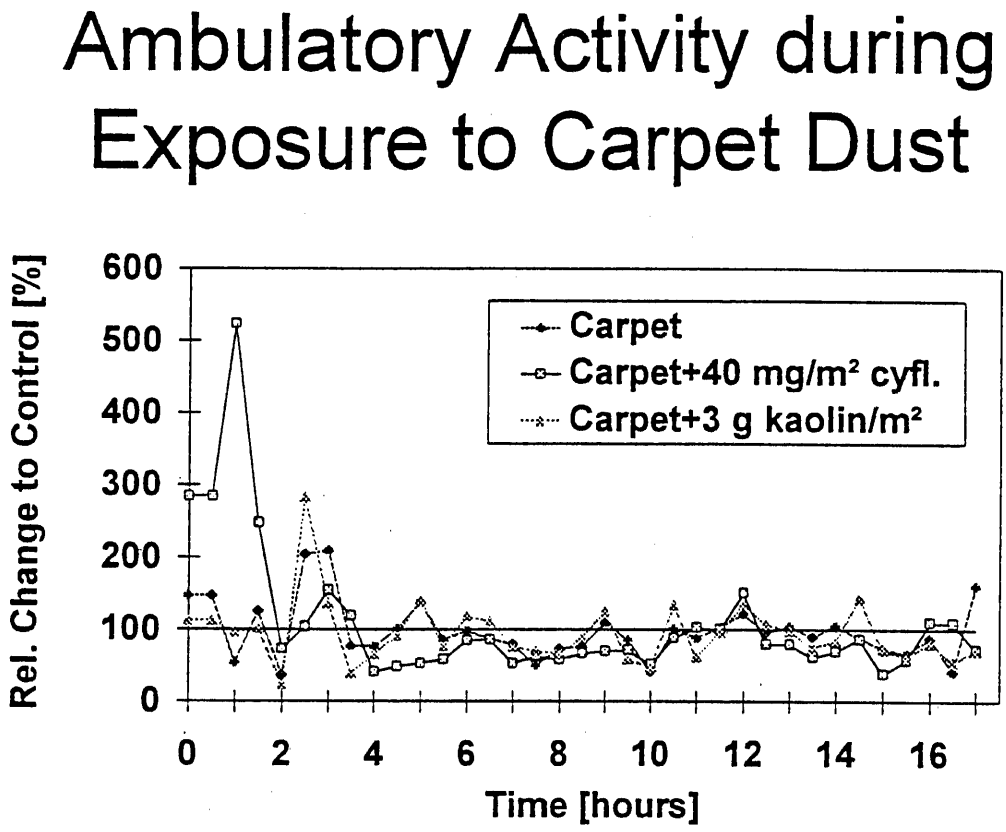
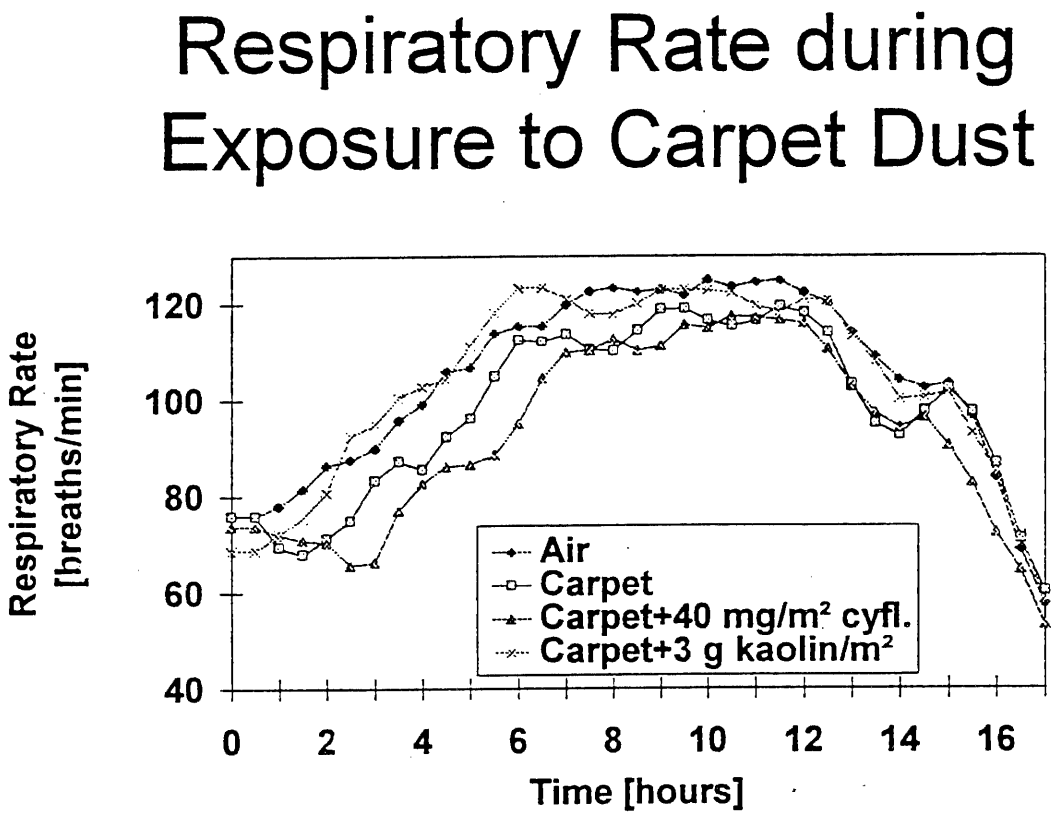

Ambulatory Activity during Exposure to Carpet Dust
Rel. Change to Control [%]
600
500
400
300
200
100
0
0
2
4
6
8
10
12
14
16
Time [hours]
Carpet
Carpet+40 mg/m² cyfl.
Carpet+3 g kaolin/m²

Figure 8:


Respiratory Rate during Exposure to Carpet Dust
Respiratory Rate [breaths/min]
120
100
80
60
40
0
2
4
6
8
10
12
14
16
Time [hours]
Air
Carpet
Carpet+40 mg/m² cyfl.
Carpet+3 g kaolin/m²

Size distribution of ambient particles and its relevance to human health

Annette Peters[1]*, Thomas Tuch[1,2], Peter Brand[3], Joachim Heyder[3], H.-Erich Wichmann[1,2]

1. GSF - Institut für Epidemiologie, Forschungszentrum für Umwelt und Gesundheit, D-85758 Oberschleißheim, Germany. Fax: +49-89-3187-3380.
2. Lehrstuhl für Epidemiologie, Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie, Ludwig-Maximilian Universität, München, Germany. Fax: +49-89-3187-3380.
3. GSF- Institut für Inhalationsbiologie, Forschungszentrum für Umwelt und Gesundheit, 85758 Oberschleißheim, Germany. Fax: +49-89-3187-2400.

* Corresponding author (peters@gsf.de).

On 145 days during the winter season 1991/92, mean size distributions of ambient particles in the range 0.01-2.5 µm were determined with a differential mobility analyzer and an optical particle counter in Erfurt, a town in East Germany. During this period 79% of the particles were smaller than 0.1 µm in diameter. The corresponding mean mass concentrations were calculated assuming an average particle density of 1.5 g cm^{-3}. 82% of the mass concentration were associated with particles in the size range 0.1 - 0.5 µm. Since the variation of particle number concentration was not highly correlated with the variation of particle mass concentration (r=0.51), these values were compared with daily mean expiratory peak flow rates of 27 non-smoking asthmatic residents of Erfurt. Elevated particle number concentration were closer associated with decreases in expiratory peak flow rate than elevated particle mass concentration. Thus, the ultra-fine particles may indeed play a role in air pollution-induced alterations of respiratory lung function.

Introduction

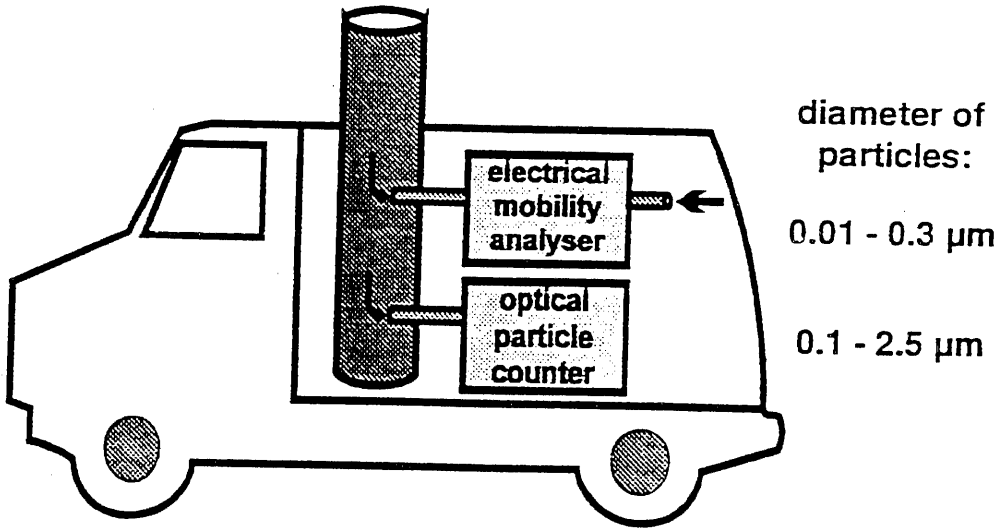
Recently it has been recognized that ambient particles might play an important role in pollution-induced respiratory responses (1-5). Fine (6) and even ultra-fine particles might be more "toxic" than coarse particles and the

"physical" toxicity of these particles might even exceed their "chemical" toxicity. Consequently more insight into health related aspects of particulate air pollution will be obtained by correlating respiratory responses with mass and number concentration of ambient particles.

Methods

The size distribution of ambient particles with the diameter d ranging from $0.01 \leq d \leq 2.5$ µm was determined with a differential mobility analyzer (DMA, TSI model 3071) and an optical particle counter (PMS model LAS-X) (7-11) (figure 1). The DMA allows separation of particles of uniform electrical mobility from a polydisperse aerosol. A condensation nucleus counter is used to determine the particle number concentration of the particles selected by the DMA. If the high voltage used to separate particles in the DMA is varied, this instrument can be applied to measure the number concentration of particles between 0.01 µm up to 0.3 µm.

Figure 1: Schematic drawing of the mobile aerosol spectrometer.



The laser aerosol spectrometer uses the light scattered by particles passing the sensing volume to evaluate the particle size. Calibration of the LAS can only be performed with particles of known refractive index. For measurements of the particle size distribution of an atmospheric aerosol with an unknown refractive index a calibration procedure is applied, which uses the DMA to select monodisperse fractions from this atmospheric aerosol (7,8).

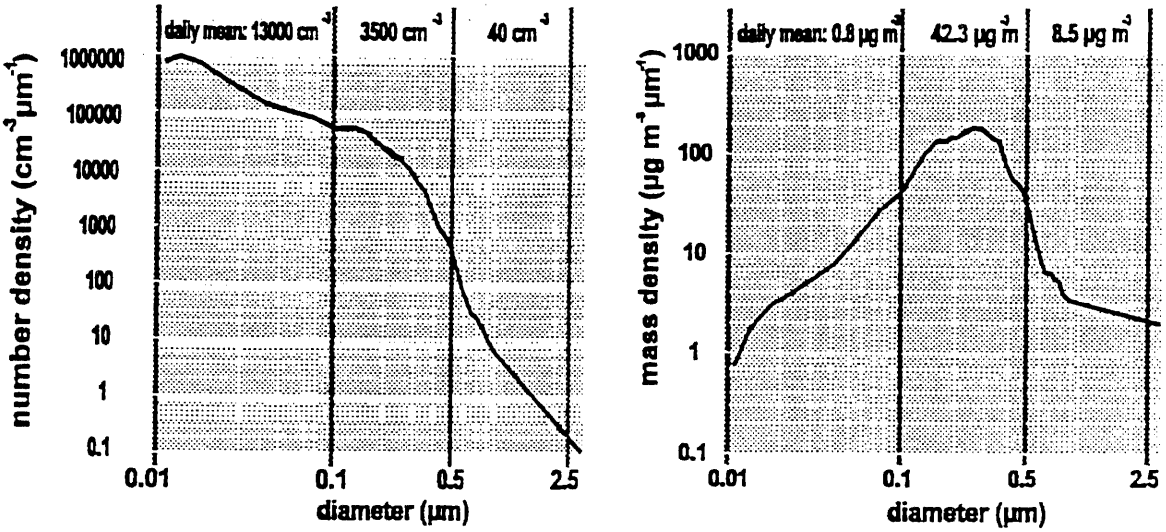
The particle size distribution can be converted into a particle volume distribution. This volume distribution can then be used to calculate the particle mass assuming an average density of the aerosol particles of 1.5 $\mu g/m^3$. This assumption of the particle density yields the agreement between the calculated mass concentrations and conventionally derived $PM_{2.5}$ measurements (10). These derived particle mass distributions can be used to calculate integral mass concentrations of particles smaller than selected cutoff diameters, which are of special interest for epidemiological studies on the effects of the environmental aerosol on human health. The following abbreviations will be used consequently: $NC_{0.01-0.1}$ for the number concentration of the ultra-fine particles, $NC_{0.01-2.5}$ for the total number concentration of fine particles, $MC_{0.1-0.5}$ for the mass concentration of fine particles with a diameter between 0.1 and 0.5 µm, and $MC_{0.01-2.5}$ for the mass concentration of the fine particles.

During the winter 91/92 27 non-smoking adults with a history of asthma participated in a panel study (11,12). They were 44 to 80 years old in 1992, and 63 percent of them were women. The panelists performed peak expiratory flow measurements three times a day and recorded the largest blow out of three attempts each time. The analysis was restricted to the winter period (from September through March) typical for the region. Data on fine and ultra-fine particles was only available after October, 1 1991. Data were obtained on 145 days. Missing data were due to vacation times and calibration procedures. Regression analysis of population averaged time-series were used to control for possible confounding by time-varying influences on peak exspiratory flow as has been described previously (11,12). Linear regression analyses were conducted for peak expiratory flow measurements in the evening before medication use (11). Each individual time-series was centered around the individual mean. The mean deviation on a given day was calculated and used as dependent variable in linear regression analyses. Regression analyses were weighted by the number of observations of the outcome variables in order to adjust for fluctuation of participants on a given day. Autocorrelation of the error term was examined and a first order autocorrelation structure was detected. The final model included 24 hour mean temperature, an indicator for weekend and a linear trend. A five-day mean was used to estimate the cumulative impact of air pollution. It was calculated by averaging the exposure on the current day and four days prior. In case of missing data the remaining measurements were taken. All regression coefficients were expressed as effects associated with a change of the exposure for one inter-quartile range.

Results

Daily mean number and mass distributions were obtained with the mobile aerosol spectrometer. Figure 2 presents the mean distribution of the number and the mass of the particles during the winter 91/92.

Figure 2: Mean number and mass distribution of ambient particles in Erfurt, 1991/92 (10).



79% of the particles were smaller than 0.1 µm in diameter. 82% of the mass concentration were associated with particles in the size range 0.1 - 0.5 µm (10,11). Since the number concentration of the particles smaller than 0.1 µm was not highly correlated with the mass concentration of particles with a diameter between 0.1 and 0.5 µm (r=0.51) (11), these two fractions and the total number and the total mass of the fine particles were chosen to evaluate the impact of the fine and ultra-fine particles on lung function measurements. Analyses were adjusted for a linear trend, mean daily temperature and weekend, but none of the covariates achieved borderline significance. A stronger association was observed for the number concentration of particles ($NC_{0.01\text{-}2.5}$) than for their mass concentration ($MC_{0.01\text{-}2.5}$) (table 1).

Table 1: Regression coefficients and 95% confidence intervals of five-day means of fine and ultra-fine particles for peak expiratory flow (11).

	Inter-Quartile Range	(l/min)	95% CI (l/min)
$MC_{0.1\text{-}0.5}$	28.8 µg/m^3	-2.13	(-3.67 , -0.59)
$NC_{0.01\text{-}0.1}$	9200 cm^{-3}	-4.04	(-6.06 , -2.01)
$MC_{0.01\text{-}2.5}$	36.0 µg/m^3	-2.30	(-4.11 , -0.49)
$NC_{0.01\text{-}2.5}$	9950 cm^{-3}	-3.80	(-5.64 , -1.96)

However, a two-sided t-test did not detect statistically significant differences between the effect estimates. PEF decreased in association with all three size fractions of fine particles (11), while the strongest association was observed for the ultra-fine particles, both for $NC_{0.01-0.1}$ and $MC_{0.01-0.1}$ (table 1). The differences of the estimates for $NC_{0.01-0.1}$ and $MC_{0.1-0.5}$ were statistically significant ($p = 0.042$).

Discussion

The measured total particle number concentration was determined by ultra-fine particles in Erfurt during the winter 91/92. The mass of the fine particles was dominated by particles between 0.1 µm and 0.5 µm in diameter. A comparison between $MC_{0.01-2.5}$ and standard $PM_{2.5}$ achieved similar results (10).

Decreases in peak expiratory flow were associated with five-day means of fine and ultra-fine particles. These adverse health effects were associated with the number concentrations and the mass concentrations of the fine particles. As the number and the mass of the particles characterize different properties of the aerosol in the atmosphere, the goal of the analyses presented here was to distinguish between them. The number concentrations of particles with a diameter less than 2.5 µm ($NC_{0.01-2.5}$) showed larger associations with peak expiratory flow (PEF) than their calculated mass ($MC_{0.01-2.5}$). On the other hand, the number of ultra-fine particles ($NC_{0.01-0.1}$) were highly correlated with ($NC_{0.01-2.5}$). Therefore, the observed decreases in PEF might be attributable to the exposure to high numbers of ultra-fine particles (11). The decrease in lung function might be caused by an inflammation in the alveoli as a reaction to ultra-fine particles, as has been hypothesized recently by Seaton et al. (13).

Air pollution in Erfurt was dominated by sulfurdioxide at the beginning of the nineties. Levels of PM_{10} and sulfate concentrations of fine particles were moderate (14). However, health effects in the adult panel were stronger associated with PM_{10} than SO_2 (12). PM_{10} and $MC_{0.01-2.5}$ showed a similar time course quantified by correlation of $r = 0.84$. The ultra-fine particles showed stronger relationship to PEF than PM_{10} (11). Therefore, the results obtained in the analyses presented here are consistent with results for PM_{10} reported in previous studies (1-4).

Conclusion

Data presented here suggests that, in order to identify the properties of particles that are responsible for the health effects, the number of ultra-fine particles appears to be an important factor to consider in the future.

References

1. Dockery DW, Pope CA. Acute respiratory effects of particulate air pollution. Annu Rev Public Health 1994;15:107-32.

2. Pope CA, Bates DV, Raizenne ME. Health effects of particulate air pollution: Time for reassessment? Environ Health Perspect 1995;103:472-80.

3. Pope CA, Dockery DW, Schwartz J. Review of epidemiological evidence of health effects of particulate air pollution. Inhal Toxicol 1995;7:1-18.

4. Brunekreef B, Dockery DW, Krzyzanowski M. Epidemiologic studies on short-term effects of low lewels of major ambient air pollution components. Environ Health Perspect 1995;103(Suppl. 2):3-13.

5. Bascom R, Bromberg PA, Costa DA, Devlin R, Dockery DW, Frampton MW, Lambert W, Samet JM, Speizer FE, Utell M. Health effects of outdoor air pollution. Amer J Respir Crit Care Med 1996;153:3-50.

6. Dockery DW, Pope AC, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG, Speizer FE. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329:1753-9.

7. Brand P, Gerhardt J. A combined DMPS-OPC-sizing system and its calibrations and application for environmental aerosols. Vienna: 12th Int. Conf. Athomaspheric Aerosols and Nucleation, Wien, Austria, 22-27 August, 1988, Springer; Berlin 1988; 202-5.

8. Brand P, Gerhardt J, Below M, Georgi B, Heyder J. Technical note: Performance of a mobile aerosol spectrometer for an in situ charcterisation of environmental aerosols in Frankfurt City. Atmos Environ Pt A-Gen Top 1996;26:2451-7.

9. Tuch, T. Erprobung eines neuen Lungenfunctiontests mit inerten Aerosolen zum Einsatz in der Umweltsicherheitstechnik 1995; Unversität Wuppertal; (Dissertation)

10. Tuch T, Brand P, Wichmann HE, Heyder J. Application of a mobile aerosol spectrometer for characterizing ambient aerosol particles in Eastern Germany. [submitted]

11. Peters A, Wichmann HE, Tuch T, Heinrich J, Heyder J. Respiratory effects are associated with the number of ultra-fine particles. [submitted]

12. Peters A, Goldstein IF, Beyer U, et al. Acute health effects of exposure to high levels of air pollutants in Eastern Germany. [In Press] Am J Epidemiol 1996;

13. Seaton A, MacNee W, Donaldson K, Godden D. Particulate air pollution and acute health effects. Lancet 1995;345:176-8.

14. Cyrys J, Gutschmidt K, Brauer M, Dumyahn TS, Heinrich J, Spengler JD, Wichmann HE. Determination of acidic sulfate aerosols in urban atmospheres in Erfurt (FRG) and Sokolov (former CSSR). Atmos Environ Pt B-Urban 1995;29(23):3545-57.

Should Occupational Exposure Limits be Re-evaluated in Response to Recent Epidemiologic Associations Between Environmental Particulate Exposure and Human Health?

Robert F. Phalen, Community and Environmental Medicine, and Center for Occupational & Environmental Health, College of Medicine, University of California, Irvine, CA 92697-1825, U.S.A.

I. Introduction

A. Epidemiological Associations

Today, few if any scientists doubt the validity and reproducibility of the observed associations between small incremental increases in urban air particulate concentrations and acute increases in human mortality and morbidity (Bates, 1995; Pope et al., 1995; Ostro et al., 1995, HEI, 1995). The number of cities studied, the number of investigators reporting such associations and the coherency of the associations (with respect to short and long-term effects, to type of adverse effects seen, and to categories of pollutants implicated), all lend strength to the aforementioned associations. It is clear that the epidemiologists have identified a potential problem that could have significant economic and public health implications. The implications for workplace exposure limits are the subject of this paper.

B. Challenges to a Cause-and-Effect Relationship

Because the relative risks associated with particulate exposures below the National Ambient Air Quality Standards are small - on the order of 1.1 for excursions of 100 $\mu g/m^3$ - the issue arises as to whether the air-pollutant particles themselves are causal. That is, whether the associations occur because small increased concentrations of particles cause the increases in death and disease, or alternatively, whether the particles are markers of another cause, or causes (Goldberg, 1996).

Other challenges to a cause-and-effect relationship are based on a lack of clinical and toxicological data that lend support for the possible life-threatening effects of low concentrations of inhaled particles (Utell & Frampton, 1995; Schlesinger, 1995). However, the clinical and toxicological models used thus far to study the effects of particulate exposure may not have focussed on the appropriate at-risk populations, on the appropriate exposure materials, or on the appropriate mechanisms of injury (Phalen & McClellan, 1995; Driscoll, 1996).

Although candidate particulate species that could cause the observed effects have been suggested, the causal particulate agent (or property of that agent), or the characteristics of a causal combination, have not been defined.

C. Occupational Exposure Limits

Occupational exposure limits (OELs) include air concentrations of particulate material that should not be exceeded in workplace air when unprotected workers are present. Hundreds of particulate materials are addressed by OELs, and the exposure metrics are targeted to address the most relevant exposure; for example, respirable particulate mass (eg., quartz dust), thoracic particulate mass, inhalable particulate mass, and number concentration (e.g., asbestos) are recommended for specific agents by the American Conference of Governmental Industrial Hygienists (ACGIH) in their annually-updated Threshold Limit Values for Chemical Substances

and Physical Agents and Biological Exposure Indices (ACGIH, 1995). In addition to case-by-case exposure limits, a broad category, Particulates Not Otherwise Classified (PNOC), has a limit of 10 mg/m^3 of total dust and 3 mg/m^3 for respirable dust. PNOC are not inert in the respiratory tract (no particles are), but the reaction with lung tissue does not change air space architecture, produce significant scar tissue, or produce potentially non-reversible effects. The National Institute for Occupational Safety and Health (NIOSH), the Occupational Health and Safety Administration and other governmental agencies worldwide, also publish recommended and permissible exposure levels (RELs from NIOSH and PELs from OSHA, for example) for hundreds of particulate materials. These limits also specify appropriate metrics for materials on a case-by-case basis (NIOSH, 1994a).

OELs differ in several significant ways from U.S. National Ambient Air Quality Standards (NAAQS). Notably, OELs are not intended to be protective for all segments of the working population, such as "hypersusceptible" individuals, or people with "pre-existing" conditions due to factors such as age, genetics, disease states, previous exposures, personal habits or medication usage (ACGIH, 1995). As for the NAAQS, OELs frequently specify the range of particle sizes that must be measured. The history of such size-selective particulate air sampling in the U.S. can be traced to the early 1950's, and present-day standards are highly-evolved (Lioy, Lippmann and Phalen, 1985; ACGIH, 1995). There has been progress in the control of workplace air contaminants. Thus, statistical data assembled by NIOSH in their report, Work-Related Lung Disease Surveillance Report (NIOSH, 1994b) indicate that the lung disease rates in U.S. workers due to particulate exposures are generally in decline, and for many substances the associated disease rates are approaching negligible values.

II. Comparison of Occupational and Environmental Exposures to Airborne Particulate Material

The assumption that occupational and environmental exposures to airborne particles are comparable is tempting, but it must be carefully examined. The two types of exposures differ substantially in the following ways.

A. Populations Exposed

Workers are generally more fit than many segments of the general population for many reasons. Worker ages are usually between 18 years and 65 years; thus, two potentially-sensitive subpopulations, children and the very old, are excluded from workplace considerations. Workers, at least while working, are healthy enough to leave home and spend an average of 8 hours on the job; this population does not include many people who are seriously ill, and certainly not those who are bedridden. However, some people are able to work who have serious, even life-threatening, conditions such as asthma, liver diseases, and cardiovascular diseases.

Worker populations must be assumed to be selected for lack of sensitivity to those specific air-contaminants that are associated with their jobs. Hypersusceptible individuals would be expected to leave problematic jobs voluntarily, or to be assigned to jobs with lower exposures. In addition, persons with known sensitivities to particulate air pollutants would not be expected to seek employment in the "dusty trades", if alternative employment is available.

B. Particulate and Mixture Characteristics

Occupational air pollutants differ from environmental air pollutants in important ways. Particles in occupational settings are generally found in mixtures that are less complex than environmental mixtures. The number of pollutants in urban air is enormous, due to the myriad sources, long-range transport and opportunities for complex chemical reactions. Photochemistry produces new, often transient and highly reactive species in the outdoor environment (Kao & Friedlander, 1994; Lippmann, 1992), but photochemical activation is not common in the workplace.

Some pollutants that may be problematic for susceptible individuals, for example endotoxins, pollens, other biogenic allergens, tobacco smoke, and wood smoke, are unlikely to be constituents of workplace air (except in some specific occupational settings such as farms, and animal husbandry buildings). On the other hand, occupational particulate air concentrations can greatly exceed concentrations found in the general environment, and some occupations involve potential exposure to very toxic air pollutants (such as Be, As, Pb, asbestos, and trimellitic anhydride.)

C. Exposure Patterns

Temporal patterns of exposure of workers to particulate air pollutants differ substantially from those of the general population. Occupational exposures are typically 8-10 hours/day, 4-5 days/week, 50 weeks or less per year, and seldom longer than about 40 years in total duration. Environmental exposures of non-workers are commonly 24 hours/day, 7 days/week, 52 weeks/year, and more than 70 years total duration. Furthermore, workers are allowed to take approximately 3 breaks daily, during which the particulate exposure is presumably greatly reduced. Thus, workers may have many periods of non-exposure where clearance and repair mechanisms can proceed uncomplicated by concurrent exposure to the specific agents under consideration. This may not occur in environmental exposure situations, where episodes may last for days.

In addition, health and safety professionals in the workplace can be expected to monitor particulate exposures, and provide administrative, engineering and personal-protective controls that reduce or eliminate excessive exposures. In the environmental situation, alerts that lead to modification of behavior are usually called in cases of significant excedence of air standards, if at all. In the workplace, air sampling takes place in areas where exposures occur and chemical analyses of acquired samples are performed by trained industrial hygienists. When exceedences are detected, controls are frequently instituted. Such health-related corrective actions are common in the workplace, but rare in the environmental exposure arena.

D. Confounders

Some known confounding factors that may exacerbate the consequences of environmental particulate exposures are unlikely to be found in workplaces. Extremes in weather-related variables, such as high and low ambient temperature and humidity, are not generally found in workplaces. Similarly, indoor exposures in homes, including those with smokers, are largely limited to environmental exposure scenarios. These confounding exposures would be expected to increase the health impact of environmental exposures over those in the workplace. An exception would occur for dusty jobs that have accompanying thermal stress. Also, workers in some trades may be expected to smoke more heavily than does the general population.

E. Other Factors

It is likely that most workers have better health surveillance regarding their exposures than does the population at large. This surveillance can include periodic pulmonary function testing in addition to general physical examinations and personal inquiries relating to their health status. Such surveillance is presumably essentially absent in relation to environmental exposures.

The level of risk (in relation to air-pollutant exposures) that is acceptable to workers, who are also directly compensated, is likely to be higher than the level that is acceptable to several segments of the population at large. Also, workers presumably would be generally more familiar with potential risks than would be the general population. These factors, direct benefit and familiarity with the potential hazards, serve to increase the acceptance of risk by workers when compared to the population at large (Slovic, 1987).

F. Comment

Considering the foregoing discussion, it appears that workplace particulate exposures differ from environmental particulate exposures in significant ways, most of which would be expected to reduce the risks faced by workers compared to the general population when exposed to equivalent particulate concentrations. That is, if the epidemiological associations for low levels of environmental particles do represent a cause-and-effect relationship, a similar relationship would not be expected a-priori in workplaces. The major reasons in support of this conclusion are that workers have better health, better surveillance and protection, briefer exposures and they are exposed to air pollutants that are less-complex (in terms of number of chemical species and reactivity). There are exceptions for specific occupations, including those with thermal extremes, heavy biogenic exposures, and possibly heavy exposures to combustion products.

III. Research Needs and Recommendations

Given the special circumstances of occupational exposures, are there significant needs for research on low-level particulate exposures? According to NIOSH (NIOSH, 1995), even cautious estimates indicate that about "137 workers die each day from workplace diseases." This toll, along with accidental deaths and other injuries, produces a drain on U.S. productivity that is "estimated to exceed $100 billion annually", with medical costs for chronic occupational illness constituting $30-40 billion. This circumstance has understandably led to defining research priorities for workers. Among the priority areas for research cited by NIOSH are: occupational lung disease (prevention and surveillance); hazard control technologies; and disease treatment (NIOSH, 1995, 1996).

Considering the epidemiologic associations for environmental particulate exposures, the following recommendations are offered:

* Improvements are needed in the means by which data relating to the potential development of particle-related disease in workers are gathered and analyzed. This is especially true for workers who are exposed to fine particles, acid aerosols, reactive aerosols, iron (and other metals catalytic for oxidant formation) aerosols, combustion products, and aeroallergens.

* Exposure characterization should be improved through sophistication of particle deposition and clearance models that take into account particle characteristics, the presence of co-pollutants, and individual variations in anatomy and physiology. Thus, those who are genetically or physiologically predisposed could be identified prior to the development of disease.

* Follow-up of retired workers who have had heavy exposures to particles is needed in order to look for late, progressive lung disease and sensitivity to non-occupational air pollutants.

* Workers currently exposed to significant levels of particulate air pollutants should be more intensively monitored for the development and/or exacerbation of cardiovascular as well as pulmonary diseases.

* Instrumentation used for monitoring particles should be improved to provide a) better chemical form vs. aerodynamic size data, and b) more continuous sampling.

* The mechanisms by which particles may establish or exacerbate disease are not well explored, and require additional research. This is true in relation to both acute and chronic effects, and for ultrafine particles. Such research holds promise for devising strategies for prevention and treatment of disease.

In addition, improved training and education of health and safety personnel, as well as the workers themselves, is needed so that potential particulate hazards can be recognized and controlled.

IV. Conclusion

The epidemiologic associations for particles and health that have been reported for environmental exposures are not necessarily a cause for new concerns for most workers in most workplaces. Nevertheless, occupational lung and cardiovascular diseases are still a major problem, and particulate exposures undoubtedly contribute to health and productivity-related costs of billions of dollars annually. Also, the epidemiological findings relating population exposures to particles should not be ignored with respect to workplace implications. Targeted research, both basic and applied, must be strongly encouraged in order to pinpoint and to reduce the known and potentially unrecognized risks related to particulate air-pollutant exposures.

V. References

American Conference of Governmental Hygienists: Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices, American Conference of Governmental Industrial Hygienists, Cincinnati, OH (1995).

Air Sampling Procedures Committee: Particle Size-Selective Sampling in the Workplace. American Conference of Governmental Hygienists, Cincinnati, OH (1985).

Bates, D.V.: Summary of the Colloquium on Particulate Air Pollution and Human Mortality and Morbidity, Irvine, California, 24 and 25 January, 1994. Inhal. Toxicol. 7(1);ix-xii (1995).

Driscoll, K.E.: Factors Influencing Particle Toxicity: Particle Composition and Size. Proceedings of the Second Colloquium on Particulate Air Pollution and Human Mortality and Morbidity, May 1996, Park City, UT, (in press).

Goldberg, M.S.: Particulate Air Pollution and Daily Mortality: Who Is at Risk? J. Aerosol Med. 9(1):43-53 (1996).

Health Effects Institute: Particulate Air Pollution and Daily Mortality, Replication and Validation of Selected Studies, The Phase I Report of the Particle Epidemiology Evaluation Project. Health Effects Institute, Cambridge, MA (1995).

Kao, A.S.; Friedlander, S.K.: Chemical Signatures of the Los Angeles Aerosol (d_p<3.5 μm). Aerosol Sci. Technol. 21(4):283-293 (1993).

Lippmann, M., Ed.: Environmental Toxicants: Human Exposures and Their Health Effects. Van Nostrand Reinhold, New York, NY (1992).

National Institute for Occupational Safety and Health: NIOSH Pocket Guide to Chemical Hazards, DHHS (NIOSH) pub. No. 94-116. National Institute for Occupational Safety and Health, Cincinnati, OH (1994a).

National Institute for Occupational Safety and Health: Work-Related Lung Disease Surveillance Report 1994, DHHS (NIOSH) Pub. No. 94-120. National Institute for Occupational Safety and Health, Cincinnati, OH (1994b).

National Institute for Occupational Safety and Health: NIOSH Research and Demonstration Grants, Fiscal Year 1994, DHHS (NIOSH) Pub. No. 95-112. National Institute for Occupational Safety and Health, Cincinnati, OH (1995).

National Institute for Occupational Safety and Health: National Occupational Research Agenda, DHHS (NIOSH) Pub. No. 96-115, National Institute for Occupational Safety and Health, Cincinnati, OH (1996).

Ostro, B.D.; Lipsett, M.J.; Mann, J.K.: Air Pollution and Asthma Exacerbations Among African-American Children in Los Angeles. Inhal. Toxicol. 7(5):711-722 (1995).

Phalen, R.F.; McClellan, R.O.: PM-10 Research Needs. Inhal. Toxicol. 7(5):773-779 (1995).

Pope, C.A. III; Dockery, D.W.; Schwartz, J.: Review of Epidemiological Evidence of Health Effects of Particulate Air Pollution. Inhal. Toxicol. 7(1):1-18 (1995).

Schlesinger, R.B.: Toxicological Evidence for Health Effects From Inhaled Particulate Pollution: Does It Support the Human Experience? Inhal. Toxicol. 7(1):99-109 (1995).

Slovic, P.: Perception of Risk. Science 236(4799):280-285 (1987).

Utell, M.J.: Frampton M.W.: Particles and Mortality: A Clinical Perspective. Inhal. Toxicol. 7(5):645-655 (1995).

Acknowledgements: This paper was supported in part by grants from CDC/NIOSH, the California Air Resources Board, and the National Heart, Lung and Blood Institute (RO1-39682), and by the University of Utah and the U.C. Irvine Centers for Occupational and Environmental Health. Richard Mannix and Marie Tonini assisted with editing and word processing.

A:Limits/6