Review and Evaluation of Recent Literature

Occupational Exposure to SULFURIC ACID
REVIEW AND EVALUATION OF RECENT LITERATURE

OCCUPATIONAL EXPOSURE TO
SULFURIC ACID

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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I. INTRODUCTION

On June 6, 1974, the National Institute for Occupational Safety and Health (NIOSH) recommended to the Department of Labor an occupational health standard for exposure to sulfuric acid. That criteria document also reviewed the available information on toxic effects, sampling and analysis, work practices, and engineering controls. In it, NIOSH recommended a permissible exposure limit of 1 mg sulfuric acid mist/m$^3$ of air as a time-weighted average (TWA). Occupational exposure to sulfuric acid was considered to occur when the concentration of liquid, mist, or special dry powder of sulfuric acid or sulfur trioxide associated with oleum (fuming sulfuric acid) was equal to or above one-half the recommended permissible exposure limit (PEL). Medical monitoring, to be directed toward the teeth, eyes, skin, and cardiopulmonary system was recommended. While the PEL was based on pulmonary irritation, NIOSH also recognized that the corrosive, oxidizing, and sulfonating properties of sulfuric acid warrant a strong program of work practices to prevent skin and eye contact with sulfuric acid.

Since completion of the criteria document, several important issues concerning sulfuric acid have arisen. One is the use of catalytic converters. While these converters decrease other automobile emissions, they increase the amount of sulfuric acid in the atmosphere near roadways. A second issue is acid rain. In 1979, according to Babich et al [1], the President called for a minimum of 10 million dollars per year for research into the acid rain problem over the next 10 years. Sulfuric acid contributes to the acid rain problem when sulfur oxides are oxidized in the atmosphere. Smelters and coal-fired electric plants are the primary sources of these sulfur oxide emissions. Even though sulfuric acid is the largest volume chemical produced in the United States, little information concerning workplace exposure was found.

This report reviews and evaluates information that has become available since the 1974 document was completed. New information is described on sampling and analysis, work practices and engineering controls, and toxic effects reported in humans and animals exposed to sulfuric acid. This report considers information that could be identified as research needs in the criteria document, but does not extensively review the toxic effects that were thoroughly described in that earlier report. Articles describing new standards, uses, or sources as well as toxic effects were sought, and this information is presented if it indicates any change in the potential exposure of employees to sulfuric acid.
II. HUMAN EFFECTS

The adverse effects resulting from direct skin contact with concentrated sulfuric acid in humans are well known. These effects include charring and burning of the skin, mainly due to the acid's strong affinity for, and exothermic reaction with, water.

Jelenko et al in 1974 [2] reviewed the effects of ingestion of mineral acids and described the case histories of five patients they had examined. Three were turpentine workers who had accidentally ingested 50% W/V sulfuric acid. One, who did not actually swallow the acid, suffered severe burns of the mucous membranes of the mouth but recovered in 6 days. The other two required extensive hospitalization and had not fully recovered after 3 months; one examined a year after the accident still had esophageal strictures, although this did not interfere with his normal activities.

Coagulation necrosis developed wherever the acid had touched the patients [2]. Changes were observed along the entire alimentary tract, from lips to colon. Damage was more severe to the stomach, especially the pylorus and antrum, than to the esophagus. The patients developed severe stomatitis; strictures of the esophagus, gastroesophageal junction, and gastric antrum; coagulation necrosis of the stomach, duodenum, jejunum, and ileum; pancreatitis; omental fat necrosis; and severe peritonitis. Surgical intervention was necessary in four cases. From the clinical courses of their patients and others, and from laboratory studies of gastric and duodenal healing, the authors concluded that patients who survive initially are likely to develop necrotizing lesions involving at least the stomach and pylorus. This may lead to injury of the deeper tissues of the wall of the stomach and the small bowel. Regeneration of the mucosa would be a slow process accompanied by diminished production of substances such as gastric acid and pepsin. Stricture and scar formation, frequently involving the pylorus and less often the esophagus, usually result.

Newhouse et al [3] examined pulmonary mucociliary function in 10 healthy adults following inhalation of sulfuric acid mist at 1 mg/m$^3$ with a particle mass median diameter (MMD) of 0.5 mm. All subjects were nonsmokers, and each person served as his or her own control. The subjects inhaled 20 breaths of a radioactive aerosol with a MMD of 3 mm generated from a $^{99}$technetium-albumen solution. After the subjects rested 30 minutes, sulfuric acid mist or distilled water was introduced into the exposure chamber. Relative humidity was maintained at 70% and temperature was 22°C. During exposure, they exercised for five 4-minute periods in the next 30 minutes and then rested for 90 minutes. At 2 hours, the subjects retained an average of 55.8% of the inhaled technetium (control) aerosol, but they retained only 47.3% on the average when exposed to sulfuric acid. However, sulfuric acid produced much less bronchoconstriction than was observed for 5 ppm of sulfur dioxide under the same experimental conditions. The authors concluded that the speeding in
clearance was probably an irritant response and a direct effect of exposure to the acid mist.

Changes in mucociliary function were also reported by Leikauf et al [4] who examined the clearance of a $^{99}$Te-Fe$_2$O$_3$ aerosol in response to inhalation of sulfuric acid mist (0.5 μm) at 0, 110, 330, and 980 μg/m$^3$ for 1 hour. In contrast to the method of Newhouse et al [3], acid aerosol was inhaled through a nasal mask, thereby reducing the possibility of neutralization by ammonia in the mouth. The air delivered through the masks was maintained at 46% relative humidity and 25.7°C. Exposures were randomized with respect to acid concentration over 4 separate days.

The control experiments revealed a considerable variation in bronchial clearance half-times (TB$_{1/2}$) among the subjects, 10 healthy nonsmokers. These differences were reflected in the individual responses to sulfuric acid. Six subjects with control TB$_{1/2}$'s greater than the group (n=10) mean showed a significant increase in TB$_{1/2}$ following exposure to sulfuric acid at 110 μg/m$^3$. After the 980-μg/m$^3$ exposure, however, five of the six subjects showed clearance rate depressions that were statistically significant. These changes were still significant (P<0.02 and 0.03, respectively) when the results of all 10 subjects were included in the calculations. The other four subjects displayed high control clearance rates (TB$_{1/2}$ less than the group mean) and appeared not to respond to any of the acid concentrations used. However, when the acid aerosol (1,020 μg/m$^3$) was administered before the deposition of the tagged aerosol, three of these four subjects showed a statistically significant decrease in TB$_{1/2}$ with no change in 24-hour retention values. The authors suggested that in these subjects bronchial clearance of the $^{99}$Te-Fe$_2$O$_3$, administered before acid exposure, was essentially complete by the time an effect could be observed.

The investigators also examined the effects of sulfuric acid aerosols on tracheal mucociliary transport rates and a variety of pulmonary function indices including forced vital capacity (FVC), forced expiratory volume at 1 second (FEV$_1$), midmaximal expiratory flow, forced expiratory flows at 75, 50, and 25% FVC, thoracic gas volume, airway resistance, and Becklake's distribution of ventilation index (BDVI). No significant changes from control values were observed following sulfuric acid exposures.

Sackner et al [5] in 1978 reported exposing groups of five or six adults, normal or asthmatic, to sulfuric acid or sodium chloride at 10-1,000 μg/m$^3$. Aerosol exposure was by mouthpiece for 10 minutes. Relative humidity was 30% and sulfuric acid particle diameters were approximately 0.1 μm. There was no significant alteration of lung volumes, distribution of ventilation, ear oximetry, dynamic mechanics of breathing, oscillation mechanics of the chest-lung system, pulmonary capillary blood flow, diffusing capacity, oxygen consumption, or pulmonary tissue volume. No delayed effects on pulmonary function or exacerbation of bronchial asthma were observed in the few weeks following exposure. The authors concluded that a single exposure to sulfuric acid did not produce any immediate or delayed adverse effect on cardiopulmonary function. It should be noted
that the highest concentration tested for 10-minute exposures was the same as the current permissible exposure limit for sulfuric acid in the workplace.

Avol et al [6] exposed volunteers, six with asthma and six clinically normal, to aerosols of sulfuric acid with a particle mass median aerodynamic diameter (MMAD) of 0.5 or 0.59 μm, respectively. Each subject received blind exposures for 2 hours a day for 1 or 2 days to purified air followed by 2 or 3 consecutive days to sulfuric acid at 100 μg/m³. The exposure chamber was maintained at 31°C and 40% relative humidity. To about double their minute volume ventilation, all subjects exercised 15 minutes of each half-hour for the 2-hour exposure. Neither group had significant adverse changes in pulmonary function, including FVC, FEV₁, maximum expiratory flows with 50% and 25% of FVC remaining to be expired, total lung capacity, residual volume, or total respiratory resistance. The experiment was designed to simulate "worst case" exposures during Los Angeles smog episodes.

Chaney and colleagues [7], reporting in 1980, measured six biochemical blood parameters to assess the effects of a single exposure to sulfuric acid aerosol. Thirty-five nonsmoking, Caucasian, male university students were exposed for 4 hours, including a 15-minute exercise period, to ambient air. On a subsequent day, 18 of these students were exposed for 4 hours, including the exercise period, to sulfuric acid aerosol (100 μg/m³, 0.5 μm MMMD). The 17 controls were exposed to ambient air. The exposure chamber was maintained at 22°C and 40% relative humidity. Aerosol generation techniques and methods used to measure sulfuric acid air concentration and particle size were not described. Immediately before and after all exposure situations, blood samples were drawn and analyzed for glutathione, lysozyme, glutathione reductase, serum glutamic-oxaloacetic transaminase (SGOT), serum vitamin E, and 2,3-diphosphoglyceric acid. The investigators reported no statistically significant differences in these factors between test and control subjects. A battery of pulmonary function tests was administered to all subjects during the exposure. Chaney and colleagues [7] stated that details of this portion of their study would be presented in a future report. However, they mentioned that no statistically significant effects on pulmonary function were observed for the aerosol-exposed group. In their discussion of the data, the authors referred to the work of Larson et al [8] and suggested that the absence of apparent adverse health effects resulted from neutralization of the sulfuric acid by ammonia present in the lungs.

Larson et al [8], in 1977, described significant concentrations of ammonia gas in the human respiratory tract. This work offers evidence supporting the existence of a body defense mechanism that may protect against low levels of acid aerosols and vapors. Ammonia gas (NH₃) was measured in air collected from subjects engaged in a variety of active and passive breathing protocols designed to determine the contributions from particular tract components; oral/oropharyngeal (mouth), nasal, tracheobronchial, and alveolar. Samples were collected by transfer of a known quantity of respired air into a Teflon®-lined bag or by continuous airstream monitoring.
Carbon dioxide monitoring was used during protocols designed to minimize the contribution of alveolar ammonia. Health, smoking, and dental histories were not given for the 16 subjects. No attempt was made to control for other possible confounding factors such as diet and time from last meal.

Ammonia concentrations in exhaled air were found to depend on the last pathway component through which the air passed. Air exiting the mouth contained the highest concentrations of ammonia, which ranged from 29 to 520 µg/m³ (42-750 ppb). Ammonia concentrations in air exiting the nose ranged from 7 to 62 µg/m³ (10-89 ppb). One sample of alveolar/tracheobronchial air was obtained by means of an inserted endotracheal tube. The ammonia concentration in this sample was 29 µg/m³ (42 ppb). The authors noted that this value approximates the reported concentration of blood ammonium ion. Levels of ammonia originating in the mouth were found to be inversely related to the air flowrate.

In a preliminary test of the authors' hypothesis that ammonia present in the airways can neutralize inhaled acid aerosols, one subject was exposed to sulfuric acid at 12±0.2 mg/m³ and 0.6±0.1 mg/m³ (MMD between 0.6-1.0 µm at 50% relative humidity). The subject's exhaled ammonia concentration at the time of exposure was 0.1±0.025 mg/m³ during quiet mouth breathing. Analysis of the expired aerosol showed ammonium ion-to-sulfate ion ratios consistent with those predicted from the stoichiometry of the starting reactants. The authors emphasized that their method did not determine the kinetics of the neutralization reaction from the time the sulfuric acid was inhaled to the time when the exhaled aerosol was collected, 0.5 second after exhalation. Employing a series of reasonable assumptions and the experimentally determined mean ammonia concentrations, the authors calculated that complete neutralization of sulfuric acid particles at 20 µg/m³ (0.3-µm MMD, 30% relative humidity) would occur after about 0.5 second in the nose and 0.1 second in the mouth. The authors were careful to point out that acid particles may reach the lower airways before complete neutralization. This possibility is more likely under conditions of lower ammonia concentrations and shorter particle residence times, such as occur during quiet nose breathing or rapid mouth breathing.

Partial neutralization of sulfuric acid aerosol by exhaled ammonia was reported by Kleinman et al [9]. The 1981 study tested whether sulfuric acid aerosols contribute to the pulmonary function decrement caused by ozone (O₃) and sulfur dioxide (SO₂). Nineteen volunteers with mixed smoking and allergy histories, but exhibiting normal pulmonary function, were exposed for 2 hours to sulfuric acid mist (100 µg/m³) and to ozone and sulfur dioxide (0.37 ppm each). As a control, they were exposed 2 hours to purified air on the previous day. Both test and control environments were maintained at 31±1°C and at 40±5% relative humidity. Exposures included alternating 15-minute periods of light exercise and rest. A battery of pulmonary function tests was given immediately before and following the exposures. Symptom interviews were also given before exposure, while subjects were in the chamber, and later in the day. The
experimental protocol, exposure conditions, and physiological and chemical analyses as described in this report seem to have been well controlled.

In addition to monitoring the gas and aerosol concentrations before their introduction into the exposure chamber, the investigators periodically analyzed the atmosphere in the chamber. The reported concentrations were as follows:

<table>
<thead>
<tr>
<th>Component (units)</th>
<th>Control</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO(_2) (ppm)</td>
<td>0±0.01</td>
<td>0.36±0.02</td>
</tr>
<tr>
<td>O(_3) (ppm)</td>
<td>0±0.01</td>
<td>0.36±0.02</td>
</tr>
<tr>
<td>Total Suspended Particles (µg/m(^3))</td>
<td>34±16</td>
<td>193±26</td>
</tr>
<tr>
<td>SO(_4)(^{-2}) (µg/m(^3))</td>
<td>0±2</td>
<td>103±28</td>
</tr>
<tr>
<td>NH(_4)(^{+}) (µg/m(^3))</td>
<td>0±1.8</td>
<td>18±16.2</td>
</tr>
</tbody>
</table>

Based on stoichiometric considerations, the probable composition of aerosol particles was judged to be H\(_2\)SO\(_4\) at 7 µg/m\(^3\), and NH\(_4\)HSO\(_4\) (ammonium bisulfate) at 115 µg/m\(^3\). These data indicated that 93% of the sulfuric acid introduced into the chamber was being partially neutralized by expired ammonia gas. Although the aerosol particle MMAD was reported to be 0.5±0.1 µm, analysis of particle size revealed a bimodal distribution with modal peaks at 0.2 and 2 µm. It is estimated that approximately one-third of the particles was distributed about the 0.2-µm mode.

Analysis of pulmonary function data showed small but significant aerosol-related decrements in the mean values for FVC, forced expiratory volumes (FEV\(_1\), FEV\(_2\), FEV\(_3\)), maximum midexpiratory flowrate (V\(_{max50}\) V\(_{max25}\)) and vital capacity (VC). Seventy percent of the subjects showed a statistically significant decrement in at least one pulmonary function; two subjects indicated exposure-related improvement and four subjects were apparently unaffected. Results of symptom interviews taken immediately after exposure did not differ between control and test conditions. Following aerosol exposure, later-in-the-day symptom scores showed a statistically significant change, with substernal irritation, a symptom typically associated with ozone exposure, being commonly reported.

Furthermore, the degree of pulmonary function decrement found was reported to resemble that in earlier studies using ozone alone at 0.37 ppm. Nevertheless, the authors pointed out that decrements in pulmonary function were shown in 70% of the subjects in this study while previous studies at 0.37 ppm of ozone alone predicted 30-50% showing decrements.
The authors, extrapolating from dose-response curves derived from their past studies, indicated that for an exposure to 0.37 ppm ozone the following decrements could be predicted: FVC, 2.3%; FEV\textsubscript{1}, 2.8%; and \( V_{\text{max50}} \), 4.5%. For this study the values were 2.8%, 3.7%, and 6%, respectively.

Although the data hint at possible synergism between sulfur dioxide, sulfate aerosols, and ozone, the authors were reluctant to make this conclusion because of dissimilar methods and protocols in the current and past studies.
III. ENVIRONMENTAL STUDIES

Since 1974, four NIOSH health hazard evaluations (HHE's) have been conducted in plants using large quantities of sulfuric acid. They studied two wire cleaning processes [10,11], one steel pickling operation [12], and one electrochemical drilling operation [13]. Generally, area and breathing zone samples showed time-weighted average (TWA) concentrations of sulfuric acid to be within acceptable limits. Excursions to concentrations greater than 1 ppm were reported in all cases. At one plant [13], excursions were said to have caused evacuation of the facility about four times a year. A complaint common to workers in these plants was upper respiratory and conjunctival irritation which, at one plant [10], was reportedly experienced by nearly all workers on hot, humid days. Nevertheless, the HHE reports noted that there was no evidence of chronic illness which could be related to occupational sulfuric acid exposure. In all instances, recommendations were made to improve the area and local exhaust ventilation.

Shy and Finklea [14] stated in a 1973 review of the Environmental Protection Agency's (EPA's) Community Health and Environmental Surveillance System (CHESS) that adverse health effects reported in studies completed in 1970-71 were more consistently related to suspended sulfates than to sulfur dioxide or suspended particulate matter. This problem has received particular attention recently because of the possibility that sulfuric acid and acid sulfate aerosols are increasingly prevalent air pollutants, due in part to their emission from catalytic converters used for automobile exhaust.

An extensive test of the increase in atmospheric sulfate concentrations as the result of automobile emissions was conducted in 1975 by General Motors [15]. The maximum measured sulfate concentrations, ranging from 3 to 15 μg/m³ above a background of 0.3-19.5 μg/m³, occurred at 0.5 m above ground level a few meters from the roadway. The aerosol emitted from the automobile catalyst had a 0.01-0.1 μm particle diameter. An independent group from Brookhaven National Laboratory also involved in the study indicated that the sulfur emitted from the automobiles was in the sulfate form, probably sulfuric acid [16]. The particles had a half-life, described as being on the order of tens of seconds, that was dependent on ambient ammonia concentrations.

Finklea and coworkers [18] predicted the increased sulfate exposure expected due to the introduction of catalytic converters by three mathematical models (carbon monoxide dispersion, lead surrogate, and carboxyhemoglobin level surrogate estimates). The models predicted exposure increases for particulate sulfates and sulfuric acid of 2-9 μg/m³ for automobile passengers and pedestrians in normal weather. These values closely agreed with the results of the General Motors tests [15]. However, under the worst possible meteorologic conditions (which the authors thought might occur about 3-4 days a year) their values were considerably higher than those of GM. The models assumed that 25% of the cars had converters
and that commuters traveled for 30 miles in an hour on a 10-lane expressway. Finklea et al. thought that adverse health effects would occur in susceptible individuals at 8-10 μg/m³ as a 24-hour average, a figure that would be reached or exceeded if all cars were equipped with converters.
IV. ANIMAL TOXICITY

A factor that must be considered when assessing the potential toxicity of sulfuric acid mist is the hygroscopic nature of sulfuric acid. Cavender and coworkers [17] found that sulfuric acid aerosols prepared in an atmosphere of 5% relative humidity can triple in size in the respiratory tract. At 60% relative humidity, the particles can double in size, while at high humidity the size increase will be small. Regardless of the initial molarity of the solutions used to prepare the aerosols, equilibration occurred either through a gain or loss of water. Acid concentration of aerosol particles was about 4-5 M at 60% relative humidity.

The relationship of particle size to the acute lethality of sulfuric acid aerosols in guinea pigs has been examined [19]. For 8-hour exposures at a relative humidity of 70-80%, the LC$_{50}$ was 30 mg/m$^3$ for mists of 0.8-µm MMAD. The corresponding LC$_{50}$ for 0.4 µm was more than 109 mg/m$^3$, the highest concentration studied. At 109 mg/m$^3$, 37.5% of the animals died of exposure, and the time between onset of labored breathing and death was much shorter for the 0.4-µm aerosols. Animals that died when exposed to the 0.4-µm mists had hyperinflated lungs. Those that died from exposure to the larger mists also had hemorrhage and transudation. The authors suggested that the primary influence leading to death was bronchoconstriction in the upper airways.

Amdur and coworkers [20] examined changes in the respiratory mechanics of guinea pigs exposed for 1 hour to sulfuric acid. Relative humidity in the exposure chamber was 50%, and groups of 20-25 animals were exposed to aerosols containing particles of 1-µm MMD at 0.11, 0.4, or 0.69 mg/m$^3$. Other groups were exposed to aerosol particles of 0.3-µm MMD at 0.1, 0.51, or 1 mg/m$^3$. All exposures produced dose-related increases in pulmonary flow resistance, although the 0.3-µm size produced a greater response. Except for animals exposed at 0.11 mg/m$^3$ to the larger particle size, pulmonary flow resistance did not return to normal values by 30 minutes after exposure. A decrease in pulmonary compliance also resulted, in all cases for the smaller aerosols and at the two highest doses for the larger aerosols. Pulmonary compliance remained depressed 30 minutes after exposure. The authors noted that the response produced from the 0.3-µm MMD sulfuric acid was 6-8 times the response they had previously observed for an equal amount of sulfur administered as sulfuric acid.

In contrast, Pepelko et al [21] reported in 1979 few toxic effects in rats exposed to auto exhaust emissions containing sulfuric acid at about 5 mg/m$^3$, 0.1-0.2 µm MMD. Groups of 20 animals were exposed 16 hours daily, 7 days a week for 45 or 90 days, and the only alteration that persisted throughout the 90-day exposure was an increase in total lung capacity. The ratio of functional residual capacity to total lung capacity was lower at 45 days. There was no evidence of any hematologic alterations. At necropsy, the lungs contained an increase of alveolar macrophages with black pigmentation and small foci of mononuclear cells.
Alarie and coworkers conducted two studies in which cynomolgus monkeys and guinea pigs underwent long-term exposures to sulfuric acid mists [22,23]. In all cases, chamber temperature was 22.2°C and the relative humidity was 50%.

In the first experiment, four groups of nine monkeys each were exposed to sulfuric acid at 0.38 mg/m³ (MMD of 2.15 μm), 0.48 mg/m³ (MMD of 0.54 μm), 2.43 mg/m³ (MMD of 3.60 μm), or 4.79 mg/m³ (MMD of 0.73 μm) [22]. At the two higher concentrations, definite alterations in pulmonary structures were seen in all animals of both groups. Microscopic changes consisted mainly of hyperplasia and hypertrophy of bronchiolar and bronchial epithelia. In addition, impaired pulmonary ventilation was evident in these animals. In the group exposed at 0.48 mg/m³ (MMD of 0.54 μm), no microscopic alterations were noted in the lungs. However, one animal died after 16 weeks of exposure and was found to have moderate pulmonary edema and pigment in the lungs; the exact cause of death was not determined. In the group exposed at 0.38 mg/m³ (2.15 μm), slight bronchiolar epithelial hyperplasia was present in five of nine animals. Other effects attributed to the exposure were slight thickening of the walls of the respiratory bronchioles in three of nine animals and a slight focal bronchial epithelial hyperplasia in four of nine animals. One animal in this group died during the 4th week of exposure and exhibited pulmonary edema and myocardial hypertrophy. Other findings were a large amount of serosanguineous froth in the trachea and bronchi and a gelatinous material in the coronary groove of the heart. The differences in response to low concentrations of sulfuric acid mist (0.38 and 0.48 mg/m³) were apparently related to particle size. These results differed from those obtained using higher acid aerosol concentrations, which demonstrated no differences in toxicity attributable to particle size. Although one death occurred in both low concentration groups, with the probable cause being pulmonary edema, this effect was not seen in either group exposed at higher levels to sulfuric acid.

As part of the second study by the same investigators [23], cynomolgus monkeys were exposed to sulfuric acid mists in combination with fly ash, sulfur dioxide, or both. Sixteen groups of nine animals each inhaled the mixtures for 18 months in an exposure chamber. Sulfuric acid concentrations in the mixtures ranged from 0.09 mg/m³ (MMD of 2.37 μm) to 0.99 mg/m³ (MMD of 0.64 μm).

Detrimental effects were noted in three of the four groups exposed at the highest concentrations of sulfuric acid (0.88-0.99 mg/m³ with MMD of 0.5-0.64 μm). Most notable among these adverse reactions were microscopic changes in the lungs that were characterized by alterations in the bronchial mucosa. In certain areas, focal goblet cell hypertrophy and occasional hyperplasia were seen; in other areas the mucosa was abnormally thin and possessed focal areas of squamous metaplasia. In addition to these effects, several groups of monkeys displayed an inconsistent pattern of increased pulmonary flow resistance. Previous work with sulfuric acid concentrations
up to 4.79 mg/m³, as discussed above, did not reveal this tendency [22]. The fourth group of monkeys, exposed to sulfuric acid mist at 0.97 mg/m³ (MMD of 0.52 μm) in combination with sulfur dioxide, did not develop microscopic changes in the pulmonary tissues. In contrast, fly ash and sulfur dioxide produced no effects when tested singly or in combination at the same levels as present in the mixtures. The authors concluded that exposure to sulfuric acid mist at concentrations between 0.1 and 1 mg/m³, regardless of particle size, were usually able to induce slight but definite histopathologic changes in pulmonary tissues of cynomolgus monkeys. Furthermore, at concentrations in excess of 2.5 mg/m³, regardless of particle size, impaired pulmonary function was also induced [23].

Guinea pigs exposed under similar experimental conditions demonstrated a relative resistance. In the first study [22], two groups of guinea pigs, with 50 males and 50 females each, were exposed to sulfuric acid mist at either 0.10 or 0.08 mg/m³. Particle sizes were 2.8 or 0.8-μm MMD, respectively. The duration of exposure was up to 52 weeks at 23 hours a day. In the second study [23], equal numbers of guinea pigs were similarly exposed to sulfuric acid mist at 0.9 mg/m³ (MMD of 0.49 μm), or to combinations of sulfuric acid and fly ash. Growth and survival rates and the results of lung function tests were normal in both experiments. Blood counts and serum protein, electrolytes, and enzymes were comparable with those of controls. No exposure-related changes were evident in the lungs, trachea, peribronchial lymph nodes, heart, liver, or kidneys when examined microscopically.

In a later study, Cockrell and colleagues [24] exposed guinea pigs to sulfuric acid mist (MMD of 1 μm) 6 hours daily for 2 days at 25 mg/m³ at a relative humidity of 55–60%. On the 3rd day, the 10 female and 10 male animals were killed. Collapsed, fluid-filled areas of the lungs were evident on gross examination. Edema and hemorrhage, characterized by the authors as acute lesions, were observed by light microscopy. The lesions were segmentally distributed. Lung specimens from three males and three females were also examined by scanning and transmission electron microscopy. Numerous macrophages were apparent in the alveoli, and thickening of the alveolar walls, dried edema fluid, and strands of fibrin could also be seen. Interstitial edema and vesiculation of the capillary endothelium were notable. Changes in the airways were limited to the alveolar duct region, and no lesions were observed in the bronchi, trachea, or larynx. However, there was desquamation of bronchiolar epithelium in the distal airways.

These investigators then exposed rats and guinea pigs 6 hours a day, 5 days a week, to either sulfuric acid mist at 10 mg/m³, ozone at 0.5 ppm, a combination, or filtered air [25]. Relative humidity was 55.8–62.6%. There were 70 animals of each species, equally divided by sex, in each group. After 6 months of exposure, tissues of killed animals were examined microscopically, and a statistical analysis for the significance of 31 variables, including body weight change, organ weights, hematology results, and blood chemistry tests, was performed. Rats exposed to sulfuric acid had only mild respiratory changes similar in nature and degree to those seen in
controls. Guinea pigs had minimal proliferation of alveolar macrophages and mild tracheal changes. There was no evidence of a synergistic effect for combined exposures to ozone (0.5 ppm) and sulfuric acid for either species. Of 31 variables measured in 140 animals exposed to sulfuric acid, the number of significant changes far exceeded that predicted by chance alone. However, no single variable was affected for both sexes and both species. The authors concluded that the absence of significant acid-induced lesions suggests that sulfuric acid mist at 10 mg/m³ is relatively nontoxic to the rat and guinea pig.

Examining functional rather than morphological parameters, Last and Cross [26] in 1978 reported evidence for synergistic effects of mixtures of ozone and sulfuric acid aerosols on respiratory mucus production in rats. Two groups of six, young, male Sprague-Dawley rats each were exposed to sulfuric acid at 1.1 mg/m³ and ozone at 0.5 ppm. After 3 and 14 days of exposure, the rate of tracheal glycoprotein secretion was significantly elevated as compared with controls. Sulfuric acid alone had no effect at 3 days, and ozone alone at 3 days indicated slightly depressed secretion. Lung homogenates were analyzed for DNA, RNA, and protein content. Three days of exposure to sulfuric acid alone had no effect, ozone significantly increased DNA content, and the mixture greatly enhanced this effect on DNA while also increasing RNA content. Dry weights of lungs, expressed as percent of wet weight, were also measured; sulfuric acid had no effect, ozone significantly decreased the dry weight, and the combination further enhanced this decrease. The effects, however, were reversible in rats exposed to the mixture for 14 days and then allowed to recover for 7 days. Actually, rebound decreases compared with controls were observed, but the changes were not statistically significant (P<0.05).

A similar pattern was found when the activities of the lysosomal hydrolases, acid phosphatase, beta-N-acetylglucosaminidase, and lysozyme were measured in lung homogenates. Similar results were observed when rats were exposed to sulfuric acid at 3 mg/m³ and ozone at 0.4 ppm for 14 days. Lung homogenate assays yielded similar trends, but changes were not significant. The lowest concentration of sulfuric acid tested in combination with 0.5 ppm of ozone was 11 µg/m³. After 3 days of exposure, the increase in secretion of glycoprotein in tracheal sections was significantly increased compared with the ozone-exposed group. Assays of lung homogenates demonstrated changes comparable in magnitude to those elicited by ozone alone. The authors noted that the levels tested were similar to concentrations that occur in natural urban pollution basins and selected occupational exposures. They concluded that the lack of toxic effects noted upon exposure of animals to individual pollutants at near-ambient levels should be interpreted with caution in view of accumulating evidence that pollutant mixtures may show synergistic or additive effects.

Crose et al [27] pursued the findings of Last and Cross [26] by conducting a combined in vivo/in vitro study designed to elucidate the effects of exposure to ozone and sulfuric acid, singularly and sequentially, on the mucociliary clearance system of male Syrian Golden hamsters.
Animals were exposed for 2 hours to sulfuric acid aerosol at around 1 mg/m\(^3\) (0.24-0.3-μm volume mean diameter, VMD) or to ozone for 3 hours at 196 μg/m\(^3\) (0.1 ppm). The exposure chamber was maintained at 48±11% relative humidity. At 0, 24, 48, and 72 hours following exposure, test and control animals were anesthetized and, after exsanguination, their tracheas were excised and tracheal ring cultures prepared for assay (incubation followed by microscopic observation) under stroboscopic illumination. Observations were made at 24-hour intervals for 72 hours to determine changes in ciliary beating frequency (cbf) and gross cellular morphology. Tracheal cultures prepared from hamsters sacrificed directly after exposure were allowed a 4-hour in vitro stabilization period before being examined.

Ciliary activity in sulfuric acid-exposed hamsters was significantly depressed immediately following exposure. Tracheas maintained in vitro still exhibited significantly reduced cbf's at 72 hours. However, tracheas allowed to recover in vivo for various time periods showed almost normal cbf's by 72 hours. Exposure to O\(_3\) alone at 196 μg/m\(^3\) (0.1 ppm) resulted in an immediate cbf reduction that was not significant.

In the sequential exposure experiment, hamsters were exposed to ozone and then to sulfuric acid. Immediately following the exposures there was a statistically significant lowering of the cbf. Its magnitude, however, was significantly less than in either of the experiments with sulfuric acid alone. After 72 hours of in vivo maintenance, cbf values were not significantly different from control values, indicating substantial recovery.

Based on comparisons of cbf reduction data, the authors concluded that "the hypothesis of no antagonism between ozone and sulfuric acid is rejected at the P<0.05 probability level." They offered several possible explanations for their seemingly paradoxical determination that the result of the sequential exposure was an antagonism including differences in model systems, subsequent response of target cells, disparity in exposure regimens, animal species used, or a combination of several of these.

An earlier study by Schiff et al [28] that used protocols similar to those reported above [27] examined the singular and combined effects of sulfuric acid aerosol and carbon particles on tracheal morphology and cbf.

The investigators exposed hamsters for 3 hours to sulfuric acid aerosol (mean diameter 0.12 μm) at 1.1 mg/m\(^3\), 1.5 mg/m\(^3\) carbon black particles (0.3 μm), or carbon black particles onto which sulfuric acid vapor had been condensed (0.4 μm).

In vivo exposure and maintenance experiments showed that cytotoxic effects on tracheal tissue of animals exposed to carbon/acid particles were greater than the damage produced by either acid or carbon alone. The mean cbf of carbon-exposed animals was not significantly different (P<0.05) from control values. Mean cbf's for acid or carbon/acid-exposed animals measured immediately and 24 hours after exposure were significantly
lower than controls. At 72 hours after exposure, the cbf for acid-exposed animals was significantly lower than that of all other exposure groups [28].

Examination of tracheal tissue maintained in vitro after in vivo exposure revealed epithelial changes similar to the in vivo maintenance results. Mean cbf's, however, returned to normal by 24 hours following exposure of animals to carbon or carbon/acid particles. The sulfuric acid-exposed group recovered after 48 hours.

Results of in vitro exposure and maintenance experiments with tracheal ring cultures showed cytotoxic effects similar to those found in the in vivo exposure experiments. However, the mean cbf for carbon/acid-exposed tracheas was significantly lower than that of all other exposure groups. By 48 hours, cbf's of all groups returned to normal.

In comparing the results of in vivo and in vitro maintenance experiments, the authors suggested that sulfuric acid exposure produced two effects—one directly on the ciliated epithelium, and another that delayed recovery [28].

To examine whether or not the EPA CHESS studies associating suspended sulfate and sulfur dioxide with the incidence of asthma and symptoms of upper airway irritation could be related to alterations of respiratory function caused by sulfuric acid exposure, Fairchild and coworkers measured the clearance of a 32p-labeled, group C Streptococcus culture from the respiratory tracts of mice [29] and guinea pigs [30] exposed to sulfuric acid at a relative humidity of 50-55%. In mice, inhalation of 15 mg/m³ sulfuric acid aerosol with a 3.2-μm count median diameter (CMD) for 4 hours following exposure to the bacteria reduced the rate of clearance of nonviable bacteria from lungs and noses. The clearance rate of viable bacteria, however, remained normal [29]. When mice were exposed to the acid for 90 minutes daily for 4 days before introduction of the bacteria, only nasal clearance of the nonviable organisms was decreased. Four daily 90-minute exposures to sulfuric acid at 1.5 mg/m³ (0.6-μm CMD), either before or after exposure to the bacteria had no effect on normal clearance mechanisms.

Fairchild et al also exposed guinea pigs to sulfuric acid for an hour and then to Streptococcus [30]. At the highest concentration, 3 mg/m³ (1.8-μm CMD), a 60% greater deposition rate of the bacteria occurred because of increased deposition in the nasopharynx. No effect was demonstrated at 0.32 mg/m³ (0.6-μm CMD). At 0.03 mg/m³ (0.25-μm CMD), a significantly greater amount of bacteria was located in the trachea. The authors concluded that sulfuric acid exposure can result in pathophysiologic effects of greater consequence than respiratory physiologic alterations alone.

Expanding on the work of Schiff et al [28], Fenters et al [31] studied the response of mice to long-term inhalation of carbon or carbon/sulfuric acid particles at low concentrations. Mice were exposed for 3 hours a day
for up to 20 weeks to air, carbon black particles (0.3-μm mean particle diameter, MPD), or carbon black particles onto which sulfuric acid vapor had been condensed (0.4-μm MPD). Mean concentrations were 1.4±0.4 mg H₂SO₄/m³ and 1.5±0.4 mg carbon/m³. The results of exposure were discussed for an extensive array of morphological and physiological parameters. In most instances, observed exposure-related effects were more pronounced for the carbon/acid exposure group.

The mean body weight for both carbon and carbon/acid groups was considerably lower than that of the control group for most of the 20-week exposure. The differences in growth rates were particularly marked during the rapid growth phase, 0-8 weeks.

For detection of the subtle changes in the respiratory epithelium in mice exposed to both carbon and carbon/acid particles for 12 weeks, the scanning electron microscope was reported to be more sensitive than conventional histopathologic examination. Bronchial abnormalities included congestion with loss of interalveolar septa and enlarged alveolar pores. Tracheas showed evidence of an increased mucous cell population and cell death. Fewer abnormalities were observed in these tissues at 20 weeks of exposure, indicating that the animals had adapted to some degree.

No exposure-related effects were observed on blood indices, including hematocrit, total and differential cell counts, platelet counts, and hemoglobin values, as well as concentrations of various enzymes.

Analysis of serum immunoglobulins revealed at least a transient period of significantly depressed levels for IgA, IgG₁, and IgG₂α in the exposed groups. Levels of IgG₂β were significantly increased at 1 and 20 weeks of exposure. IgM levels were high at week 1, but then depressed throughout the remaining 20-week exposure period. The authors [31] commented that although increases in certain immunoglobulin levels had been observed in persons with chronic lung disease, the significance of these findings remains speculative.

The primary antibody response of mouse spleen cells to foreign red blood cell antigens (a functional measurement of IgM production) was also assayed at 4, 12, and 20 weeks of exposure. Relative to the air-exposed control group, the particulate-exposed animals showed transient increases in sensitized spleen cells at 4 weeks. By 20 weeks, both particulate-exposed groups showed marked decreases in sensitized cells. The decrease found in the carbon/acid group was statistically significant when compared to both the air- and carbon-exposed groups.

Lung bacteriocidal activity against Klebsiella pneumoniae inoculated intranasally after 4, 12, and 20 weeks of exposure was reportedly [31] reduced to the same extent in both particulate-exposed groups. The results at 4 and 12 weeks of exposure were significant (p < 0.05).

Resistance to a challenge of aerosolized viral influenza (A₂/Taiwan/64) was not affected by exposure to carbon or carbon/acid
particles at 4 weeks. By 20 weeks, however, the carbon/acid-exposed mice showed a marked (P<0.1) change in all measured indices of resistance (reduced percent mortality and relative mean survival ratios, and increased degree of pulmonary consolidation) compared with combined results of air- and carbon-exposed groups.

The authors [31] concluded, "Thus the alterations of the defense system suggest that prolonged exposure to low concentrations of sulfuric acid and carbon particle mixtures reduces the ability of mice to resist the secondary stress of respiratory infection." They suggested that further, perhaps life-long, studies would resolve the questions raised by their results.

Schlesinger et al [32] examined the effect of exposure to sulfuric acid mist on mucociliary clearance in donkeys. Two animals were exposed to mists at 102 μg/m³ (0.46-μm MMAD) and two others at 10 μg/m³ (0.51-μm MMAD). Exposures were for 1 hour a day, 5 days a week, for 6 months through a nasal catheter connected to a generator producing mists at a relative humidity of 45%. No changes were observed in the regional deposition pattern when the donkeys were exposed to ferric oxide with a MMAD of about 5 μm. However, bronchial clearance half-times became erratic within the 1st week of exposure. Variability increased by 4.3–9.5 times that in control tests, and two animals showed sustained impairment of mucociliary clearance even during the 3-month followup period.

In a lecture on the impact of combined air pollutants on the lung, Amdur [33] noted that although about 10% of the population is hypersensitive to sulfur dioxide, hypersensitivity has not been demonstrated for sulfuric acid. In 50 guinea pigs exposed to sulfuric acid at 0.08–1 mg/m³, she saw no cases where the individual response was more than three times that of the mean value for the group. These results apparently differ from a personal observation of a toxicologist who commented in the discussion following a presentation at a meeting that persons employed at a sulfuric acid plant did develop adaptive mechanisms [34]. However, these workers were exposed to sulfur dioxide as well as sulfuric acid mist.

Amdur also noted that a given amount of sulfur is more irritating when present as sulfuric acid than as sulfur dioxide [33]. In terms of irritant potency in guinea pigs (measured as increased respiratory flow resistance), a given amount of sulfur was two to five times as potent when present as sulfuric acid. This irritant potency increased with decreasing particle size. When sulfur dioxide and sulfuric acid were administered together at low concentrations (0.2 ppm and 0.1 mg/m³ of 1-μm particles, respectively), the effects were described as purely additive.

Osebold et al [35] tested the hypothesis that "air pollutants can increase the number of allergically sensitized individuals in an environment containing inhalant allergens and effective concentrations of oxidant air pollutants." They did so by continuously exposing (except for cage cleaning) control and sensitized SPF female Swiss-Webster mice to either ambient air or sulfuric acid and/or ozone for various periods. Nominal ozone
concentrations were 0.8 ppm (±10%) and 0.5 ppm in the third experiment. Exposures to sulfuric acid aerosol were at 1 mg/m³.

In the first ("A") experiment, mice were exposed to ozone for 3 days before being exposed for 30 minutes to 1% aerosolized ovalbumin (OA) followed by an intraperitoneal (ip) injection of heat-killed Bordetella pertussis cells to augment the responsiveness of mouse IgE-producing cells to OA. The animals were then held in ambient air for "a few days," whereupon the air pollutant/aerosolized antigen exposure cycle was repeated up to four times, with the fourth exposure on day 28 of the experiment. All animals were scrutinized for signs of atopic reactivity, and the ozone-exposed ones showed varying degrees of "pawing at the face, scratching, ruffled hair, huddling and sneezing." There was no severe dyspnea or collapse. Control mice (OA aerosol only) showed "mild" signs of reactivity [35].

Testing for systemic anaphylaxis was performed 6–8 days after the last aerosolized OA treatment by injecting OA into the tail vein (iv) and looking for signs of anaphylaxis and for recovery or death over a 2-hour period. Ninety-three percent of the ozone-exposed mice showed "clear evidence of anaphylactic shock," and half of them died in shock. The entire positive control group (10 animals sensitized with two ip injections of OA) went into shock following the iv injection, and all but one animal died. On the other hand, a "normal" group of mice was unaffected after the iv injection, and only one of the four aerosolized control mice became anaphylactic and died. The difference between ozone-exposed and control mice was significant at P<0.018.

In the second experiment, "B", the extrinsic antigen was administered in seven treatments, the first four on days 3-6 of ozone exposure [in order to bracket what had been found to be the exposure period in which occurred the greatest loss of respiratory membrane activity (increased vascular permeability = compromised antigenic barrier)]. To simulate intermittent high pollution episodes, the remaining three treatments were given at 11-day intervals beginning on day 17. A heterologous antigen control group of mice received the first six 2% OA aerosol treatments, but received aerosolized equine myoglobin in the seventh treatment. They were unreactive to the myoglobin, much as "normal" mice were unreactive to a first OA treatment [35].

Upon iv injection of OA (after day 47), anaphylactic shock occurred in all of the ozone-exposed mice and in all of the OA-sensitized positive control mice, resulting in 34% and 80% mortalities, respectively. Seventy-four percent of those mice with repeated contact with aerosolized OA without ozone exposure also became anaphylactic, but the difference in sensitization frequency between the two groups was significant (P<0.007).

In experiment "C", mice were exposed either to sulfuric acid, ozone, or both pollutants at the same time. In addition, the mice were exposed to aerosolized 2% OA six times followed by iv challenge with OA. Only 10% of the acid-exposed mice demonstrated anaphylaxis after the iv challenge, and
only one (5%) of the aerosolized control group died from anaphylaxis. Ninety percent, however, of the mixed exposure group went into shock and 55% died from the process. Exposure to 5% ozone alone also resulted in "allergic enhancement," with 85% of the mice going into shock (only 25% died from this group). The incidence of anaphylactic shock was significant (P<0.001) in comparison with the control group. The differences in lethality between the mixed and single exposure groups would seem to indicate synergism between sulfuric acid and ozone.

The teratogenic potential of sulfuric acid mist has been examined in several species [36,37]. Pregnant mice and rabbits were exposed 7 hours a day to 5 or 20 mg H₂SO₄/m³ during the major period of organogenesis. Little evidence of toxicity was observed in the fetuses of either species, and teratogenicity was not seen [36]. Hoffman and Campbell [37] exposed 40 chicken eggs to sulfuric acid (MMD: 0.2–0.3 μm) at 6.5 mg/m³ for 14 days. Embryonic weights were significantly reduced (P<0.05), but survival rate and organ/body weight ratios for heart, liver, and spleen were not. Surviving embryos did not exhibit any gross abnormalities, but further evidence of potential teratogenicity was not sought. Serum lactic dehydrogenase (LDH) activity of surviving embryos was significantly reduced compared with controls, but the activities of other intracellular enzymes tested were not reduced. Hematocrit values were within normal limits. The authors stated that the LDH results could indicate a delay in normal development [37].
V. EXTENT AND CONTROL OF EXPOSURE

Sulfuric acid was the highest volume chemical produced in the United States in 1979 [38]. Annual production was 84 billion pounds (38.1 Tg), an increase of 2.2% from the previous year. Average annual production had grown over the previous 10 years, the average increase being 3.5% for 1969-79, 4.9% for 1974-79, and 7.1% for 1977-78. Much of the increased production appears attributable to demand in the phosphate industry (Federal Register 44:15742, March 15, 1979).

As of 1970, sulfuric acid was produced in about 250 U.S. plants [39]. The greatest capacity for production, 34.2 Tg a year, was via the contact process used in 215 plants of 179 separate establishments. About 30% also could produce some oleum. The chamber process, an older technology, accounted for about 803 million kg of sulfuric acid produced at 37 plants. Some additional acid was manufactured in 29 establishments with drum-type concentrators, and some smelter operations recovered sulfuric acid as a byproduct of pollution controls for sulfur dioxide. All newly constructed sulfuric acid plants have used the contact process. Since 1971, 32 such plants have been constructed (Federal Register 44:15742, March 15, 1979). Sulfuric acid is available in four grades—commercial, electrolyte, textile (low organic content), and reagent grade [39]. Nearly all sulfuric acid is used either on site or by other industries within 200-300 miles of the supplier.

Sulfuric acid is used in the wet process phosphoric acid industry (endproduct, phosphate fertilizer); petroleum refining; alcohol, titanium dioxide, ammonium sulfate, and superphosphate production; iron and steel pickling; caprolactam manufacture; and in the production of surface active agents, methyl methacrylate, hydrofluoric acid, and aluminum sulfate [39]. There are numerous lesser uses for sulfuric acid. In a survey of 5,000 industries conducted in 1972-74 by NIOSH, 211 different occupational categories had at least some workers potentially exposed to sulfuric acid. This represented about 825,000 workers in the United States. The total amount of sulfuric acid used in the United States exceeds the annual production figures since some is used within plants and not sold on the market. In addition, some industries, in particular petroleum refining and alcohol production, regenerate much of the acid from the plant operation [39].

Considerable attention has been given to the development of engineering controls to decrease emissions from sulfuric acid plants. Sittig [39] has described devices available for control of emissions released into the tailgas stack. A number of systems for recovery of sulfur dioxide from tail gases result in recovery of product sulfuric acid for sale. Control devices that remove sulfuric acid and sulfur trioxide as well generally recover additional products or provide material for recycle. Dual pad mist separators, tubular-type mist separators, panel-type mist separators, and electrostatic precipitators recover sulfuric acid mist in the form of sulfuric acid, and venturi scrubbers recover a sulfate salt or a dilute
acid solution. Most of the above devices are commercially available and many were in use by 1970. With sufficient in-plant air movement through an adequate ventilation system, these emissions control devices can also improve air quality in the sulfuric-acid work area.

The need for good work practices to prevent skin or eye contact with sulfuric acid is generally recognized. Only a few accounts [40,41] illustrating certain aspects of the safe handling, use, and production of sulfuric acid have appeared in the recent literature. Other information is available through the Chemical Manufacturers Association and sulfuric acid producers.

An incident in Germany involved the explosion of a sulfuric acid tank that had not been properly drained [40]. A drain had been placed too high for adequate drainage, resulting in a residue of sulfuric acid remaining in the bottom of the tank, even after flushing with water. Hydrogen, which formed by the action of the diluted acid on the tank steel, accumulated in the dome of the vessel due to improperly functioning gas drainage outlets. An explosion occurred when the hydrogen/air mixture in the top of the tank was ignited by a welding spark, which had been sucked into the tank through a gas drainage outlet.

A report stressing the importance of safety equipment in the unloading of sulfuric acid from barges was published in France in 1973 [41]. Suggested technical safety measures to be employed included: (a) the use of flexible hose between the barge and receiving factory, (b) the use of protective covers over the joints between hose and valve sockets, (c) protection of tanks by an overflow device or alarm, and (d) the use of proper personal protective equipment and staff training procedures.
VI. SAMPLING AND ANALYSIS

The advent of automobile catalytic converters coupled with concerns about acid rain and the increased use of coal has stimulated considerable interest in methods for sampling and analyzing atmospheric sulfur compounds. As reported in Volume 12, 1978, of Atmospheric Environment [42], an International Symposium held in Dubrovnik, Yugoslavia was devoted to a state-of-the-art discussion of sulfur and its compounds in the atmosphere. Other excellent reviews include those by Uron [43] and Jaworowski and Mack [44]. Few of the reported sampling and analytical methods are directly applicable to most workplaces. In general, the sampling trains described are too complicated for routine workplace monitoring. In addition, the analytical instrumentation is generally considered to be more expensive and sophisticated than is necessary for the laboratory specializing in industrial hygiene analysis.

Many problems in sampling for and analysis of sulfuric acid aerosols are universal regardless of the environment sampled. Chemical reaction of sulfuric acid, particularly complicating in filter collection techniques, is a common source of misleading data. In samples analyzed for total acidity, negative interference occurs through neutralization of filter-collected sulfuric acid by metal ions and ammonia. Positive interference by soluble metal and ammonium salts must always be reconciled in filter samples analyzed for sulfate ions. Sulfur dioxide and sulfites will rapidly oxidize to sulfuric acid in the presence of metals. Organic vapors or particulates further complicate most sampling and analytical procedures. All of the methods discussed below employ some form of solid matrix collection as the method of choice for aerosols. They have been developed sufficiently for routine use or testing in most occupational environments.

The NIOSH criteria document on sulfuric acid recommended that 100-liter samples be collected on cellulose membrane filters at a flow rate of 1.5 liters per minute. The acid was desorbed from the filter in water, and the resulting solution was diluted with isopropanol. The sulfuric acid content was then determined by titration with barium perchlorate to the endpoint indicated by Thorin [o-(2-hydroxy-3,6-disulfo-1-naphthylazo) benzenearsonic acid]. The method was not specific for sulfuric acid because it also measured sulfate salts [45].

Since the criteria document was completed, NIOSH has published four analytical methods for sulfuric acid [46-49]. Method S174 is the same as that in the criteria document, although additional information is reported as the result of validation tests conducted for NIOSH, the Standards Completion Program [46]. Of particular relevance are the sampling rates, ranges, and sensitivities listed for the method. NIOSH now recommends a sample size of 180 liters, still using a flow rate of 1.5 liters per minute. The method has been validated over the range of 0.561-2.577 mg/m³; the coefficient of variation for the total sampling and
analytical method was only 0.082 with a collection efficiency of 0.967±0.030. The useful range was estimated to be 0.1-3 mg/m³.

A second NIOSH method, P&CAM 187, involves turbidimetric analysis [47]. Sulfuric acid mist is absorbed in 10-15 ml of water in a midget impinger. The sulfate in the sample solution is precipitated as barium sulfate and the turbidity of the suspension is measured at 420 nm with a spectrophotometer. The range of the method is listed as 0.1-4 mg/m³ in a 100-liter sample with a coefficient of variation of 0.09 for analysis of samples at 2.6 mg/m³. However, the method is given only an "E" (proposed) classification.

Analytical method P&CAM 267 [48], also classified as proposed, is based on the hygroscopic and oxidative properties of H₂SO₄. An open-faced cassette containing cellulose filter paper is used for sampling. Sulfuric acid chars the cellulose when heated for 72 hours at 120°C. The intensity of the charring is compared with known controls. Although the method is relatively easy to use, preparation of control filters requires a sulfuric acid aerosol generator such as the one developed by Thomas et al [50]. Ideally, the control aerosols should be collected under the same conditions of temperature and humidity as were present during collection of the unknown samples. The working range for a 100-liter sample is 0.2-2 mg/m³. Some sulfates and sulfites have been shown to interfere in this method.

The fourth method, P&CAM 268 [49], involves analysis of particulate sulfate by anion exchange chromatography [51-53]. Concentrations are measured by conductivity determinations of the eluted product. As described, the sampling train is set up for simultaneous collection of sulfates, sulfites, and sulfur dioxide. Particulate sulfates and sulfites are trapped on a cellulose ester membrane filter that is permeable to sulfur dioxide. The gas is absorbed by a backup cellulose filter impregnated with potassium hydroxide-glycerine solution. Diffusion of sulfuric acid to the backup filter can be a source of negative bias, particularly when high concentrations of the acid are present. The second filter is omitted when sampling only for aerosols. Under circumstances where significant metal ion concentrations may be present, samples are initially eluted through a cation exchange column. The suggested working range for a 200-liter sample is 0.1-10 mg/m³ H₂SO₄. Although P&CAM 268 carries a NIOSH (E) classification, the method is currently used by NIOSH for routine analysis of sulfuric acid samples collected during health hazard evaluations. The Occupational Safety and Health Administration's (OSHA's) Industrial Hygiene Field Operation Manual [54] lists ion chromatography analysis for sulfuric acid as the method to be used in field compliance operations.

To improve the sampling procedures for atmospheres containing mixed inorganic acids, Cassinelli and Taylor [55] have developed a modified silica gel sampling tube. The glass tube, 7 mm O.D., is packed with 700 mg of extensively washed silica gel, 20-40 mesh. A 200-mg backup section and a glass fiber prefILTER are separated from the primary section of the tube by polyurethane plugs. Following extraction into boiling water or buffer, the tube contents are analyzed by ion chromatography [55]. Preliminary
results obtained in the laboratory with nebulized mixed acids indicated that the silica gel was more efficient than impingers or bubblers in collecting acid vapors (HCl and HNO₃).

The collection efficiencies of the silica gel tubes compared with cellulose filters for H₂SO₄ and H₃PO₄ aerosols were 90 and 88%, respectively. No breakthrough into the backup section was observed for mixed acid samples collected at twice the OSHA permissible exposure concentrations. Samples containing inorganic acids were stable for at least 10 days. Field tests are being performed for H₂SO₄, HCl, and HNO₃ at an electroplating operation, and for H₃PO₄ at a metal preparation operation (M Cassinelli, personal communication, April, 1981).

The assumption implicit in using any of the methods described above is that the sulfate concentration determined in the sample accurately reflects the amount of airborne sulfuric acid. This assumption holds for most workplace situations in which the significant air pollutant is likely to be sulfuric acid. Nevertheless, because these methods are relatively insensitive, long sampling times are required (at least 2 hours at 1.5 liters/min for 0.1 mg/m³ H₂SO₄). The longer the sampling time, the greater are the risks of flowrate disturbances and chemical reactions between trapped sulfuric acid and other contaminants.

The following described methods are reported to be either more sensitive or more specific for sulfuric acid than methods now being used.

Hoffer et al [56] evaluated a simple, colorimetric procedure based on the reaction of a barium-dye chelate [2,7-bis(4-nitro-2-sulfophenylazo)-1,8-dihydroxynaphthalene-3,6-disulfonic acid, disodium salt] with sulfate ion. The decrease in the absorbance at 642 nm of the chelated dye is directly related to the concentration of added sulfate. As described [56], the efficiency of sulfate extraction from glass fiber or cellulose acetate filters was 99% and the working range was 5–63 μg/sample. Within the ranges of 30–63 μg/sample and 5–23 μg/sample, the coefficients of variation were 3 and 13%, respectively. Since cation exchange pretreatment of extracted samples sometimes resulted in increased sulfate values, the authors examined the effects of a number of common air contaminants. Calcium ion, which is extracted from glass fiber and is present in soil particulates, gave a high negative interference. Sulfide and sulfate ions exhibited even stronger positive interferences. Thiosulfate, phosphate, bicarbonate, and silicate gave negligible or no interference at concentrations up to 7.5 times the sulfate concentration. Interference by colloidal clay was slightly positive or negative depending on its concentration. Results obtained by this method on ambient air samples compared favorably with values measured by other, more established methods.

West and coworkers [57] suggested a ring–oven method based on measurement of dissociated protons to analyze sulfuric acid collected on filter paper tapes. The detection limit for the method was reported to be 0.5 μg with the optimum range being 1–10 μg. Protons from the acid reacted with bromide and bromate ions to form bromine. The free bromine then
reacted with fluorescein to form eosin. Sulfate was measured by visual comparison of the color intensity of the developed spot of the sample with standard spots. While sulfate salts would not interfere, other protonic acids could (eg, phosphoric acid). Procedures were outlined for measuring the concentration of total protonic acid or nonvolatile acids. The latter method would eliminate interferences by acids such as hydrochloric and nitric acids. Relative errors ranged from 10 to 15%. The method has not been well documented for practical applications in environmental or industrial sampling.

Maddalone and coworkers [58], elaborating on the method of Dubois et al [59], examined the efficiency with which sulfuric acid diffused from collection filters and established conditions for maximum recovery of sulfuric acid in the presence of sulfate salts. After an 32S-labeled sulfuric acid aerosol sample was collected on a membrane filter, it was dried and placed in a petri dish, the cover of which was coated with sodium hydroxide. Maximum diffusion of the labeled sulfuric acid occurred when the petri dish assembly was heated for 1-6 hours at 125ºC. Under these experimental conditions, the investigators found that sulfuric acid diffused readily from Teflon® and graphite filters whereas little or no acid was released from glass fiber or cellulose acetate filters. The authors attributed the latter to neutralization in situ by resident cations. Since little sulfate was lost from cellulose acetate after 3 hours at temperatures of at least 100ºC, sample losses during collection and subsequent handling before analysis should not be significant for the NIOSH-recommended methods.

In an attempt to prevent on-the-filter reactions of trapped sulfuric acid with other contaminants during and subsequent to collection, Thomas et al [60] used glass fiber filters impregnated with a sulfate-specific organic absorber, pyrimidylammonium bromide (PDA-Br). (Two moles of the absorber react rapidly with 1 mole of sulfate.) Sulfates other than sulfuric acid were removed from the filter by a rinse with PDA-Br in methanol. Pyrolysis of the sample filter quantitatively converted bound sulfate to sulfur dioxide, which was analyzed for sulfur by flame photometry. The working range was reported to be 1-50 µg/sample. In another experiment, lead, iron, and aluminum oxides collected simultaneously with the sulfuric acid aerosol gave no interference [61].

A modification of the above technique, the authors claim, further reduces the chance of interference by contaminating ammonium sulfate salts [62]. By lowering the relative humidity of the sample stream to 40%, the authors maintained that ammonium and other sulfates are collected as solid particulates that can then be rinsed away with barium acetate solution. Forrest and Tanner [63], however, pointed out that 40% relative humidity is not low enough to prevent deliquescence of most ammonium sulfates.

A preliminary assessment of the Thomas et al method [60] was performed on samples collected by NIOSH during a health hazard evaluation of a wire cleaning operation. The published report [10] noted that, compared with
anion chromatography, the PDA-Br method gave lower and irreproducible recovery values. Actual data and details of the analytical protocol were not provided. However, the concentrations of sulfuric acid aerosol were found to range from 0.11-2.94 mg/m³. At the reported sampling rate (1.5 liters/min) and duration (1.5 hours), it is possible that the capacity of the absorber was greatly exceeded.

Consideration of the methods described above [58,60] led to the development of a sensitive analytical method which was reported by Dharmarajan et al [64] to be specific for sulfuric acid. Aerosol samples collected on membrane filters were placed in a petri dish as in the microdiffusion protocol [58]. The cover, however, was coated with PDA-Br instead of sodium hydroxide. The entire assembly was heated for 2 hours at 125°C in a nitrogen-purged oven. Under these conditions it was reported that (NH₄)₂SO₄ and NH₄HSO₄ were not volatilized [64]. Pyrolysis of the absorber-sulfate complex at 500°C for 2.5 min quantitatively converted the bound sulfate to free sulfur dioxide, which was analyzed by flame photometry, one of a number of acceptable analytical methods. Maximum recovery of sulfuric acid from fluoropore membrane filters was never more than 84%, but this value was observed to be reproducible under the conditions described above. Although the method was sensitive to 1 µg H₂SO₄, the data suggest a working range of approximately 5-50 µg H₂SO₄.

Several innovative methods have been developed to determine individual components, including sulfuric acid, in atmospheric pollution. One method is based on visualization of the reaction of soluble sulfate particles with an immobilized film of dry barium chloride. Various sulfates can be identified by their characteristic appearance under an electron or optical microscope [65]. Another method involves the use of a continuous, sulfur-specific flame photometer [66-68]. A prototype chromatograph based on the electrical mobility of the aerosol particles has also been tested [69]. The method reported by Leahy et al [70] and evaluated by Tanner et al [71], which used benzaldehyde to selectively extract sulfuric acid in the presence of (NH₄)₂SO₄ and NH₄HSO₄, has met with less favorable results when tested on ambient air samples by other investigators [72]. Other techniques that have been used to characterize sulfur-containing atmospheres include chemical ionization mass spectrometry [73], laser Raman spectroscopy, electron spectroscopy for chemical analysis (ESCA), infrared (IR) spectroscopy, and a variety of methods employing the principles of differential volatilization and reaction enthalpies [74]. The more exotic methods remain experimental. Their potential usefulness for workplace monitoring is not known.
VII. OTHER STANDARDS

The following countries have adopted the same occupational exposure standard for sulfuric acid, 1 mg/m$^3$ as a time-weighted average (TWA), as the United States: Australia, Belgium, Bulgaria, Czechoslovakia, Finland, German Democratic Republic, Federal Republic of Germany, Hungary, Italy, Japan, Netherlands, Poland, Sweden, Switzerland, USSR, and Yugoslavia. Romania recommends 0.5 mg/m$^3$ as a TWA exposure with a ceiling concentration of 1.5 mg/m$^3$ [75].

The EPA promulgated standards of performance for sulfuric acid plants in December 1971 (40 CFR 60.80). No new production unit is permitted to discharge into the atmosphere any gases that contain sulfur dioxide in excess of 2 kg/Mg (4 pounds/ton) of acid produced; any gases that contain acid mist, expressed as 100% sulfuric acid, in excess of 0.075 kg/Mg of acid produced (0.15 pounds/ton); or any gases that exhibit 10% or greater opacity. EPA has reviewed these standards (Federal Register 44:15742, March 15, 1979). No evidence was found that demonstrated a need for revision.
VIII. SUMMARY AND CONCLUSIONS

Information characterizing the effects of exposure to sulfuric acid in the workplace was limited to a report by Jelenko et al [2] and four NIOSH health hazard evaluations [10-13]. These reports contributed no new information on toxicity, but did demonstrate that hazardous conditions still exist in plants using sulfuric acid. The HHE's concluded that such conditions could be remedied with proper labeling of containers and equipment and feasible ventilation controls. Other studies in humans were more appropriate to testing of short-term excursions at concentrations of sulfuric acid found in polluted air [3-9]. Two studies [3,4] with healthy adults showed exposure-related effects of sulfuric acid aerosol on bronchial clearance rates. Newhouse and coworkers [3] found increased clearance rates after 2 hours at 1 mg/m$^3$. Leikauf et al [4] also observed increased rates, but only at concentrations well below the permissible limit. At 1 mg/m$^3$, however, these investigators found that rates were significantly depressed. Leikauf et al attempted to explain these contradictory results by suggesting that since subjects in the Newhouse et al study had their nasal passages blocked, mouth breathing may have lead to an accumulation of ammonia within the exposure chamber. If this occurred, then partial neutralization of sulfuric acid by ammonia might reduce the effective acid concentration, bringing the results of Newhouse et al more in line with those of Leikauf et al.

Evidence for partial neutralization in an exposure chamber has been reported by Kleinman et al [9]. However, a close comparison of the Kleinman et al and Newhouse et al exposure conditions, eg, exposure concentrations, chamber sizes, and air exchange rates, reveals that appreciable neutralization probably did not occur during the Newhouse et al study. More likely, the added exercise period and extended exposure time in the Newhouse et al study (2 hours vs 1 hour), may have simply yielded an equally valid result. In addition, the reported differences in the relative humidity of the delivered aerosol may have affected the particle deposition pattern [17].

These findings [3,4] suggest an adverse response to inhalation of sulfuric acid aerosols at the permissible exposure limit. Whether or not adverse effects occur in individuals exposed for extended periods of time has not been determined.

All studies of humans which examined pulmonary air flow and volume indices in response to inhaled sulfuric acid at 1 mg/m$^3$ or less reported negative findings [3-7]. A possible exception is the study by Kleinman et al [9] which suggested that more individuals were adversely affected by ozone in the presence of sulfuric acid at 100 µg/m$^3$ than were affected by ozone alone.

In attempts to explain absent or contradictory findings, a number of investigators [4,7,9] turned to the results of Larson et al [8]. Only one report [9] described the extent to which ammonia neutralization of sulfuric acid occurred. Larson et al [8] made a considerable effort in their discussion of the data to limit over-interpretation of their results. The
ammonia concentration in the mouth (the source of highest concentration) varied widely among subjects. The concentration is very likely dependent on general health, diet, oral hygiene, and time since the last meal, factors not controlled in the experimental design. Heavy mouth breathing rapidly reduced oral ammonia concentrations. Larson et al pointed out that the location within the respiratory tract where neutralization actually occurred was not established. The kinetics of neutralization within the airways probably depends on those factors mentioned above as well as aerosol particle size, humidity, and whether the acid is adsorbed to, or coated with, other air contaminants.

Nevertheless, the authors [8] did demonstrate that ammonia in concentrations sufficient to neutralize low levels of sulfuric acid is present in human airways. Whether such neutralization constitutes a significant protective effect has not been experimentally established.

Experiments in animals provide further information on the effects of sulfuric acid on mucociliary clearance. In donkeys, exposure to sulfuric acid (0.51-μm MMAD) for 1 hour a day for a 6-month period resulted in erratic clearance rates [32]. Two animals previously exposed recovered more quickly than two others. This suggests an adaptive mechanism, or it could have been simply individual variability. Experiments in mice and guinea pigs showed a definite decreased rate of clearance at high concentrations [29,30]. Information on guinea pigs exposed at lower concentrations, however, was not consistent, possibly because of differences in particle size. At 0.03 mg/m³ (0.25-μm CMD), guinea pigs retained a significantly greater amount of bacteria in the trachea, but comparable results were not found at higher levels when the particle size was 0.6 μm [30]. A transient reduction in lung bactericidal activity was also reported for mice exposed to sulfuric acid/carbon particles at 1.4 mg/m³ (0.4 μm) [31]. In hamsters, ciliary beating frequency was reversibly depressed following exposure to 0.3-μm sulfuric acid particles at 880 μg/m³ [28]. These results could have adverse implications for persons who may be subjected to mixed exposures or to bacterial infections.

Other apparent inconsistencies in studies of experimental animals may be the result of differences between species or in age, aerosol size, or relative humidity. The rat appears to be a relatively resistant species. Rats showed only an increase in total lung capacity when exposed at 5 mg/m³ for 90 days [21]. At 10 mg/m³ a day, 5 days a week for 6 months, rats showed only mild respiratory changes [25].

Numerous other studies have examined the effects of sulfuric acid exposure in guinea pigs. Again, certain inconsistencies are evident. For acute toxicity, aerosols of larger, but still respirable, size were more lethal than those of smaller size [19]. However, changes in pulmonary function were more severe for aerosols of smaller diameter [20]. Definite decrements in pulmonary function were observed at 0.1 mg/m³ (MMD of 0.3 μm) for exposures of only 1 hour. In a separate study, guinea pigs exposed continuously for 52 weeks to sulfuric acid mist at 0.9 mg/m³ (MMD of 0.49 μm) did not show altered pulmonary function [23]. Possibly, this difference in results
represents adaption because the first measurements of pulmonary function were taken after 3 months of exposure. Age of the animals could also be a factor.

Experiments involving long-term exposure of guinea pigs and monkeys to sulfuric acid indicate that the monkey is a more sensitive species [22,23]. Evidence of slight, but increasingly severe microscopic lesions occurred in monkeys exposed at concentrations between 0.1 and 1 mg/m$^3$ regardless of aerosol particle size. Definite impairment of pulmonary ventilation occurred above 2.5 mg/m$^3$.

Several investigators have examined possible interactions of various air pollutants with sulfuric acid. No additional toxicity was found in monkeys when they were also exposed to sulfur dioxide and fly ash [23]. Another investigative group [25] observed that lesions in the lungs produced by these two substances occurred in different regions. Most evidence, however, supports either an additive or synergistic action by sulfuric acid at concentrations at or below the permissible exposure limit. Last and Cross [26] found some biochemical and functional evidence of synergism in studies with rats, a relatively resistant species. The ciliary beating frequency was reduced in hamsters exposed to acid-coated carbon particles [28], the effect of the mixed exposure being greater than the effect produced by acid or carbon particles alone. Mice exposed for 3 hours a day to acid/carbon particles showed lowered resistance to viral respiratory infection [31]. Since this effect was not observable until 20 weeks of exposure, the importance of examining the consequences of long-term exposures is emphasized. In that report [31], carbon particles alone did not lower resistance. These investigators also found continued depression of circulating and bound IgM levels. Perhaps the most interesting results were those reported by Osebold et al [35], who showed that intermittent exposure of mice to a mixture of ozone (0.5 ppm) and sulfuric acid (1 mg/m$^3$, 0.041-μm CMD) resulted in an increase in allergic lung sensitization. The increase due to the mixed exposure was greater than that for either component.

The information now available from studies in experimental animals suggests possible alternative approaches to the current permissible limit for occupational exposure to sulfuric acid. For aerosols containing particle sizes that can penetrate to the lung, at least two mechanisms of action have been demonstrated. Aerosol particles that deposit in the upper lung appear to be more acutely harmful because reflexive bronchoconstriction occurs. Somewhat smaller aerosol particles, however, appear to cause greater alterations in pulmonary function and eventually in microscopic lesions. Exposure to very large particles would not lead to either of these effects. This all suggests that any future revision of the occupational exposure limit should consider aerosol particle size.

The results from animal experiments suggest that a decrease in the permissible exposure limit may be warranted. The very limited information from donkeys [32] and guinea pigs [20] exposed at 0.1 mg/m$^3$ for various intervals suggests the possibility of decreased pulmonary function and disturbances of mucociliary clearance. Lungs of monkeys exposed at
similar levels showed microscopic evidence of slight damage [22,23]. While monkeys were exposed continuously so that they received about four times the exposure represented by a normal 8-hour workshift, extrapolation of such information to a workplace setting is questionable. Extrapolation to humans is further complicated in that most of the experimental animals used to date have not been mouth breathers.

However, the information available suggests that workers may be at increased risk of respiratory disease at exposure levels acceptable under the current Federal standard, especially if the aerosol particles are of a respirable size and other air pollutants are present. Persons whose work involves routine exposure to sulfuric acid are regularly exposed to pollutants in the general environment. The fact that workers in one plant experienced an increased incidence and degree of irritative symptoms on hot, humid days [10] is consistent with results in animals receiving mixed exposures. In addition to the effects on particle size caused by higher humidity [17], hot weather is often accompanied by increased concentrations of ozone and other pollutants. Sulfuric acid concentrations around 0.1 mg/m³ can be reached in the general atmosphere during severe pollution episodes.

The increased sulfuric acid concentrations being released into the general atmosphere as the result of the introduction of catalytic converters [15,16] are expected to increase adverse health effects in susceptible individuals [18]. Such effects were considered likely at 8–10 µg/m³ [18]. These adverse effects observed in susceptible individuals have only indirect relevance to worker populations. It seems likely, however, that members of road crews and other persons who work close to highways would relate health changes to exposure to sulfuric acid. The incidence of respiratory disease might increase in these persons as the result of increased exposure to sulfuric acid.

The reviewed methods of sampling and analysis offer a selection of promising, sensitive techniques. The majority, however, still lack testing and validation under a variety of field conditions. Membrane filter entrapment, despite its many associated problems, remains the method of choice for workplace sampling of sulfuric acid aerosols. Anion exchange chromatography, used in conjunction with cation exchange pretreatment and conductimetric analysis, has become the generally accepted method for sulfate measurement in the workplace.
IX. RESEARCH NEEDS

NIOSH's recommended occupational exposure limit for sulfuric acid aerosol is based, for the most part, on the subjective responses of human volunteers exposed for very short durations. Recently published epidemiologic studies, however, suggest that chronic exposures to sulfuric acid aerosols in microgram quantities may significantly contribute to an increased incidence of respiratory and cardiac disease among susceptible persons. There is a need, therefore, to define more fully the consequences of low-level, long-term exposure to sulfuric acid among workers. Studies should be designed to correlate long-term effects on resistance to infectious microorganisms as well as respiratory and cardiac disease with exposures that do not produce subjective symptoms of respiratory irritation. Such studies should consider not only airborne concentrations of sulfuric acid, relative humidity, and aerosol size, but also the presence of other air contaminants. NIOSH is currently conducting a study of mortality, focusing on malignant and nonmalignant respiratory diseases among pickling workers in the steel industry.

In addition, the role of respiratory ammonia as a possibly protective mechanism against low concentrations of sulfuric acid needs to be evaluated.

Animal studies have established that pathologic and functional changes to the respiratory tissues can occur with chronic and continuous exposure to sulfuric acid mist at 0.1-1 mg/m$^3$. Additive or synergistic effects have also been demonstrated at very low concentrations of sulfuric acid in combination with ozone, sulfur dioxide, and particulate carbon. Based on these observations, more definitive information is needed in the following areas:

(a) Investigation of the possible effects of relative humidity, particle size, ambient temperature, and pH on toxicity.

(b) Evaluation of the combined effects of sulfuric acid mist exposures with common airborne industrial pollutants (e.g., ozone, sulfur dioxide, nitrogen dioxide, organic particulates, metal oxides and sulfates) on the susceptibility of animals to respiratory disease and infection.
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