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The effect of exposure to sulphuric acid on the early asthmatic response to inhaled grass pollen allergen

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The effect of exposure to sulphuric acid on the early asthmatic response to inhaled grass pollen allergen. W.S. Tunnicliffe, D.E. Evans, D. Mark, R.M. Harrison, J.G. Ayres. ©ERS Journals Ltd 2001.

ABSTRACT: Particulate sulphates, including sulphuric acid (H_2SO_4), are important components of the ambient aerosol in some areas and are regarded as air pollutants with potentially important human health effects. Challenge studies suggest little or no effect of H_2SO_4 exposure on lung function in asthmatic adults, although some epidemiological studies demonstrate an effect of acid species on symptoms in subjects with asthma. To date, the effect of H_2SO_4 on allergen responsiveness has not been studied.

The effect of exposure to particulate H_2SO_4 on the early asthmatic response to grass pollen allergen has been investigated in 13 adults with mild asthma. After establishment of the provocative dose of allergen producing a 15% fall in forced expiratory volume in one second (FEV_1) (PD_{15}) for each subject, they were exposed to air, 100 $\mu g \cdot m^{-3}$ or 1,000 $g \cdot m^{-3}$ H_2SO_4 for 1 h, double-blind in random order $\geqslant$2 weeks apart, through a head dome delivery system 14 h after each exposure subject underwent a fixed-dose allergen challenge (PD_{15}).

Ten subjects completed the study. The mean early asthmatic responses (maximum percentage change in FEV_1 during the first 2 h after challenge) following air, 100 $\mu g \cdot m^{-3}$ H_2SO_4, and 1,000 $\mu g \cdot m^{-3}$ H_2SO_4, were -14.1%, -16.7%, and -18.4%, respectively. The difference between 1,000 $\mu g \cdot m^{-3}$ H_2SO_4 and air was significant (mean difference: -4.3%, 95% confidence interval (CI: -1.2–-7.4%, p=0.013). The difference between air and 100 $\mu g \cdot m^{-3}$ H_2SO_4 approached significance (mean difference: -2.6%, 95% CI: 0.0–-5.3%, p=0.051).

These results suggest that, at least at high mass concentration, sulphuric acid can potentiate the early asthmatic response of mild asthmatic subjects to grass pollen allergen, although the effect is limited.
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Several epidemiological studies from both Europe and America have demonstrated an association between day-to-day changes in the concentration of airborne particulate matter and acute health effects [1–6]. These range from increases in respiratory and cardiovascular mortality and hospital admissions, to day-to-day changes in lung function and symptoms. Groups considered to be at increased risk from particulate air pollutant exposure include those with pre-existing respiratory disease, both chronic obstructive pulmonary disease (COPD) [7] and asthma [8], although the association with asthma attacks is less consistent. This may, in part, be due to the variable metrics used to describe particulate exposure [9] and differences in the definition of "attacks" of asthma. In addition, the component(s) or characteristic(s) of the ambient aerosol responsible for health effects remain unclear, although recent interest has focused on smaller particles (<2.5 μm) [10].

Particulate sulphates are an important component of the ambient aerosol. They are principally secondary particles, formed when gas phase species react to give rise to products with low vapour pressures, which consequently condense [11]. Their chief source is the atmospheric oxidation of sulphur dioxide (SO_2) to sulphuric acid (H_2SO_4). H_2SO_4 exists in air in particle form; it reacts irreversibly in two stages with ammonia gas (NH_3) to form ammonium bisulphate (NH_4HSO_4) or ammonium sulphate ($(NH_4)_2SO_4$) [12].

Laboratory challenge with particulate H_2SO_4 in normal subjects has mostly failed to elicit any response following exposure to concentrations of $\leqslant$1,500 $\mu g \cdot m^{-3}$, although one study recorded an increase in nonspecific bronchial reactivity 24 h after a 4-h long exposure to 450 $\mu g \cdot m^{-3}$ [13]. In subjects with asthma, results are conflicting, with some showing bronchoconstriction after inhalation of concentrations of H_2SO_4 <1,000 $\mu g \cdot m^{-3}$ [14, 15], and in one study, with concentrations of only 100 $\mu g \cdot m^{-3}$ [16]; most studies [17–19], including the authors' own (unpublished data), have shown no significant effect on lung function.

Ambient H_2SO_4 levels are now, in general, low in the UK, but a recent study from CA, USA [20] has identified an association between health effects and day-to-day changes in the concentrations of this

pollutant. One explanation for the differences between the epidemiological and challenge findings could be an interaction between H_2SO_4 and an unmeasured co-pollutant, such as an aeroallergen.

The potential for air pollutants such as ozone (O_3) and nitrogen dioxide (NO_2) (with or without SO_2) to enhance the specific bronchial reactivity of the asthmatic airway to allergen is now well documented [21], and this has been proposed as a possible mechanistic pathway for some of their respiratory health effects in susceptible populations. There have been no previous studies in humans of the effects of H_2SO_4 exposure on bronchial responses to allergen. To explore this possibility further, the effect of exposure to 100 $\mu g \cdot m^{-3}$ and 1,000 $\mu g \cdot m^{-3}$ highly characterized H_2SO_4 aerosol (mass median diameter (MMD) ~300 nm) on the early asthmatic responses of subjects with mild asthma to inhaled grass pollen allergen was examined.

Methods

Subjects

Thirteen nonsmoking, atopic, asthmatic adult volunteers were studied (table 1). At a baseline screening visit, they underwent skin-prick testing with grass pollen (Bayer, Newbury, Berkshire, UK), positive (histamine) and negative control solutions, spirometry and bronchial challenge to grass pollen allergen (Cocksfoot and Timothy, Bayer). Only subjects that satisfied the following inclusion criteria were recruited: aged 16–60 yrs; nonsmokers; physician-diagnosed asthma taking inhaled medication only, the dose of inhaled beclomethasone or budesonide not >500 $\mu g \cdot 24\ h^{-1}$; baseline forced expiratory volume in one second (FEV1) and a ratio of FEV1 to forced vital capacity (FVC) $\geq$70% predicted [22]; positive skin-prick test (mean wheal diameter >3 mm) to grass pollen; and positive early asthmatic response (>15% fall in FEV1 from baseline) to bronchial challenge with grass pollen. All subjects gave written informed consent and the project was approved by the East Birmingham Health Authority Research and Ethics Committee.

Study design

The grass pollen bronchial challenge dose-response curves at enrolment were used to establish the provocative dose of allergen required to produce a 15% fall in each subject's FEV1 (PD15) [23]. On three subsequent occasions, $\geq$2 weeks apart, in the presence of a stable baseline, FEV1 subjects underwent an air or H_2SO_4 (at 100 $\mu g \cdot m^{-3}$ and 1,000 $\mu g \cdot m^{-3}$) exposure for 1 h in a randomized, double-blind manner at ~19:00 h. This was followed 14 h later by a fixed-dose allergen challenge, being the PD15 from the enrolment challenge.

Measurements

Lung function measurements, pre- and postexposure and during allergen challenge, were made using a Fleisch pneumotachograph (Vitalograph, Buckingham, UK) and the Spirotrach III system (Vitalograph) calibrated before each exposure and each bronchial challenge. The best of at least three technically acceptable blows was taken as the measured value at each point. European Community Coal and Steel predicted values were used [22]. Following completion of allergen challenge, subjects were requested to record their FEV1 using a hand-held logging spirometer (Vitalograph 2110 electronic peak expiratory flow (PEF)/FEV1 diary, Vitalograph), at least hourly while awake for the remainder of the day, to detect any significant change in their lung function beyond the study period.

Bronchial challenge

Bronchial challenges were made with a breath-triggered Mefar MB3 dosimeter (Markos-Mefar,

Table 1. – Clinical characteristics and experimental details of subjects

Subject	Sex	Age yrs	IS# $\mu g \cdot day^{-1}$	FEV1 L (% pred)	FEV1/FVC value (% pred)	PD15 unit+	Exposure order
1	F	42	200	2.15 (71)	0.72 (83)	3.5	Air:1000 $\mu g \cdot m^{-3}$:100 $\mu g \cdot m^{-3}$
2	F	29	400	2.93 (86)	0.71 (82)	100	100 $\mu g \cdot m^{-3}$:Air:1000 $\mu g \cdot m^{-3}$
3¶	F	24	nil	3.12 (92)	0.84 (96)	64	100 $\mu g \cdot m^{-3}$:1000 $\mu g \cdot m^{-3}$:Air
4	F	21	nil	2.97 (103)	0.90 (103)	36	Air:100 $\mu g \cdot m^{-3}$:1000 $\mu g \cdot m^{-3}$
5	F	30	500	2.65 (87)	0.81 (93)	220	1000 $\mu g \cdot m^{-3}$:Air:100 $\mu g \cdot m^{-3}$
6	F	21	nil	3.33 (98)	0.86 (98)	41	1000 $\mu g \cdot m^{-3}$:100 $\mu g \cdot m^{-3}$:Air
7	M	54	nil	2.77 (73)	0.71 (89)	5	100 $\mu g \cdot m^{-3}$:Air:1000 $\mu g \cdot m^{-3}$
8	M	17	nil	3.94 (98)	0.85 (91)	1500	1000 $\mu g \cdot m^{-3}$:100 $\mu g \cdot m^{-3}$:Air
9¶	M	39	400	4.04 (98)	0.74 (90)	48	1000 $\mu g \cdot m^{-3}$:Air:100 $\mu g \cdot m^{-3}$
10	F	29	400	2.82 (86)	0.77 (88)	24	Air:1000 $\mu g \cdot m^{-3}$:100 $\mu g \cdot m^{-3}$
11	F	32	nil	3.49 (112)	0.86 (100)	8	100 $\mu g \cdot m^{-3}$:1000 $\mu g \cdot m^{-3}$:Air
12¶	F	40	nil	2.12 (92)	0.73 (85)	7	Air:100 $\mu g \cdot m^{-3}$:1000 $\mu g \cdot m^{-3}$
13	M	27	nil	3.97 (94)	0.82 (98)	17	100 $\mu g \cdot m^{-3}$:Air:1000 $\mu g \cdot m^{-3}$

IS: inhaled steroid; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; % pred: percentage of predicted; PD15: provocative dose causing a 15% fall in FEV1; F: female; M: male. #: IS $\mu g \cdot day^{-1}$of beclomethasone or equivalent; ¶: subjects who failed to complete the study; +: 1 breath unit defined as five inhalations of a 50 $unit \cdot mL^{-1}$ solution (arbitrary units).

Bovezzo, Italy). They were not performed within 4 weeks of an upper respiratory tract infection. Those subjects using inhaled steroid medication discontinued them on the day of exposure ($\geq$24 h prior to allergen challenge) and recommenced them at completion of their allergen challenge the following day. Antihistamine medication was discontinued for $\geq$1 week before each challenge and subjects maintained their usual daily consumption of ascorbic acid of caffeine-containing foodstuffs for the duration of the study. Dosimeter activation was set to 0.6 s during five consecutive full inspirations from functional residual capacity, followed by a 10 s breath-hold for each concentration of allergen. Each subject used the same nebulizer and their own trigger sensitivities throughout the study. At the start of each challenge, FEV1 was measured before and 1 min after diluent (phosphate buffered saline) delivery. If the values differed by <5%, the postdiluent FEV1 value was taken as baseline for that study day. If the value following diluent was $\geq$15% lower than the prediluent value, the challenge was abandoned for that day. If neither criterion was met, the procedure was repeated until one had been fulfilled. The same batch of grass pollen allergen was used throughout the study. One breath unit of allergen was defined as a single inhalation of a 50 units·mL^{-1} solution. All challenges were avoided during the pollen season.

On the preliminary assessment day, doubling incremental concentrations of allergen were delivered, with FEV1 measurements 3, 5, and 10 min after each five-inhalation cycle until a fall in the postdiluent FEV1 of >15% was achieved. A dose-response curve was drawn for each subject and interpolation used to establish the PD15. This cumulative dose was used in that subject's series of allergen challenges. The provocative dose was divided into two or three five-breath deliveries so that the challenge could be abandoned prematurely if necessary. On completion of allergen delivery, FEV1 measurements were made at 20, 40, and 60 min and then hourly for 7 h. If symptoms or recordings indicated a decline in FEV1, recordings were made more frequently.

The maximum reduction in FEV1 (percentage change from postdiluent FEV1) during the first 2 h after allergen inhalation was taken as the early asthmatic response. After recovery of FEV1 towards baseline, any subsequent fall in FEV1 (expressed as percentage change from postdiluent FEV1) was also recorded and defined as the late asthmatic response [24].

Exposures

Exposures were $\geq$2 weeks apart, of an hour's duration at rest and conducted at the same time of day for each individual. The pollutants were calculated to provide concentrations of 100 μg·m^{-3} or 1,000 μg·m^{-3} particulate H_2SO_4 (MMD 300 nm). All exposures were conducted *via* a purpose-built, head-only exposure system with an integral particle generator and a head dome [25] (fig. 1). Flow through the system for each exposure was maintained at 120 L·min^{-1} to prevent any significant re-breathing within the head

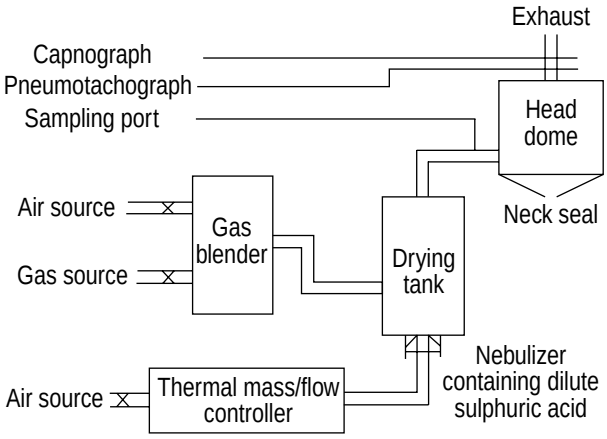

Fig. 1.–Particle generator and exposure system. Gas blender: thermal mass/flow controller regulating turbulent carrier flow of dry medical air to 120 L·min^{-1}; Thermal mass/flow controller: controller regulating nebulizer driving gas flow, for each mass concentration flow=4.5 L·min^{-1}; Nebulizer containing dilute sulphuric acid: MicroCirrus nebulizer (Intersurgical Ltd); Drying tank: 25 L drying chamber allowing mixing of nebulizer output with turbulent carrier stream.

dome. A technical description of the performance of the particle generator will be published elsewhere (unpublished data), but, in brief, the exposure aerosols were generated using a standard medical Micro Cirrus nebulizer (Intersurgical Ltd, Wokingham, UK) driven by bottled medical air under mass flow control and containing a dilute solution of the H_2SO_4. Its output was mixed with a dry, turbulent carrier stream of bottled air in a drying chamber and delivered to the breathing zone of the volunteer. The mass concentrations of the exposure aerosols were determined by the concentration of the material in the nebulizer solution and verified by sampling on a polytetrafluoroethylene filter (Whatman International Ltd, Maidstone, Kent, UK), followed by extraction into distilled deionized water and analysis of sulphates by ion chromatography. The aerosols were also characterized by electrical low pressure impaction, micro orifice uniform deposit impaction and scanning mobility particle sizing. For air (placebo) exposures, the nebulizer ran containing deionized water. For each exposure, the subject was required to sit in a comfortable chair with their head contained within a cast acrylic dome. The entry port in the wall of the dome was positioned within the breathing zone and the exit port was in the roof of the dome. A neck seal was achieved with a modified diving suit neck piece. Before each exposure, subjects brushed their teeth and gargled with an antiseptic mouth rinse to reduce the possibility of neutralization of the exposure aerosols by oral ammonia.

Data analysis

Based on previous experience of early asthmatic responses following repeated fixed-dose allergen challenge (PD15) [26], it was estimated that a sample size of at least nine subjects was required to detect a difference in response of similar magnitude

(4–5% in absolute terms) to that observed for gaseous pollutants. Matched-pair analysis was used to compare FEV1 values following the bronchial challenges. Paired t-tests were used for significance testing. A p-value of <0.05 was considered statistically significant.

Results

Demographic and baseline spirometric details of the study participants are shown in table 1, as are their respective exposure orders and provocative doses of allergen. All exposures were well tolerated and there were no significant changes in FEV1 or FVC with any exposure (data available on request).

Three subjects failed to complete the study; two due to a significant deterioration in their asthma control following their first and second fixed-dose allergen challenge, respectively. The third withdrew due to the development of another, unrelated medical condition. Their results are excluded from the data analysis.

Aerosol characteristics

Temperature and relative humidity were measured in the head dome and logged at the beginning of and at 5 min intervals during each exposure. The mean (range) temperature and relative humidity for the exposures are listed in table 2. In addition, the median mass of H_2SO_4 recovered from a random selection of filter trapped samples, five for each type of exposure, collected during actual exposures are displayed in table 2. There were no significant differences in temperature or relative humidity between the exposures, and the recovered median masses (107 $\mu g \cdot m^{-3}$ and 1,144 $\mu g \cdot m^{-3}$) fitted closely with those required by the authors.

The active exposure aerosols were characterized at the beginning of the study. Superimposed representative outputs of the instruments used are shown in figures 2a and 2b. The outputs were broadly concordant; for both mass concentrations, the MMD of the aerosols was ~300 nm. The vast majority of particles were submicronic, with the count mode for each aerosol lying around 30 nm.

Changes in lung function

There were no significant differences in baseline postdiluent FEV1 values after the various exposures.

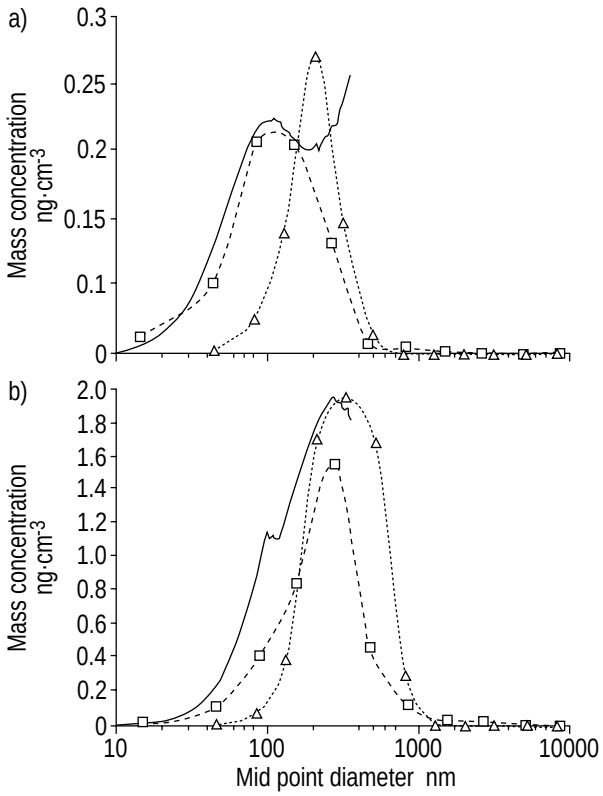

Fig. 2.–Exposure aerosol characteristics. Scaled superimposed outputs from Electrical Low Pressure Impaction (ELPI; △), Micro Orifice Uniform Deposit Impaction (MOUDI; □) and Scanning Mobility Particle Sizing (SMPS; —) devices. a) Low dose sulphuric acid (H_2SO_4) 100 $\mu g \cdot m^{-3}$ and b) high dose H_2SO_4 1,000 $\mu g \cdot m^{-3}$.

Matched pair analysis demonstrated a significant difference of -4.3% (95% confidence interval (CI): -1.2–-7.4%, p=0.013, table 3) between the early asthmatic response following air and following 1,000 $\mu g \cdot m^{-2}$ H_2SO_4 exposures. The difference in early response following air and following 100 $\mu g \cdot m^{-3}$ H_2SO_4 exposures of -2.6% failed to achieve statistical significance (95% CI: 0.0–-5.3%, p=0.051). There was no significant difference between the early responses following the 100 $\mu g \cdot m^{-3}$ and 1,000 $\mu g \cdot m^{-3}$ H_2SO_4 exposures.

The mean late asthmatic response following air exposures was -6.0%, -5.5% following 100 $\mu g \cdot m^{-3}$ H_2SO_4 exposures and -6.7% following 1,000 $\mu g \cdot m^{-3}$ H_2SO_4 exposures. There were no significant differences between these values (table 4).

Table 2.–Physical properties of exposure aerosols

Exposure	Temperature °C	Relative humidity %	Mass concentration H_2SO_4 $\mu g \cdot m^{-3}$ median (IQ range)
Air (placebo)	17.1 (15.92–18.54)	14.8 (9.91–15.89)	0.0
100 $\mu g \cdot m^{-3}$ H_2SO_4	16.8 (15.86–18.13)	15.0 (9.92–15.76)	107 (102–111)
1000 $\mu g \cdot m^{-3}$ H_2SO_4	16.7 (15.77–17.92)	14.6 (9.82–16.02)	1144 (1080–1248)

Data are presented as mean (range) unless otherwise stated. H_2SO_4: sulphuric acid; IQ: interquartile (range).

Table 3. – Early asthmatic response

Subject	Air			100 μg·m^{-3} H_2SO_4			1000 μg·m^{-3} H_2SO_4		
	Baseline FEV1	Minimum FEV1	% change	Baseline FEV1	Minimum FEV1	% change	Baseline FEV1	Minimum FEV1	% change
1	1.94	1.66	-14.43	2.10	1.56	-25.71	2.05	1.47	-28.29
2	2.80	2.39	-14.64	2.82	2.38	-15.60	2.86	2.20	-23.08
4	2.85	2.42	-15.09	2.97	2.45	-17.51	3.11	2.55	-18.01
5	2.79	2.47	-11.47	2.37	2.03	-14.35	2.45	2.06	-15.92
6	3.31	2.81	-15.11	3.24	2.59	-20.06	3.30	2.72	-17.58
7	2.81	2.43	-13.52	2.75	2.38	-13.45	2.78	2.42	-12.95
8	3.96	3.58	-9.60	3.81	2.36	-11.81	4.12	3.59	-12.86
10	2.81	2.31	-17.79	2.76	2.21	-19.93	2.64	2.17	-17.80
11	3.01	2.51	-16.61	2.93	2.53	-13.65	2.89	2.37	-17.99
13	3.62	3.17	-12.43	3.55	3.02	-14.93	3.67	2.97	-19.07
Mean	2.99	2.58	-14.1	2.93	2.45	-16.7[#]	2.99	2.45	-18.4[¶]

H_2SO_4: sulphuric acid; FEV1: forced expiratory volume in one second. [#]: p=0.051 against air exposure; [¶]: p=0.013 against air exposure.

Discussion

These results suggest that, at least at high mass concentration (1,000 μg·m^{-3}), fine particulate H_2SO_4 can potentiate the early asthmatic response of asthma patients to inhaled grass pollen allergen. They are broadly concordant with the observations of BYLIN *et al.* [27] of enhancement of early asthmatic responses to birch pollen in asthmatic volunteers exposed to particulate matter (particles with a 50% cut-off aerodynamic diameter of 2.5 μm ($PM_{2.5}$) >100 μg·m^{-3}) and NO_2 (>300 μg·m^{-3}) in a road tunnel. The effect size (-4.3%) that was observed is small, but it is similar to that observed for the potentiating effect of other pollutants, such as O_3 and NO_2, on the early airway response of asthmatics challenged with allergen, when examined in studies of similar design [27, 28]. This may reflect a limitation of this sort of study design, in that it prevents assessment of any change in the slope of the dose-response curve for allergen. Alternatively, it raises the question of whether air pollutants might be able to exert an "all or nothing" effect on what might prove to be a finite response of asthmatic airways to air pollutants. Nonetheless, these results may offer a potential explanation for the observed association between particulate air pollution and exacerbations of asthma at a population level. Unfortunately, despite the use of a highly characterized aerosol, these results do not allow the authors to conclude whether the observed effect might be dependent on the simple presence of particles or on their chemical composition or acidity.

Mechanisms to produce the observed changes are not clear. Theoretically they may reflect changes in the permeability of the respiratory epithelium to allergen [29], the priming or activation of cellular and/or chemical cascades involved in allergen handling [30], or even dynamic changes in the autonomic control of airway tone, in response to pollutant exposure [31]. The finding that allergen responsiveness exposure is affected 14 h after H_2SO_4, suggests a long-lasting priming effect. This mechanistic uncertainty is further compounded by the limited understanding of the fate of exposure aerosols once they have been inhaled, despite the rigor with which the authors have attempted to characterize them. It remains unclear

Table 4. – Late asthmatic response

Subject	Air			100 μg·m^{-3} H_2SO_4			1000 μg·m^{-3} H_2SO_4		
	Baseline FEV1	Minimum FEV1	% change	Baseline FEV1	Minimum FEV1	% change	Baseline FEV1	Minimum FEV1	% change
1	1.94	1.78	-8.25	2.10	1.92	-8.57	2.05	1.78	-13.17
2	2.80	2.48	-11.43	2.82	2.42	-14.18	2.86	2.51	-12.24
4	2.85	2.85	0.00	2.97	2.87	-3.37	3.11	3.11	0.00
5	2.79	2.63	-5.73	2.37	2.37	0.00	2.45	2.45	0.00
6	3.31	2.88	-12.99	3.24	3.02	-6.79	3.30	2.80	-15.15
7	2.81	2.81	0.00	2.75	2.62	-4.73	2.78	2.78	0.00
8	3.96	3.96	0.00	3.81	3.81	0.00	4.12	4.02	-2.43
10	2.81	2.64	-6.05	2.76	2.61	-5.43	2.64	2.47	-6.44
11	3.01	2.88	-4.32	2.93	2.93	0.00	2.89	2.78	-3.81
13	3.62	3.22	-11.05	3.55	3.14	-11.55	3.67	3.18	-13.35
Mean	2.99	2.81	-6.0	2.93	2.77	-5.5	2.99	2.79	-6.7

H_2SO_4: sulphuric acid; FEV1: forced expiratory volume in one second. There were no significant differences in the late asthmatic responses between exposures.

to what extent the aerosols will be modified by exposure to the humid environment of the human airway. Individual particles may be subject to growth and this might be expected to have significant effects on their regional deposition within the respiratory tract. Such uncertainty is mirrored by the authors' limited knowledge of the regional fate of the ambient aerosol in the normal human airway [12] and in the presence of disease states such as COPD [32].

The authors failed to detect any significant effect of particulate H_2SO_4 exposure on the late asthmatic responses of the volunteers. The study was not designed to test this hypothesis as subjects were recruited on the basis of their early asthmatic responses. No conclusions about the effect of H_2SO_4 exposure on the late asthmatic response can be drawn.

In the UK, sulphates account for 20–25% of urban, total suspended master by mass [11], of which 85% is in the fine (<2.5 μm) fraction. In the USA, sulphates comprise 20–40% of measured particles with a 50% cut-off aerodynamic diameter of 10 μm (PM10) [33]. Few measurements of atmospheric H_2SO_4 concentrations have been made in the UK, and most were made in the 1950s and 1960s. In a more recent study from rural Essex, the peak concentration recorded over a 62 day period in 1987 was 8.7 $\mu g \cdot m^{-3}$ [34]. Data from rural sites in North America have shown higher values, with maximum daily means $\leqslant 15$ $\mu g \cdot m^{-3}$ in the summer months during 1983–1986, and values of $\leqslant 27$ $\mu g \cdot m^{-3}$ over shorter periods in the late 1970s [35]. Maximum hourly average urban concentrations in the UK now rarely rise >50 $\mu g \cdot m^{-3}$, although earlier this century, hourly averages may at times have exceeded 1,000 $\mu g \cdot m^{-3}$.

In summary, the authors have shown potentiation of the early asthmatic response to grass pollen allergen of subjects with mild asthma by particulate sulphuric acid, and that the degree of this potentiation is similar to that previously shown for nitrogen dioxide and ozone. The reasons for this are not clear, but exploration of sulphuric acid exposures in the presence of other pollutants (including insoluble particles), and, possibly, studies of the autonomic consequences of such exposures, are needed to elucidate the likely mechanisms and to determine how these volunteer studies might relate to real-life exposures.

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