

Human Health Effects of Exposure to Airborne Acid

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This paper summarizes and critiques a series of reports on the health effects of acid aerosol exposure, presented at the Symposium on the Health Effects of Acid Aerosols and compares these data to selected previous studies. The role of the two major defenses against acid aerosols, the conversion of acid to the ammonium salts by respiratory ammonia and buffering of acid by airway surface liquid are discussed in relation to airway acid burdens expected from typical inhalation exposures. The roles of particle size and hygroscopicity on airway deposition of aerosol are also included. The major health effects studied were the effects of acid aerosol on mucociliary clearance in healthy individuals and changes in lung function in asthmatics, an important sensitive subpopulation. The broad range of response in asthmatics suggests the need for further study.

The level of complexity involved in investigating the human health effects of airborne acidic compounds is considerably greater than that for common gaseous pollutants such as ozone. A comprehensive understanding of the issues involved in the generation of chamber exposure atmospheres, deposition, and neutralization in the human respiratory tract, and the mechanisms of response is essential to the long range goal of understanding the health consequences of atmospheric acids. Table 1 shows some of the factors that must be considered in assessing the effects of exposure to two pollutants, ozone (O₃) and sulfuric acid (H₂SO₄) aerosol.

Deposition

One of the major determinants of the response to particulate acid is the distribution of the deposited aerosol within the respiratory tract. Variables that alter deposition include partitioning of airflow between the oral and nasal airways, particle size distribution, hygroscopicity, and several factors related to the breathing pattern. The paper by Bowes et al. describes the marked variability in upper airway deposition of "acid fog" aerosol despite efforts to control many of these variables (1). It was pointed out that the geometry of the oral airway is a critical factor in deposition of these large aerosols; modification of position of the tongue and separation of the teeth may alter deposition.

Defenses

There are two important lines of defense against acid aerosols: neutralization by oral and airway ammonia and buffering by the mucus lining of the airways. The model presented by Larson and co-workers (2) describes the effects of oral versus nasal breathing on the deposition of acid, a major determinant of which is the quantity of acid neutralized in the upper respiratory tract, since a portion of the acid will be converted to the ammonium salt prior to deposition. Depending on the ammonia concentration, flow rate (or residence time in the airway), particle size, and hygroscopicity, up to 100% of the acid may be neutralized before it passes into the trachea. The model estimates presented by Larson are in general agreement with previous model calculations (2,3).

A series of papers have been presented by Holma et al. (4,5) describing the capacity of airway mucus to buffer changes in airway surface pH that result from acid deposition in the respiratory tract. A man breathing 100 µg/m³ of H₂SO₄ aerosol at 20 L/min for 30 min will inhale approximately 60 µg of acid. If only 50% is deposited, this amounts to only 30 µg or 0.6 µmole of H⁺. Holma estimated that 8 to 16 µmole of H⁺ would be required to decrease the pH of 2.1 mL of mucus (the estimated volume that coats the airways at any one time) from approximately 7.4 to approximately 6.5 (5); ciliostasis has been observed at pH values ranging from 5.2 to 6.4. The normal pH of the airways in man ranges from 6.5 to 7.5, with a mean value of about 6.9 (6), but the airway pH may be more acidic in the case of airway inflammation or respiratory acidosis. Holma's estimates are based on expectorated sputum from

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Table 1. Comparison of O₃ and H₂SO₄ exposure studies.

Factor	O ₃	Acid aerosol
Factors affecting dose		
Exposure duration	Yes	Yes
Ventilation	Yes	Yes
Oral/nasal partitioning	Minimal effect	Important
Concentration	Yes	Yes
Particle size (MMAD)	No	Yes
Particle distribution (σ_g)	No	Yes
Humidity	Minimal effect	Yes
Temperature	Mimimal effect	Yes
Surface properties	No	Yes
Deposition/loss in upper airways	Fairly consistent	Highly variable
Air-phase neutralization	No	Yes
Reactions on airway surface	Forms byproducts	Mucus buffering Forms byproducts
Ease of measurement of sensitive physiologic end point	Yes (spirometry)	No (clearance)
Ease of generation and control of artificial environment	Simple	Complex

smokers; however, the buffering capacity of mucus from nonsmokers and especially from asthmatics, who normally have a lower mucus pH, may be considerably less. Furthermore, aerosol will not necessarily be evenly distributed over the mucus lining but will likely have considerable regional variation, depending on aerosol size.

Mucociliary Clearance

One of the major sensitive end points used to assess acid aerosol exposure is an alteration in mucociliary clearance. Earlier studies of clearance were often

inconclusive because they used larger tracer aerosols that deposited in the trachea and major bronchii and did not always measure clearance at the site of deposition of the acid aerosol. Also, the tracer aerosols were typically inhaled prior to the acid aerosol exposure to reduce the possibility of alteration of tracer aerosol deposition as a result of acid aerosol-induced changes in airway diameter. This sequence probably caused investigators to miss some of the effect of acids on clearance (7) (Fig. 1). The recent study by Spektor et al. addresses many of these problematic concerns (8). In this study, a more homogeneous population of subjects, most of whom had normally rapid clearance, clearly demonstrated a decreased clearance after exposure to 100 $\mu\text{g}/\text{m}^3$ H₂SO₄ for 1 hr. After a 2-hr exposure, the depression of clearance was greater and tended to persist for a longer period of time.

Spektor's recent study suggests some design features that should be considered in studies of clearance associated with acid aerosol exposure. First, tracer aerosols should be given after exposure as long as there is no evidence of major changes in lung mechanics, since, in the postexposure period, the effects of acid will be more pronounced than at the beginning of exposure. Second, a relatively homogeneous population of subjects with normally rapid clearance should be used because such subjects appear to be a more measurable, and possibly, a more sensitive population. Finally, tracer aerosols should have approximately the same deposition pattern within the lung region of interest as the acid aerosol to which the subjects are being exposed.

It is important to continue this line of research to determine effects of even longer acid aerosol exposures, including exercise and unencumbered breathing. Also, repeated exposure appears to have cumulative effects in animals; this must be evaluated in man. Since both O₃ and H₂SO₄ depress clearance, investigation of the effects of a combined exposure on clearance is obviously indicated.

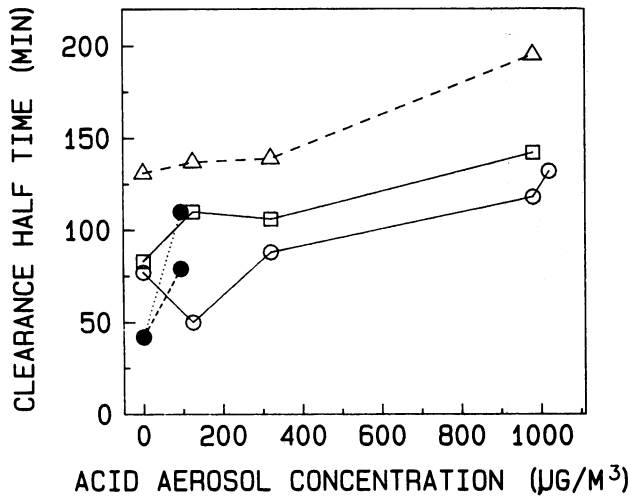


FIGURE 1. The clearance half time (i.e., time required to clear half the deposited tracer aerosol) as a function of the concentration of acid aerosol to which subjects were exposed. All exposures were for 1 hr to 0.5 μm H₂SO₄ aerosol, except the one 2-hr exposure reported by Spektor. Note the broad range of baseline clearance rates. (○) Leikauf et al. (7); (□) Leikauf et al. (16); (△) Spektor et al. (17); (●) Spektor et al. (8).

Studies of mucus biochemistry and rheology using directly harvested samples (from the nose or via bronchoalveolar lavage from the lung) will provide further insight into the effects of inhaled acids on the airway surface fluid layer. Holma has suggested that H^+ absorption by mucus results in increased viscosity, thus affecting momentum transfer from the underlying cilia (9). Changes in viscosity are dependent upon the concentration of mucus glycoproteins, as well as the ionic milieu of the mucus.

Asthmatics

Another highly sensitive end point for acid aerosol exposure appears to be pulmonary function responses of asthmatics. The large variability in the responses of asthmatics is shown in Figure 2 and was evidenced by two of the papers presented at this meeting. On the one hand, Koenig et al. found modest decreases in FEV_1 , FEF_{50} and other measures of lung function in adolescent asthmatics after a 40-min exposure to $68 \mu\text{g}/\text{m}^3$ of $0.55 \mu\text{m}$ droplets of H_2SO_4 (10). There was no significant increase in symptoms reported by the adolescent asthmatics. In contrast, Hackney et al. studied adult asthmatics exposed to up to $2000 \mu\text{g}/\text{m}^3$ of either $10 \mu\text{m}$ acid fog or $0.9 \mu\text{m}$ acid aerosol (11). The adult asthmatics showed pulmonary function effects from the smaller acid aerosol at concentrations in the $1000 \mu\text{g}/\text{m}^3$ range, but not at the lower concentrations. However, there was a concentration-dependent increase, primarily in lower respiratory symptoms. Increases in symptomatology were evident with both the acid fog and the smaller acid aerosol.

The marked differences between the responses in these two subject populations underscores the complexity of the issues involved in understanding the effects of acid aerosols. Certainly, the differences in exposure protocols are noteworthy (Table 2). The larger particle sizes and higher inspiratory flow would suggest greater upper (supralaryngeal) airway deposition in the adults. This could lead to increased upper respiratory symptoms with no change in airway mechanics in the acid fog studies. However, with ex-

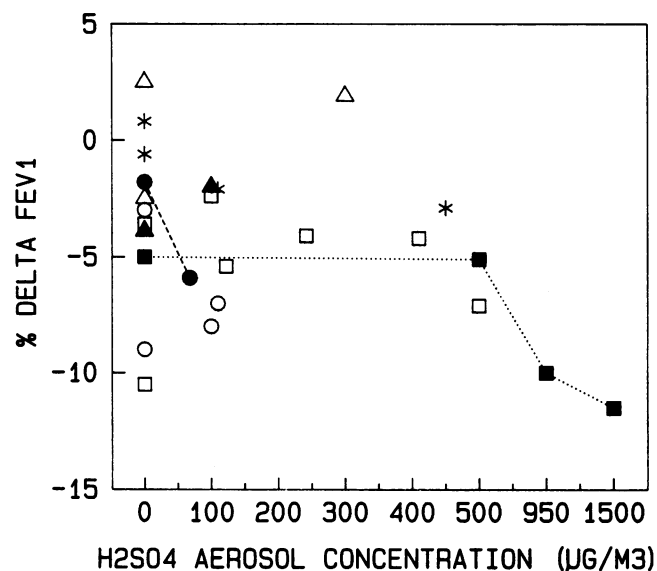


FIGURE 2. Change in FEV_1 in asthmatics exposed to various concentrations and particle sizes of H_2SO_4 aerosol. See specific references for relevant details on exposure duration, particle size, etc. (○) Koenig et al. (18,19); (●) Koenig (10); (□) Avol et al. (20,21) and Linn et al. (22); (■) Hackney et al. (11); (△) Horstman et al. (12); (*) Utell et al. (23); (▲) Spektor et al. (17). Dashed and dotted lines indicate data for the two studies presented at this symposium. Note the nonlinear scale on the horizontal axis.

posure to the smaller $0.9 \mu\text{m}$ aerosol, there was a predominance of lower respiratory symptoms, which was accompanied by small functional changes in Hackney's adult asthmatics (11). Adolescent asthmatics may have lower oral ammonia (NH_3) levels or may have a lower buffering capacity of airway mucus relative to adult asthmatics. Other factors including greater penetration of the $0.55 \mu\text{m}$ H_2SO_4 aerosol and differences in nonspecific airway reactivity or in airway permeability might also explain some of the differences. However, it is clear that further studies on adolescent asthmatics will be required to confirm these observations and to provide evidence that a dose-response relationship exists for acid aerosol-induced changes in spirometry in this subpopulation.

Table 2. Comparison of studies on asthmatics exposed to H_2SO_4 aerosol.

Variable	Koenig et al. (10)	Hackney et al. (11)
Subjects	Adolescent allergic asthmatics	Mild adult asthmatics
Acid concentration	$68\text{--}100 \mu\text{g}/\text{m}^3$	$500\text{--}2000 \mu\text{g}/\text{m}^3$
Particle size	$0.55 \mu\text{m}$	$0.9 \mu\text{m}$
Relative humidity, temperature	65%, 25°C	50%, 22°C
Fog particles	NA	$10 \mu\text{m}$
Ventilation	35 L/min	50 L/min
Breathing mode	Oral facemask	Unencumbered
Neutralization	Poorer defenses? Less ammonia?	100% for fog < $500 \mu\text{g}/\text{m}^3$?
End points	$\downarrow FEV_1$ $\downarrow FEF_{50\%}$	$\downarrow FEV_1$ at $1000 \mu\text{g}/\text{m}^3$
Symptoms	No change	\uparrow Symptoms
Deposition	Tracheobronchial? Alveolar?	More in the head?

In addition to H₂SO₄ aerosol, Keonig's subjects were also exposed to sulfur dioxide (SO₂) or the combination of acid and SO₂. Spirometric indices of lung function did not show any greater effects with the mixture of SO₂ and acid than with acid alone (Table 3). Previous work by Horstman and colleagues (12) in a study of SO₂ and acid exposures in young adult asthmatics initially suggested a slightly greater response with SO₂ plus acid than with SO₂ alone. However, since completion of this study with a larger group of subjects, this preliminary observation of the worsening of response with the combination exposure was not substantiated (D. H. Horstman, personal communication).

Response Mechanisms

In a series of papers from the Cardiovascular Research Institute, Balmes et al. (13) and Fine et al. (14) have examined the hypothesis that H⁺ availability is the primary stimulus for the increase in airway resistance observed with acid aerosol inhalation in asthmatics. At this symposium, Balmes summarized evidence that supports the titratable acidity hypothesis previously described (14). New evidence was provided in which a role was proposed for sulfite/bisulfite ion in the induction of airway narrowing. Although few asthmatics (5–10%) are reactive to ingested sulfites, many more are reactive to inhaled sulfites. These studies were originally designed to probe potential mechanisms of SO₂-induced bronchoconstriction. The studies suggest a possible role for bisulfite ion in this process. Because the levels of sulfite/bisulfite tested in these studies are much higher than would be anticipated in the ambient environment, and because the sulfites require an acidic medium to prevent oxidation, they may only be of concern when they are formed in or are attached to acid aerosols. Because of the confounding influence of SO₂ liberation from the sulfite solutions and the possible oxidation of sulfite to sulfate, further work will be necessary to understand these interesting observations.

Another factor, especially with regard to the acidic fogs, is the osmolarity of the aerosols. Hypoosmolar aerosols alone are capable of eliciting bronchoconstriction; this effect is enhanced by acidification. However, unbuffered isoosmolar acid solutions are less irritating, as was observed in the Fine study (14), which suggests there may be a synergistic effect of hypo-

osmolarity and H⁺. It is notable that, even though they were inhaled for only a brief period, extremely high concentrations (40 mg/m³) of 5 to 6 μm isoosmolar acid particles did not cause remarkable changes in airway resistance.

Field Studies

The Ontario Camp studies (15) showed some influence of O₃ and acid aerosols on lung function and, in addition, a rather striking association between ambient temperature and lung function. It is important not to arbitrarily dismiss this association because there is a good physiological explanation for such a trend. Lung function test measurements are typically corrected to BTPS (body temperature, ambient pressure, saturated). Vigorous physical activity may result in substantial increases in actual body temperature (T_{re}), which can cause a small systematic error (0.5 to 0.7% FVC/°C increase in T_{re}) in the application of the BTPS correction factor if the T_{re} is assumed to be 37°C. The effect of this errant correction factor is less if the spirometer temperature is closer to body temperature. Furthermore, activity-related elevations in T_{re} are resolved fairly rapidly; 30 min of rest or quiet activity prior to pulmonary function measurements would minimize deviations of body temperature from normal. The potentially confounding effect of changes in body temperature should be considered in the design of future field studies.

Conclusions

Greater technical efforts will be required to adequately characterize the health effects of airborne acid due in part to the multitude of factors that influence the target tissue dose. Further investigation will be necessary to define the role of NH₃ neutralization and airway surface liquid buffering and to determine the possible reasons for the individual variability in the capacity to neutralize and buffer inhaled acid. The importance of exposure duration and repetition on acid-induced changes in mucociliary clearance needs to be more fully explored because this effect may represent a critical link between acid exposures and possible exacerbation of lung disease. Combination studies of O₃ and H₂SO₄ aerosol may provide evidence of additive or synergistic effects in man, especially for end points such as change in mucociliary clearance, airway reactivity, or airway epithelial permeability. Finally, it is essential that the apparent discrepancy between the acid aerosol responses of adolescent allergic asthmatics and adult asthmatics be resolved; this will ultimately require greater understanding of response mechanisms and improved characterization of dose.

Table 3. Effects of H₂SO₄ aerosol on spirometry in asthmatics.^a

Aerosol composition	% change in FEV ₁	% change in FEF _{50%}
Air	- 1.8	- 5.2
H ₂ SO ₄	- 5.9	- 13.4
SO ₂	- 2.3	- 7.3
H ₂ SO ₄ + SO ₂	- 3.5	- 10.3
H ₂ SO ₄ - air	- 4.1	- 8.2
(H ₂ SO ₄ + SO ₂) - air	- 1.7	- 5.1

^aData from Koening (10).

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