American Thoracic Society

MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

HEALTH EFFECTS OF ATMOSPHERIC ACIDS AND THEIR PRECURSORS

Report of the ATS Workshop on the Health Effects of Atmospheric Acids and Their Precursors[1,2]

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During the twentieth century, episodes of severe air pollution associated with obvious excess mortality provided dramatic evidence that air pollution can cause adverse health effects. The high levels of air pollution in these events were produced by combustion sources releasing sulfur dioxide (SO_2), nitrogen oxides, particles, and other pollutants; levels of acid aerosols were probably quite high during these episodes. More recently, environmental degradation by acid pollution through the phenomenon of acid rain has been well documented and has become an issue of international concern. Acid aerosols in ambient air are in the respirable size range and deposit in the lung's airways and alveoli when inhaled. Injury caused by acid particles at sites of deposition could lead to a wide array of adverse acute and chronic respiratory health effects. Recent monitoring data indicate that exposure to acid aerosols is widespread throughout North America. Thus, evidence of substantial population exposure to these potentially toxic materials has provided a strong imperative for increasing our understanding of the health effects of acid air pollution.

Atmospheric acidity is defined as acids and acid precursors residing in the atmosphere in the gaseous and particulate phases. These are formed primarily from the oxidation of sulfur oxides, nitrogen oxides, and hydrocarbons originating primarily from combustion sources. There are many species of acid pollutants. Particulate acids are usually in the form of submicron-sized, sulfur-containing aerosols that are partially or completely neutralized. They may occasionally occur in the form of sulfuric acid, but more often are partially neutralized but still strong acids [i.e., ammonium bisulfate [NH_4HSO_4], letovicite [$(NH_4)_3HSO_4$] or completely neutralized ammonium sulfates. Particulate sulfur also will appear in the form of nonacidic sulfate salts. It has only been recently that measurement methods capable of determining low concentrations of acid aerosols in the environment have been available, and thus it has been necessary in most past epidemiologic studies to use measurements of other indicators as surrogates of acid aerosol exposure. Thus, particulate sulfate concentrations provide an upper limit for acid aerosol concentrations.

To address our understanding of human exposure to acid aerosols and associated health effects, a workshop was convened by the American Lung Association/Canadian Lung Association and the American Thoracic Society/Canadian Thoracic Society in Santa Fe, New Mexico, from March 22 to 24, 1990. This workshop document poses a series of key questions regarding the current state of knowledge linking acidic aerosol inhalation with human health effects, and provides responses based on a critical review of the current state of knowledge on this topic.

What Are the Present Exposures?

Although the spatial and temporal distributions of acid aerosols have not been comprehensively monitored across the United States and Canada, some aspects of the population's exposure to acid aerosols have been described. Information is available on the chemical species and the spatial and temporal distributions of acidic aerosols. These data suggest that large portions of the populations of the United States and Canada have been chronically exposed to acidic aerosols, as measured in terms of sulfate (1, 2).

Currently, because of changes in the distribution of sources and the release of large amounts of SO_2 from tall stacks, transformations to acid particles occur high in the atmosphere and long-range transport takes place (3). Exposure to acid aerosols occurs during periodic acute events and this exposure is usually accompanied by high concentrations of photochemically generated oxidants and fine particulate metals (4). Sulfate acid aerosols are in the submicron-sized fraction (5). Acid events occur more frequently during the spring and summer, and have spatial scales of hundreds of kilometers. Regions of higher particle acidity include portions of states west of the Appalachian mountains, including western Pennsylvania, West Virginia, eastern Tennessee, Kentucky, and Ohio, and extending north into southern Ontario. The predominance of the particulate acid occurs in the 4 months from May through August, when mean concentration ranges between 60 and 80 nmol/m^3 H^+ ions (3 to 4 μg/m^3 H_2SO_4 equivalent). Daily values 10 times the 4-month average have been reported. The frequency of acid events may be 20 to 30 per year in this area and each event may last hours to days (1, 2). The bounds of acid aerosol pollution extend beyond this most affected region, but events outside this region occur less often and both long-term averages and daily maximum concentrations are lower. Data are not available to describe annual trends in episode frequency and severity.

Geographic variation in exposure can be expected to occur on both a regional and a local basis. Particulate acids can be neutralized by ground level sources of ammonia and by alkaline particles. Thus, concentrations of strong acidity tend to be higher in communities away from agricultural and urban sources of ammonia. Although regional patterns of pollution predominate in the eastern United States and Canada, local sources may still be important. Acid gases and aerosols released from chemical plants, refineries, and incinerators as well as fumigation from smelters and electrical generating plants, can cause "localized" exposures. Recently, nitric acid vapor has been shown to be present not only in the densely populated urban areas of the west but also in the east.

Exposures to acids can be modified by indoor environments. Submicron-sized acidic

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[2] This Workshop was held in Santa Fe, New Mexico, March 22-24, 1990, sponsored by the American Thoracic Society/American Lung Association and the Canadian Lung Association/Canadian Thoracic Society.

aerosols can readily penetrate indoors with air exchange. Ammonia produced by occupants, pets, and household products may reduce the average acid concentration (6).

Effects of other modifiers such as air exchange rate and air-conditioner use have not been adequately characterized. Unvented combustion sources (i.e., gas and kerosene heaters) produce nitrogen dioxide (NO_2). NO_2 reacts with interior surfaces to produce nitrous acid (7). Kerosene heaters using sulfur-containing fuel also produce sulfuric acid (8). The importance of indoor nitrous acid to human exposures needs further characterization.

Accurate measurements of chemically reactive particulate materials at contemporary levels require more complex sampling systems than those used for established criteria pollutants. The sampled acidic droplets must be protected from reactive vapors, and back-up filters may be needed to correct for reaction with other sampled particulates on the primary filter. Finally, the sampling filters must be protected from neutralization prior to laboratory analyses. Sampling systems incorporating these essential elements are being used in contemporary epidemiologic studies and are expected to be in operation at numerous ambient air-monitoring stations in future years (9, 10).

What Approaches Are Used to Understand the Health Effects of Acid Aerosols?

As for other air pollutants, information on the health risks of acid aerosols comes from three complementary lines of investigation: epidemiologic studies of exposed populations; controlled exposures of human volunteers; and animal studies. Each of these types of investigations has strengths and weaknesses, and the totality of evidence is considered in making judgments concerning the causal nature of associations between exposure and disease. Epidemiologic studies address the effect of exposure as it occurs in the community, but may be limited by the difficulties of assessing health status and exposure, and of controlling for the effects of other factors also affecting disease risk. Clinical studies, involving controlled exposures of volunteers, have the advantage of permitting selection of homogeneous subject groups, careful control of exposure, and more intensive assessment of effects. However, exposures must be short; the anticipated effects must be transient; and ethical considerations may exclude the selection of subjects with the most severe disease. In animal studies, exposures also may be precisely controlled, chronic exposure studies may be performed, and a wide array of methods may be used to measure responses.

It is important to remember that extrapolation of findings in laboratory animals to humans is nearly always subject to uncertainty. Until recently, epidemiologic studies had not been carried out to specifically test for effects of acid aerosols. Thus, much of the epidemiologic evidence on acid aerosols comes from reinterpretation of already conducted studies, using surrogates or limited measurements to infer exposure. To the extent that these surrogate measures misclassify exposures to acid aerosols, the associations between exposure and health outcomes are weakened. Studies have now been designed and implemented in the United States and Canada to directly assess the effects of acid aerosols on humans.

What Are the Health Effects Associated with Exposure?

Exposures of humans and animals to acidic aerosols have been associated with a variety of health effects. Mortality occurring in association with London episodes of winter smog in the 1960s is well documented, and recent analyses have suggested that sulfuric acid aerosol might have been important in these effects (11). In North America, recent data indicate that sulfates (either directly or as surrogates for other species) are associated with indices of respiratory morbidity (12) and mortality (13, 14). Hospital admission data also have shown an association between respiratory admissions and both ozone and sulfates in the summer in southern Ontario (15). Acid aerosols have not been routinely measured by agencies responsible for atmospheric monitoring; hence, large-scale epidemiologic studies of their possible impact (using indicators such as hospital emergency visits or admissions) are not yet possible. Increased levels of aerosol acidity have been shown to be associated with an increased prevalence of bronchitis symptoms in children (16). Controlled exposure studies in humans and animals using acidic aerosol challenges at or near environmentally relevant levels have produced evidence of both acute and chronic responses. Human subjects with asthma or increased airways responsiveness often demonstrate acute bronchoconstriction with exposure to acid aerosols (17). Guinea pigs represent a good animal model for studying acute airway response to such pollutant challenges and have demonstrated increased airways reactivity at low acid aerosol levels (18). The response to inhaled irritants often depends upon their interaction with respiratory defense systems. These consist of mechanisms protecting against a wide variety of toxicants, and specific or immunologic defenses that respond to antigenic stimulation. Another acute response observed is a transient alteration in the rate at which particles are cleared from airways of the lung, which has been observed in healthy humans and several animal species (19). Daily exposure of rabbits to acid aerosols at levels that produced only transient alterations in clearance following a single exposure produced a persistent reduction of clearance rates similar to that observed in other animals chronically exposed to cigarette smoke and in human smokers. Increased airways responsiveness, an increased concentration of mucus-secreting cells in the airways, and airway narrowing also were found. These effects are characteristic of chronic bronchitis in human smokers (20). The alterations in mucociliary clearance associated with changes in secretory cell density persist for more than 3 months after the end of exposure (21). Thus, chronic exposure to acidic aerosols could contribute to the development of chronic bronchitis. Responses in the pulmonary region, such as an increase in alveolar macrophage numbers and alterations in function, also have been observed (22).

People are exposed to polluted atmospheres of varying composition, and epidemiologic studies have inevitably involved exposures to pollutant mixtures. Selected multipollutant exposures in animal and human studies are therefore warranted to assess and contrast the similarity and divergence of responses to the more active components. Some multipollutant studies have included combinations of pollutants such as O_3, NO_2, SO_2 and acidic aerosols, using variations in concentrations and duration of exposure. Animal studies have demonstrated that the effects of ozone exposures are potentiated by H_2SO_4 as evidenced by parenchymal lesions, and by changes in collagen synthesis (23). Synergistic effects have also been demonstrated in animal studies exposed to ultrafine zinc oxide particles coated with H_2SO_4 (18). Controlled human exposure studies have not demonstrated synergism in functional response between O_3 and NO_2 or H_2SO_4, but have indicated that SO_2 response is enhanced by preceding ozone exposure (24). Recent data also has demonstrated altered lung function in exercising asthmatic adolescents and adults when H_2SO_4 was combined with SO_2 (25). Chronic exposure studies to mixtures of pollutants containing new components are limited to animal experiments; one study has demonstrated progressive changes in pulmonary mechanics and lung structure in the years following relatively low long-term (5.5 yr) exposures (26). Controlled animal or human studies have typically focused on single pollutants or a limited mixture of pollutants, whereas typical ambient exposures often involve a complex and changing mixture of pollutants. Human studies using ambient mixed pollutant exposures have been conducted using mobile exposure chambers, outdoor exercise sessions and summer camps. Some of these studies have demonstrated that the effects of ambient mixtures appear larger than those attributable to ozone alone in controlled exposures (27). The possibility exists that the presence of other pollutants, in particular H^+, may enhance the O_3 effects on lung function. Epidemiologic studies inherently assess the effects of acid aerosols as components of the complex blend of pollutants in ambient air. To an extent, with proper study design and analytic techniques, separation of the effects of acid aerosols from those of other pollutants may be possible. However, such attempts to separate the individual effects of multiple pollutants may provide only artificial and simplistic representations of complex biologic phenomena.

Who Is at Greatest Risk?

Human health impacts have to be inferred from studies that have shown strong evidence of a relationship between sulfate levels and various indicators of respiratory morbidity, including hospital admissions and acute effects on children, and from controlled clinical studies that have examined responses of healthy people and volunteers with respiratory diseases. It must be presumed that every individual exposed to acid aerosols is at some risk.

At present, individuals with hyperresponsive airways and asthmatics are considered susceptible populations. At high ambient concentrations, asthmatics in chamber studies and children with hyperresponsive airways in epidemiologic studies have been found to have greater changes in pulmonary mechanics than those that occur in healthy people. Little is known about the risk to individuals with chronic obstructive airways disease. Vigorous exercise potentiates responses at a given concentration, in part by increasing ventilation and therefore the dose of irritant delivered to epithelial surfaces. Risk accrues to children and adults working or exercising outdoors for several hours during the day. Although data on ambient levels of acid aerosols are still limited for Canada and the United States 24-h H^+ concentrations in excess of 100 nmol/m^3 (5 μg/m^3 H_2SO_4 equivalent) and 12-h concentrations greater than 500 nmol/m^3 (25 μg/m^3 H_2SO_4 equivalent) have been measured. The maximum measured concentration could result in a delivered dose of more than 2,000 nmol (100 μg equivalent H_2SO_4) of H^+ ion in 12 h for an active child.

What Is Responsible for Toxicity of Acid Sulfates?

Animal and human studies have indicated that the relative potency of the atmospheric sulfates in causing respiratory effects is related to their acidity, i.e., their H^+ content. This relationship has been demonstrated for various endpoints, including pulmonary mechanics, tracheobronchial mucociliary clearance, particle clearance from the alveolar region, and macrophage function (20). H_2SO_4 is more potent than NH_4HSO_4, which in turn is more potent than $(NH_4)_2SO_4$ at equivalent concentrations of sulfates (28). Thus, it is reasonable to conclude from both human and animal studies that the biologically active portion of these compounds is H^+ rather than sulfate. But the quantitative relationship between response and H^+ content has not been characterized in detail. Some recent animal data suggest that H_2SO_4 may be more potent than NH_4HSO_4 even when the H^+ content of each compound is taken into account (29). If the effects of inhalation exposure to equal concentrations (in terms of H^+) of different chemical species of acid differ, than speciation of acid gases and acid aerosols will be important. However, pure sulfuric acid rarely occurs in the atmosphere at ground level and thus the measurement of strong aerosol acidity as total H^+ in ambient air may be adequate.

Laboratory studies are providing new understanding of the comparative effects of exposure concentration and exposure duration in determining responses to acid aerosols. A limited laboratory animal and human data base, involving single and short-term repeated exposures, points toward dependence of response on both concentration and time. For some end points, these data cover a concentration range of 50 to more than 1,000 mg/m^3 and durations of 1 to 4 h/day (30). Thus, animal and clinical studies performed at higher than ambient concentrations, but for short exposure durations, may be relevant to effects experienced by the general population.

A number of issues remain to be resolved. Most studies were performed using acid aerosols with median droplet sizes in the submicronic range (0.1 to 1.0 μm). Acid aerosols of other sizes are present in polluted air and responses to these particles may differ from those to submicron particles (31). For pulmonary function and clearance changes in laboratory animals, the smaller particles (about 0.1 μm) were more damaging than larger particles. The relative importance of mass concentration of particles and number of particles has not been addressed. The increased potency in experimental studies of surface-coated acid aerosol, which contained more particles than aerosols of pure acid droplets, indicates the need for further research on this issue. The role of endogenous ammonia is also being examined. Levels of respiratory tract ammonia, which derive from protein metabolism and bacterial degradation of food in the mouth, vary widely between individual laboratory animals and between humans, and these differences may account for part of the variation in response among individuals (32).

When considered in relation to the data summarized in this report, present levels of exposure to acid aerosols of a large population in the United States and Canada lead to the conclusion that attempts to enlarge our present understanding must be intensified. Future clinical studies should clarify the relationship between acid aerosol exposure and airway responsiveness. Animal studies may indicate target sites for effects, and work on both humans and animals may point clearly to the questions that epidemiologic studies should address in relation to acid aerosol exposures. A convincing understanding of the effects of contemporary acid aerosol exposure will only be achieved when there is concordance between data derived from all three types of study.

Conclusions

We now know that a large fraction of the population of the United States and Canada is chronically exposed to acidic air pollutants, usually accompanied by photochemical oxidants. Most exposure occurs in repeated episodes, maximal in the summer, that can deliver doses of acidic pollutants as high as those found to have effects in animal and controlled human exposure studies.

By virtue of receiving a high dose, those at greatest risk would include people working or exercising outdoors. Children and adults with increased airway responsiveness or asthma also are more sensitive than others.

Historical data indicate an association between high acid aerosol levels and mortality. Contemporary levels of acid aerosol exposure have been associated with increased respiratory symptoms in children. Acid aerosols accompanied by ozone have been shown to affect lung function in normal children exercising outdoors. Other adverse health effects have been inferred from associations of mortality, increased hospital admissions, and respiratory symptoms with raised levels of sulfates and ozone.

Animal studies have shown that acidic aerosols cause airway narrowing, changes in particle clearance, changes in response to inflammation, and in some biochemical reponses. They may also induce increased airway responsiveness. It also has been shown that acid condensed onto fine particles may be more damaging, for a given acid exposure, than when in the form of an aqueous aerosol.

Finally, the impact of acid rain on forests, lakes, and fish has been well publicized. Much less attention has been given to the human health effects of the acid aerosols, which are important precursors of acid rain. Future expansion of monitoring and innovative epidemiologic, toxicologic, and controlled human studies should give us a clearer understanding of the adverse effects of acid aerosols on human health, and the relative roles of acid aerosols and the oxidant pollutants that commonly accompany them.

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