

# Airborne Acidity: Estimates of Exposure and Human Health Effects

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Human health effects have resulted from the inhalation of ambient acidic aerosols, and there is suggestive evidence that current North American levels of exposure are producing excesses in respiratory morbidity. Annual mean mortality rates have been correlated with ambient aerosol concentration indices, with  $\text{SO}_4^{2-}$ , FP, IP, and TSP having a descending order as predictive coefficients. These pollutant indices also contain  $\text{H}^+$  in descending mass ratios, and may all be surrogates for  $\text{H}^+$  as an active agent. Controlled exposure studies in humans and animals provide evidence that acidic aerosols produce greater changes in respiratory mechanical function and rates of particle clearance than other constituents of ambient particulate matter.

The strong acid content of the ambient aerosol has not been measured in any of the population based pollutant effects studies in which it is a likely causal factor. The absence of direct measurement data on acidic aerosol in these studies, and their reliance on surrogate indices such as  $\text{SO}_2$  and  $\text{SO}_4^{2-}$ , precludes firm conclusions about exposure-response relationships. High priority areas for further investigation include (a) systematic investigation of the spatial and temporal distribution of population exposures; (b) extension and refinement of population response studies in relation to acid aerosol exposures; (c) responses of normal healthy and asthmatic human volunteers to mixtures of acidic aerosols and oxidant vapors under controlled conditions of exposure and exercise intensity; and (d) progression of changes in lung epithelia during repetitive daily exposures of experimental animals to acidic aerosols, oxidants, and their mixtures, with concurrent measurements of particle clearance and respiratory function.

## Introduction

Session 1 of this Conference was designed to address the question of whether there are human health effects from the inhalation of pollutants associated with acid precipitation. The authors presented excellent reviews in their assigned topics, including much new and important information. The session ended with a comprehensive review by Hackney, which relieves me of the need to present a summary of current knowledge on the topics that he covered. Still, it is clear that we cannot adequately describe the nature and extent of the effects of the inhalation of acidic pollutants on human health at this time. We just don't know enough about either population exposures or exposure-response relationships to make a satisfactory risk assessment.

We do, however, know a great deal about some aspects of the problem and can describe the critical data gaps on others. Thus, the Proceedings of this Conference can be of great value to NIEHS, EPA, DOE, EPRI and other research sponsors with programmatic interests in this potentially important problem. I will, therefore, rephrase the basic question into a series of more clearly defined critical issues, and attempt to summarize our current knowledge in each. I will draw extensively

on the papers presented in Session 1, and use other available information to help complete the overall assessment.

The discussion will focus primarily on acidic aerosols for several reasons. One is that their role in air pollution health effects has not been well understood or systematically discussed in the past in comparison to acidic vapors such as  $\text{SO}_2$  and  $\text{NO}_2$ . Another is that acidic aerosols may have played a much more important role in producing effects than the pollutant vapors. Finally, as secondary pollutants, acidic aerosols may be affecting a larger percentage of the population than acidic vapors, which are primary pollutants.

While acidic aerosols will be the primary focus, I will also be discussing some actual or potential health effects associated with exposures to acidic vapors. One reason is that studies on vapors demonstrate mechanisms of biological response which help us understand the effects of the aerosols. Another is that the health effects of interest may require concurrent exposure to both aerosols and vapors, or that one pollutant may potentiate the effects of the other.

The specific questions that I will address in this paper are:

- Have health effects from exposure to ambient acidic aerosols been demonstrated in the past?
- Do current North American exposures to ambient acidic aerosols produce measurable health effects?

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- What are current North American exposures to ambient acidic aerosols?
- What are the effects of single brief exposures to acidic aerosols on respiratory mechanics?
- What are the effects of single brief exposures to acidic aerosols on rates of particle clearance from the lungs?
- What are the effects of repetitive exposures to acidic aerosols on lung structure and function?
- What are the implications of persistent structural and functional alterations in the lung to the pathogenesis of chronic respiratory disease?
- Are there especially sensitive subgroups in the population? If so, who are they?
- Do other ambient pollutants potentiate the effects of acidic aerosols on the respiratory tract?
- What are the critical knowledge gaps that limit our ability to assess the health impact of inhalation exposures to acidic aerosols?

### Have Health Effects of Ambient Acidic Aerosols Been Demonstrated?

The answer to this question is clear. Kitagawa (1) identified sulfuric acid ( $H_2SO_4$ ) as the causal agent for approximately six hundred cases of respiratory disease in the Yokkaichi area in central Japan between 1960 and 1969. As shown in Figure 1, the patients, residences were concentrated within 5 km of a titanium dioxide plant with a 14-m stack which emitted from 100 to 300 tons/month of  $H_2SO_4$  in the period 1961 to 1967. The average concentration of  $SO_3$  in February 1965 in Isozu, a village 1 to 2 km south of the plant, was  $130 \mu g/m^3$ , equivalent to  $159 \mu g/m^3$  of  $H_2SO_4$ . Kitagawa estimated that the peak concentrations might be up to 100 times as high with a north wind. Electrostatic precipitators were installed to control aerosol emissions in 1967, and after 1968 the number of newly found patients with "allergic asthmatic bronchitis" gradually decreased. Kitagawa's quantitative estimates of exposure of  $H_2SO_4$  and the criteria used to describe cases of respiratory disease may well differ from current U.S. methods. The unique aspect of this report is the clear identification of  $H_2SO_4$  as the causal agent for an excess in morbidity, and the absence of likely confounding pollutant factors.

Other evidence of links between high concentration of ambient sulfuric acid and human health effects is more circumstantial. Sulfuric acid concentrations in the ambient air were certainly much higher than current levels during the classic episodes in London, Meuse Valley, and Donora, but so were many other pollutants. Similarly, the decline in the prevalence of chronic bronchitis among nonsmokers in the U.K. over the past three decades could have been due to the decline in any of several pollutants. However, on mechanistic grounds, sulfuric acid is a more plausible candidate than  $SO_2$ , carbonaceous particles, and other constituents of the London atmospheres of earlier times as the causal agent for the well documented excesses in mortality and morbidity. In Session 1, Schlesinger presented evidence linking

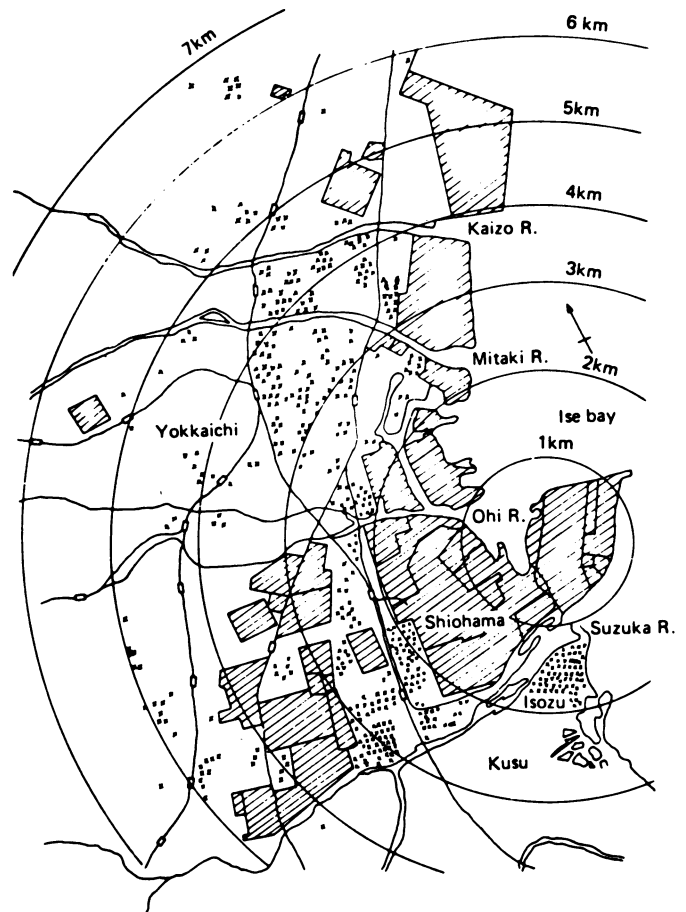


FIGURE 1. Regional distribution of patients in the Yokkaichi area: (x) patient's residence (1).

repetitive sulfuric acid exposures in animals, at concentrations which occurred regularly in the U.K., to airway changes possibly associated with the pathogenesis of chronic bronchitis.

### Do Current North American Exposures to Ambient Acidic Aerosols Produce Measurable Health Effects?

I have no definite answer to this question, but do have a strong suspicion that further research could produce a positive answer. Two recent population-based studies have demonstrated excess respiratory tract morbidity in association with pollutant exposures which did not exceed current U.S. National Ambient Air Quality Standards (NAAQSs). In addition, Ozkaynak and Spengler, in Session 1, presented a discussion of some preliminary cross sectional analyses of daily mortality in 98 standard metropolitan statistical areas (SMSAs) in 1980, showing that among the aerosol indices available, sulfate correlated best with mortality. The discussion which follows focusses on the relationships between the pollutant and health indices measured in these studies

and the concentrations of acidic aerosols.

In the first of these studies, Bates and Sizto (2) correlated 4 years of routinely collected hourly pollutant indices from 15 sampling stations in Southern Ontario with hospital admissions in all of the 79 acute care hospitals serving the same region. They found highly significant ( $p \leq 0.001$ ) associations between summertime hospital admissions for respiratory disease and  $\text{SO}_2$ ,  $\text{O}_3$  and temperature, with 24 and 48 hr lags for the environmental variables. Nonrespiratory hospital admissions were not associated with the environmental variables. Also, there were no significant associations between respiratory admission and levels of  $\text{NO}_2$  and coefficient of haze (CoH), a crude index of carbonaceous particulate matter.

More recently, Bates (3) extended these analyses by including sulfate concentrations in the multiple regressions, and demonstrated that sulfate correlated much better with asthma admissions than the other environmental variables. While asthma admissions rose in both summer and winter, total admissions declined. Sulfate concentrations also rose over the period 1976 to 1980, while all other pollutants had reduced concentrations over the same period. At the low sulfate concentrations which occurred, it is quite unlikely that ammonium sulfate could be the causal factor for the increase in asthma admissions. It is much more likely that sulfate serves as a surrogate for the more acidic sulfates ( $\text{H}_2\text{SO}_4$  and  $\text{NH}_4\text{HSO}_4$ ). Another observation was that elevated  $\text{O}_3$  appears to contribute to the effect of sulfate (or  $\text{H}^+$ ) on respiratory morbidity.

In the second study relevant to this discussion, Schenker et al. (4) studied the influence of coal combustion effluents on a downwind rural population in the Chestnut Ridge area of Western Pennsylvania. Questionnaires were administered to 5557 adult women, and they were assigned exposures on the basis of their proximity to the nearest three of the seventeen air monitoring sites in the region at which routine measurements were made of  $\text{SO}_2$  and TSP. Over the 4-year study, the 1420 women in the high exposure area had 24 hr and annual average  $\text{SO}_2$  exposures that were either at or above the current NAAQS values. For 3222 women in the medium exposure group, the  $\text{SO}_2$  exposures were below the NAAQS. The 24-hr particulate concentrations were almost all below the NAAQS, and were influenced by nonpower plant sources. The highest annual average total suspended particulate (TSP) was  $90 \mu\text{g}/\text{m}^3$ . The concentrations of  $\text{NO}_2$  were highly correlated with those of  $\text{SO}_2$ .

As a risk factor,  $\text{SO}_2$  was associated with "wheeze most days or nights" in nonsmokers, with the relative risks of residents of low, medium and high  $\text{SO}_2$  areas being 1:1.26:1.58, respectively ( $p = 0.02$ ). The relative risks for those living in the same areas for at least five years were 1:1.40:1.95, respectively ( $p \leq 0.01$ ). For grade 3 dyspnea among long-term resident nonsmokers, the relative risk for elevated  $\text{SO}_2$  was 1.23, with a confidence limit of 0.98 to 1.54 ( $p = 0.11$ ).

Thus,  $\text{SO}_2$  concentrations at and below the NAAQS

appear to be associated with increased wheeze in nonsmokers, with greater risks associated with long-term (> 5 yr) exposure. This represents the first association of a chronic health effect with  $\text{SO}_2$  at levels near the current NAAQS where the influence of black smoke or TSP did not appear to be a major confounding factor.

While it is possible that  $\text{SO}_2$  was the causal factor for the excess in wheeze, it appears more plausible that the causal factor was an associated, but not measured, pollutant. The primary effluent from the power plant stacks includes a submicrometer-sized condensation aerosol containing sulfuric acid, as well as  $\text{SO}_2$ . It is much more plausible to associate the small airway narrowing associated with wheeze with submicrometer acidic aerosol which deposits primarily in small airways, as discussed in Session 1 by Martonen, than with a relatively low concentration of an upper respiratory irritant such as  $\text{SO}_2$ .

In the report in Session 1 by Özkaynak and Spengler on a preliminary analysis of 1980 cross-sectional mortality for the U.S., predictors of mortality due to air pollution were expressed in terms of four aerosol pollutant surrogates, i.e., TSP, IP (inhalable particulate), FP (fine particulate), and  $\text{SO}_4^{2-}$  (sulfate). In order of magnitude of coefficient and level or significance between mortality rate and pollutant surrogate, they were  $\text{TSP} < \text{IP} < \text{FP} < \text{SO}_4^{2-}$ . Among these, only FP and  $\text{SO}_4^{2-}$  had statistical significance as predictors of response but these two surrogates'  $p$  values were typically less than 0.01.

In terms of mass concentration at a particular time and place,  $\text{TSP} > \text{IP} > \text{FP} > \text{SO}_4^{2-}$ . The reasons for this progression are quite simple. IP and FP are, by definition, subsets of TSP based on upper aerodynamic particle size limits.  $\text{SO}_4^{2-}$  is less than FP because essentially all of the  $\text{SO}_4^{2-}$  is in the fine particles, which also includes a variable mass fraction of nonsulfate fine particles.

The measured  $\text{SO}_4^{2-}$  includes strong acids ( $\text{H}_2\text{SO}_4$  and  $\text{NH}_4\text{HSO}_4$ ) as well as the fully neutralized salt  $[(\text{NH}_4)_2\text{SO}_4]$ . Since the known physiological responses are related to acidity, as shown in Session 1 by Utell for mechanical function responses and by Schlesinger for clearance function responses, and since the  $\text{H}^+/\text{SO}_4^{2-}$  ratio is highly variable in time and location and is often close to zero,  $\text{SO}_4^{2-}$  is a relatively poor surrogate for acid aerosol concentration. A demonstration that  $\text{SO}_4^{2-}$  is a better surrogate for the active component of FP than is FP, IP or TSP still does not necessarily make it a good one.

If  $\text{H}^+$  is, in fact, the active agent in FP, then the magnitude of its coefficient and level of significance as a predictor of excess mortality in a cross sectional study of the type described by Özkaynak and Spengler in Session 1 would be substantially greater than that for  $\text{SO}_4^{2-}$ . Unfortunately, there are no historical data for  $\text{H}^+$  concentrations to test this hypothesis. A better prospect for an evaluation of human health effects of exposure to  $\text{H}^+$  lies in the ongoing six-cities study described by Ferris and Spengler in Session 1, at least

with respect to the influence of acidic aerosols on respiratory morbidity. In another report from this study, Ferris et al. (5) found that the frequencies of bronchitis, cough, and respiratory illness in children were positively associated with measures of exposure to TSP and SO<sub>2</sub>, but noted that substantial unexplained variation of illness and symptom rates among cities raises questions about the generalizability of these findings. Among these factors were a substantial excess in symptoms in the Tennessee and Ohio cities in relation to their TSP and SO<sub>2</sub> levels. This is of special interest to this discussion in that there is a greater proportion of acidic aerosol in the TSP in these cities than in other cities. Analyses to be performed on archived Teflon filters collected in the six-cities during the past two years and on filters currently being collected may help to establish a better basis for evaluating the specific influences of acidic aerosol exposures on respiratory morbidity.

### What are Current North American Exposures to Ambient Acidic Aerosols?

Unfortunately, our knowledge of the temporal and spatial distribution of acidic aerosol concentrations is extremely limited. Reliable measurements depend upon either expensive research instruments for monitoring, as described by Ferris and Spengler in Session 1, or the use of brief sampling intervals, special sampling substrates such as Teflon or acid-washed quartz fiber filters, storage in inert atmospheres between sample collection and analyses, and sensitive analytical assays. Virtually the entire data base up through 1983 is summarized in Table 1 from a review by Liroy (6). The three tables presented by Ferris and Spengler in Session 1, describing acidic events in Kingston, TN, St. Louis, MO, and

Watertown, MA, over 6 to 12 months, constitute a substantial increment to our still meagre data base. Another significant increment is a recent report by John et al. (7) for several locations in California.

The few data we do have relate primarily to secondary acidic aerosol. We know even less about the exposures resulting from primary acidic aerosols downwind of point sources, as in the Yokkaichi region in Japan or Chestnut Ridge, PA. Eatough et al. (8) have shown that significant secondary aerosol formation can also take place within a power plant plume. The normal 2 to 4%/hr conversion of SO<sub>2</sub> increased to 30 ± 4%/hr when the fresh plume passed through a fog bank.

In summary, we just don't know enough about either peak or average ambient concentrations of acidic aerosols to adequately interpret our available population response data, as in Chestnut Ridge and Southern Ontario, or to provide an adequate base for an environmental risk assessment.

### What are the Effects of Single Brief Exposures to Acidic Aerosols on Respiratory Mechanics?

The response of human volunteers to controlled single exposures to submicrometer sized sulfuric acid aerosols were well summarized by Utell in Session 1. He clearly demonstrated that asthmatics are substantially more sensitive in terms of changes in pulmonary mechanics than healthy people, and that vigorous exercise potentiates the effects at a given concentration. The lowest demonstrated effects level was 100 µg/m<sup>3</sup> via mouth-piece inhalation in exercising adolescent asthmatics. The effects were relatively small and appeared to dis-

Table 1. Ranges and peak concentrations of SO<sub>4</sub><sup>2-</sup>, H<sup>+</sup> (as H<sub>2</sub>SO<sub>4</sub>) and H<sub>2</sub>SO<sub>4</sub>, measured in various locations in the United States.

Study	Sample duration, hr	Concn range, µg/m <sup>3</sup>		Maximum SO <sub>4</sub> <sup>2-</sup> paired with acid			Maximum acid and paired SO <sub>4</sub> <sup>2-</sup>		
		SO <sub>4</sub> <sup>2-</sup>	H <sup>+</sup> (as H <sub>2</sub> SO <sub>4</sub> ) or H <sub>2</sub> SO <sub>4</sub>	SO <sub>4</sub> <sup>2-</sup> max.	H <sup>+</sup> (as H <sub>2</sub> SO <sub>4</sub> )	H <sub>2</sub> SO <sub>4</sub>	H <sup>+</sup>	H <sub>2</sub> SO <sub>4</sub>	Paired SO <sub>4</sub> <sup>2-</sup>
Glasgow, IL	12	7-48	≈ 0-39	48	39	-	39	-	48
St. Louis, MO									
1977 Summer	1	5-60	≈ 0-28*	60	-	28	-	28	60
1978 Winter	1	3-24	≈ 0-12*	24	-	7.6	-	12.8	18
Lennox	2-8	1.2-18	0-11*	18	-	0	-	11.0	9.6
Smoky Mountains	12	6.2-17.4	2.8-9.6	17.4	8.3	-	9.6	-	16.9
High Point, NJ	6	3.0-36.6	2.2-17.8	36.6	17.8	-	17.8	-	36.6
Brookhaven, LI, NY	3	1.0-23.7	0.3-10.2	22.9	10.2	-	10.2	-	22.9
Research Triangle									
Park, NC	2,4	3.6-19.8	≈ 0-9.8	19.8	9.8	-	9.8	-	19.8
Allegheny Mt., PA	12	1-32.5	0-20	32.5	19.1	-	20	-	31.5
Shenandoah Valley,									
VA	12	2-40	0-23	40	23	-	23	-	40
Tuxedo, NY	1-12	1-41	1-8.7	41		5.2		8.5	23
						(12 hr)			(1/2 hr)
Mendham, NJ	4,20	1-3.73	0.0-6.3	37.3	6.3	-	6.3	-	37.3
Houston, TX	12	2-32.4	0.0-7.6	32.4	7.6	-	7.6	-	32.4
New York, NY	6		nm**						

\*H<sub>2</sub>SO<sub>4</sub> directly.

\*\*Not measurable.

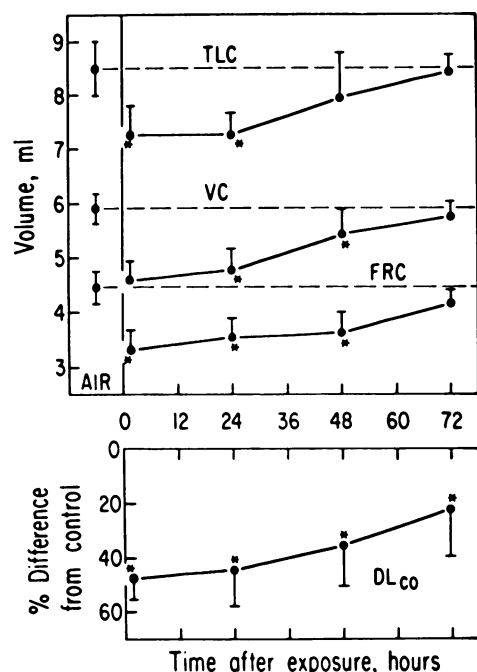


FIGURE 2. Changes in total lung capacity (TLC), vital capacity (VC), functional residual capacity (FRC), and CO-diffusing capacity ( $DL_{CO}$ ) in guinea pigs following a 3-hr exposure to 1 ppm  $SO_2$  and 5 mg/m<sup>3</sup> ZnO in a humid furnace. The asterisks (\*) indicate  $p < 0.05$  (9).

appear within about 15 minutes.

Utell also reported that a 30 min exposure to 0.3 ppm of  $NO_2$  produced mechanical function decrements in exercising asthmatics. Since the magnitude of the responses was similar to that seen in such subjects under similar test protocols in other studies with  $O_3$  concentrations of about 0.2 ppm, and since it is well established that  $NO_2$  is a much weaker oxidant than  $O_3$ , it appears likely that at least part of the  $NO_2$  response was something other than an oxidant effect. When  $NO_2$  is absorbed on airway surfaces, some of it hydrolyzes, releasing  $H^+$ . Thus, its action may be similar to that of  $H_2SO_4$  as well as that of  $O_3$ .

Some recent animal inhalation studies by Amdur (9) are of interest to this discussion because they demonstrate that effects produced by single exposures at very low acid concentrations can be persistent. She exposed guinea pigs by inhalation for 3 hr to the diluted effluent from a furnace which simulates a model coal combustor. Pulverized coal yields large particle mineral ash particles and an ultrafine ( $< 0.1 \mu m$ ) condensation aerosol. The core of the ultrafine particles consists of oxides of Fe, Ca, and Mg, covered by a layer containing Na, As, Sb, and Zn. The Zn is important because it generally has the highest concentration on the surface. As the particles cool further, there is surface formation and/or condensation of a layer of  $H_2SO_4$ . In Amdur's initial experiments, the model aerosol was a mixture containing  $SO_2$ , ZnO and water vapor. Figure 2 shows the results of a single 3-hr exposure to a mixture containing

1 ppm  $SO_2$  and 5 mg/m<sup>3</sup> ZnO passed through a humid furnace. The amount of sulfuric acid on the surface of the ZnO particles was less than 40  $\mu g/m^3$ . In control studies, neither 1 ppm of  $SO_2$  nor 5 mg/m<sup>3</sup> of ZnO alone produced any significant responses. There were also no significant responses to the mixture in the absence of water vapor and passage through the furnace. However, the humid mixture, passed through the furnace where it acquired a surface coating of  $H_2SO_4$ , produced significant decrements of total lung capacity (TLC), vital capacity (VC), functional residual capacity (FRC), and carbon monoxide-diffusing capacity ( $DL_{CO}$ ). At 12 hr after exposure, there was distention of the perivascular and peribronchial connective tissues, and an increase in lung weight. The alveolar interstitium also appeared distended. At 1 h, there was an increase in lung permeability. At 72 hr after exposure, TLC, VC, and FRC had returned to baseline levels, but  $DL_{CO}$  was still significantly depressed. Based upon her experience with pure  $SO_2$  and pure  $H_2SO_4$  exposures in the guinea pig model, Amdur concluded that the humid furnace effluent effect is an acid aerosol effect because of its persistence.

The persistent changes in function and morphological changes following exposure to very low levels of acidic aerosol suggest that repetitive exposures could lead to chronic lung disease. This possibility will be explored in future tests planned by Amdur. The implications of these changes in guinea pigs to human disease remains highly speculative.

### What Are the Effects of Single Brief Exposures to Acidic Aerosols on Rates of Particle Clearance from the Lungs?

As discussed by Schlesinger in Session 1, single brief exposures to acidic aerosols can either accelerate or retard mucociliary particle clearance, depending upon the dose distribution along the airways. As dose increases, mucus transport increases, reaches a maximal level, and then decreases. The effects, which are similar in humans and animals, are transient. In the rabbit, a single 1-hr exposure to submicrometer-sized  $H_2SO_4$  at 1 mg/m<sup>3</sup>, an exposure that produces a retardation in tracheobronchial mucociliary particle clearance, produces an increase in alveolar particle clearance during the first 2 weeks after exposure. Whether higher concentrations or longer times would produce a decrease in early alveolar clearance is not known at this time.

The effects on mucociliary clearance appear to be related to the pattern of  $H^+$  deposition on the airways. For 1-hr exposures to submicrometer-sized  $H_2SO_4$  in humans, there is no effect on tracheal transport. This should not be surprising, since there is virtually no acid deposited within the trachea. There is an acceleration of mucus transport in intermediate bronchi in which acid deposition is relatively low. Finally, there is a retardation in mucociliary clearance from the smaller conductive airways, where there is relatively more depo-

Table 2. Summary of major issues concerning exposures to airborne acidity and their human health effects.

Question	Answer <sup>a</sup>	Applicable conditions	Knowledge gap
Have health effects from exposure to ambient acidic aerosols been demonstrated in the past?	Yes	~ 600 cases morbidity; primary H <sub>2</sub> SO <sub>4</sub> ; point source avg. exposure = 160 μg/m <sup>3</sup>	Diagnostic criteria; Exposure variability in time and space
Do current North American exposures to ambient acidic aerosols produce measurable health effects?	Uncertain, but likely	Asthma admissions, secondary aerosol Wheeze, primary plume aerosol Excess daily mortality, secondary aerosol	H <sup>+</sup> vs. surrogate SO <sub>4</sub> <sup>2-</sup> H <sup>+</sup> vs. surrogate SO <sub>2</sub> H <sup>+</sup> vs. surrogate SO <sub>4</sub> <sup>2-</sup>
What are current North American exposures to ambient acidic aerosols?	Max. ~ 30 μg/m <sup>3</sup> as H <sub>2</sub> SO <sub>4</sub> (6 hr avg.)	Summer, rural N.E. United States	Spatial, diurnal, and seasonal variations
What are the effects of single brief exposures to acidic aerosols on respiratory mechanics?	Transient bronchoconstriction in exercising asthmatics	100 μg/m <sup>3</sup> H <sub>2</sub> SO <sub>4</sub> , adolescents 350 μg/m <sup>3</sup> H <sub>2</sub> SO <sub>4</sub> , adults	Effects in more severely disabled patients
	Persistent reduction in DL <sub>CO</sub> in guinea pigs	< 40 μg/m <sup>3</sup> H <sub>2</sub> SO <sub>4</sub>	Significance to human health effects
What are the effects of single brief exposures to acidic aerosols on particle clearance from the lungs?	↑ - mucociliary clearance ↓ - mucociliary clearance ↑ - alveolar clearance ↑ - activation of macrophages	≤ 100 μg/m <sup>3</sup> H <sub>2</sub> SO <sub>4</sub> , humans ≤ 250 μg/m <sup>3</sup> H <sub>2</sub> SO <sub>4</sub> , rabbits > 500 μg/m <sup>3</sup> H <sub>2</sub> SO <sub>4</sub> , humans > 750 μg/m <sup>3</sup> H <sub>2</sub> SO <sub>4</sub> , rabbits 1000 μg/m <sup>3</sup> H <sub>2</sub> SO <sub>4</sub> , rabbits 1000 μg/m <sup>3</sup> H <sub>2</sub> SO <sub>4</sub> , rabbits	Effects on lung epithelium
What are the effects of repetitive exposures to acidic aerosols on lung structure and function?	↑ secretory cells ↑ epithelial thickness ↑ alveolar clearance	250-500 μg/m <sup>3</sup> , 1 hr/day, 5 day/wk, rabbits	Progression of epithelial changes
What are the implications of persistent structural and functional alterations in the lung to the pathogenesis of chronic respiratory disease?	T-B tree: unknown, of concern because early changes parallel those from cigarette smokers  Alveolar region: unknown, of concern because persistent inflammation can lead to abnormal repair processes	Repetitive daily exposure to irritants, stimulation of mucus secretion  Continuous mild inflammatory response	Effects on respiratory mechanics and symptoms at later stages  Effects of macrophage activation and protracted recruitment of inflammatory cells and fibroblasts; structural changes in deep lung
Are there especially sensitive subgroups in the population? If so, who are they?	Yes: asthmatics, especially adolescents and with vigorous exercise	Bronchoconstriction, 100 μg/m <sup>3</sup> H <sub>2</sub> SO <sub>4</sub> or 0.3 ppm NO <sub>2</sub>	Effects in more severely disabled patients
Do other ambient pollutants potentiate the effects of acidic aerosols on the respiratory tract?	Yes		Other mixtures, sequences of exposures

sition of acid. In the rabbit, H<sub>2</sub>SO<sub>4</sub> is at least twice as effective per mole as NH<sub>4</sub>HSO<sub>4</sub>, and (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> and Na<sub>2</sub>SO<sub>4</sub> have no detectable effects on mucociliary clearance.

The effects of H<sub>2</sub>SO<sub>4</sub> on mucociliary clearance in asthmatics were similar to those seen in healthy nonsmokers, but the asthmatics had slower baseline clearance and also had effects on their respiratory function not seen in the healthy nonsmokers (10). Thus, they may have less capacity to cope with repetitive H<sub>2</sub>SO<sub>4</sub> exposures.

### What Are the Effects of Repetitive Exposures to Acidic Aerosols on Lung Structure and Function?

In Session 1, Schlesinger demonstrated that repetitive daily exposures of donkeys and rabbits to H<sub>2</sub>SO<sub>4</sub> at concentrations which, upon single exposure, produced either minimal transient effects or no effects on tracheobronchial mucociliary clearance function produced highly variable clearance rates and persistent shifts from baseline clearance rates. After 20 days of 1

Table 2. (continued)

Question	Answer <sup>a</sup>	Applicable conditions	Knowledge gap
What are the critical knowledge gaps that limit our ability to assess the health impact of inhalation exposures to acidic aerosols?	<p>Systematic data on the spatial and temporal distribution of population exposures.</p> <p>Extension and refinement of population response studies in relation to acid aerosol exposures.</p> <p>Progression of changes in lung structure during repetitive daily exposures of experimental animals to acidic aerosols, oxidants, and their mixtures, with concurrent measurements of particle clearance and respiratory mechanical function.</p> <p>Response of normal healthy and asthmatic human volunteers to mixtures of acidic aerosols and oxidant vapors under controlled conditions of exposure and exercise intensity.</p>		

<sup>a</sup> ↑ an acceleration in rate; ↓ a retardation in rate.

hr exposures, rabbits exhibited an increased density of secretory cells and thickened epithelial layers in medium and small conducting airways. During repetitive daily exposures, there was an acceleration of early alveolar clearance during the first 2 weeks of exposure and a similar acceleration at 8 to 10 weeks of exposure. The progression, or possibly the regression, of these changes in clearance rate during further periods of daily exposures needs to be determined. Hopefully, these issues will be clarified as the results from longer periods of exposure become available.

### What Are the Implications of Persistent Structural and Functional Alterations in the Lung to the Pathogenesis of Chronic Respiratory Disease?

The significance of the changes in particle clearance rate in the lungs from repetitive daily exposures to acidic aerosols, in terms of the pathogenesis of chronic respiratory disease, is not yet clear. However, the close correspondence between the effects of cigarette smoke and sulfuric acid aerosol on mucociliary clearance following both short-term and long-term exposures, the similarities in the epithelial changes following repetitive sulfuric acid inhalation in rabbits to those seen in the lungs of young smokers in post-mortem examinations, and the well established role of smoking in the etiology of chronic bronchitis combine to suggest that chronic bronchitis could result from long-term repetitive exposures to sulfuric acid (11). The fact that the incidence

of chronic bronchitis among nonsmokers was higher in the U.K. when ambient acid aerosol concentrations were high lends further plausibility to a causal relationship.

While there is plausibility for an association between chronic exposure to ambient acidic aerosols and chronic bronchitis, much more evidence is needed to demonstrate a clear causal relationship. Furthermore, even if one does exist, it may require higher levels of exposure than those currently occurring in North America. In any case, the widespread nature of exposures from fossil fuel combustion sources and the appreciable incidence of bronchitis among nonsmokers makes it important to study the possibilities.

### Are There Especially Sensitive Subgroups in the Population?

Utell's paper in Session 1 clearly demonstrated that asthmatics are an especially sensitive segment of the population with respect to the bronchoconstrictive effects of sulfuric acid and nitrogen dioxide. Furthermore, adolescent asthmatics may well be an especially sensitive subsegment of the asthmatic group. The evidence for asthmatics being especially sensitive to the effects of sulfuric acid on clearance function has not been established, although, as discussed by Spektor et al. (10), such sensitivity is likely on the basis that they have less reserve capacity for coping with stresses to the clearance system, and because their bronchoconstriction will lead to enhanced deposition of aerosols on their airways.

## Do Other Ambient Pollutants Potentiate the Effects of Acidic Aerosols on the Respiratory Tract?

Actually, this question may be misstated. In the examples of the combined effects of multiple pollutants presented by Schlesinger in Session 1, the acid material potentiated the effects of the other pollutants. Unfortunately, we know very little about the mechanisms by which the pollutants combine to produce their effects. The fact that real world exposures to ambient air always involve mixtures of acid aerosols, oxidant vapors, carbonaceous particles and various other pollutants with potential effects on lung epithelia provides a strong justification for additional research on the effects of mixed pollutants.

## What Are the Critical Knowledge Gaps?

Based upon the preceding discussion, it is clear that the gaps are both broad and deep. Among the high priority areas for further investigation are: systematic investigation of the spatial and temporal distribution of population exposures; extension and refinement of population response studies in relation to acid aerosol exposures; responses of normal healthy and asthmatic human volunteers to mixtures of acidic aerosols and oxidant vapors under controlled conditions of exposure and exercise intensity; and progression of changes in lung epithelia during repetitive daily exposures of experimental animals to acidic aerosols, oxidants and their mixtures, with concurrent measurements of particle clearance and respiratory function.

## Summary and Conclusions

The ten specific questions posed in the Introduction are restated in Table 2, along with summaries of my best attempts to answer them. Human health effects can result from the inhalation of ambient aerosols containing strong acids, and may be occurring at current peak ambient levels. The health effects seen from ambient exposures in recent population based studies, such as wheeze and hospital admissions for asthma, are consistent with the airway changes in animals seen after repetitive low-level exposures to  $\text{H}_2\text{SO}_4$  and the bron-

choconstrictive responses seen in human inhalation studies in asthmatics. However, the absence of direct measurement data on acidic aerosols in these studies, and their reliance on surrogate pollutant indices such as  $\text{SO}_2$  and  $\text{SO}_4^{2-}$ , prevents us from making any firm conclusions about the health effects of acidic aerosols at this time. The most critical knowledge gap is in the area of human exposure to acidic aerosols. The general lack of such data limits the value of population based exposure-response studies, and makes it impossible to perform a realistic risk assessment.

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