United States
Environmental Protection
Agency

Health Effects Research
Laboratory
Research Triangle Park NC 27711

Research and Development

EPA-600/S1-82-012 Sept. 1982

EPA

Project Summary

Pulmonary Function and Bronchial Reactivity in Human Subjects with Exposure to Ozone and Respirable Sulfuric Acid Aerosol: An Environmental Chamber Study

Thomas J. Kulle, H. David Kerr, Bernard P. Farrell, Larry R. Sauder, and David L. Swift

A three-year chamber study of human subjects is presented in two phases: investigation of the effects of sulfuric acid aerosol on pulmonary function and a study of pulmonary function and bronchial activity after exposure to ozone and respirable sulfuric acid aerosol.

In Phase I, sulfuric acid aerosol was used to determine the respiratory effects of low levels of sulfuric acid aerosol such as those anticipated in ambient air in the near future. Twenty-eight normal subjects were exposed for 4 hours to 98 $\mu g/m^3$, 0.14 μm H_2SO_4 aerosol in an environmentally-controlled exposure chamber. Of the 28 subjects, equal numbers were nonsmokers and cigarette smokers. None of the subjects complained of symptoms attributable to the exposure. Measurements of pulmonary function were obtained 2 hours into the exposure, immediately following exposure, and 2 and 24 hours post-exposure. These measurements were compared with control values obtained at comparable hours on the previous day when the subjects breathed filtered clean air. No significant differences in pulmonary function were observed during the exposure, immediately after exposure, or 2 and 24 hours post-exposure.

Phase II used ozone and sulfuric acid aerosol. Studies of recent air pollution episodes in the U.S. and Southern England have shown atmospheric co-existence of ozone (O_3) and H_2SO_4 aerosol. Previous exposure of human subjects to low levels of these pollutants (0.3 ppm O_3 and 98 $\mu g/m^3$, 0.14 μm H_2SO_4 aerosol), as separate exposures, produced no significant changes in pulmonary function. Single O_3 exposures to slightly higher levels (0.4-0.5 ppm) have produced decrements in pulmonary function. Repeating this ozone exposure on the following day results in a greater decrement in function occurring on the second day, suggesting an effect of the previous exposure on a subsequent exposure. To determine if an O_3 pre-exposure around "threshold" would produce a significant decrement in function with this H_2SO_4 exposure, 12 healthy nonsmokers were exposed first to 0.3 ppm O_3 for 2 hours, followed by 100 $\mu g/m^3$, 0.13 μm H_2-

SO_4 aerosol for 4 hours. Separate exposures to O_3 and H_2SO_4 were also done. Three consecutive weeks were employed, one each for O_3, H_2SO_4, and O_3 with H_2SO_4. In each week three consecutive days represented control, exposure, and post-exposure days. Pulmonary function (body plethysmography and spirometry) and bronchial reactivity to methacholine were measured following exposure and 24 hours post-exposure, and compared to control clean-air values. No significant changes in pulmonary function or bronchial reactivity were observed with the ozone, the sulfuric acid aerosol or the sequential ozone-sulfuric acid aerosol exposures. Ozone pre-exposure does not appear to enhance the response to respirable H_2SO_4 aerosol at or near environmentally-observed levels.

This Project Summary was developed by EPA's Health Effects Research Laboratory, Research Triangle Park, NC, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

This report presents the research results associated with a study funded by the Environmental Protection Agency under Grant Number R803804. The three-year work effort using the University of Maryland Environmental Chamber, consisted of two phases Phase I investigated the "Effects of Sulfuric Acid Aerosol on Pulmonary Function in Human Subjects" Phase II studied "Pulmonary Function and Bronchial Reactivity in Human Subjects with Exposure to Ozone and Respirable Sulfuric Acid Aerosol."

Sulfuric Acid Aerosol — Phases I and II

Atmospheric sulfur dioxide (SO_2) is oxidized to sulfur trioxide (SO_3) which combines immediately with water vapor to form H_2SO_4 in the form of droplets. Cox and Penkett have shown in laboratory experiments that when the photochemical smog reaction, involving unsaturated hydrocarbons (RH) and oxides of nitrogen (NO_x), takes place in the presence of SO_2, oxidation of the SO_2 to H_2SO_4 occurs at a significant rate, even when the concentrations of RH and NO_x were typical of the levels (~ 0.1 ppm) during moderate pollution episodes.

Sulfuric acid mist has been suggested as one of the irritants contributing to the increased mortality and morbidity resulting from the prolonged polluted fogs of Donora, London, and the Meuse Valley. Catalytic converters presently installed on automobiles to control pollution may become a source of increased sulfates and sulfuric acid mist in the breathing zone of pedestrians and motorists in urban areas. Sulfuric acid has been shown to be more toxic than sulfur dioxide in animal and human studies, with the acid particle size and relative humidity affecting toxicity.

Past measurements (1961) of urban atmospheric levels of sulfuric acid mist in the United States (Los Angeles) show levels up to 50 $\mu g/m^3$ for a 3-hour period With the increased use of high sulfur fuels for combustion and the more widespread use of catalytic-converter equipped automobiles, the peak urban atmospheric burden of H_2SO_4 aerosol of 20 $\mu g/m^3$, estimated by EPA in 1976, could possibly increase to 60-80 $\mu g/m^3$. EPA air quality data reported 24-hour sulfate levels of 162 $\mu g/m^3$ in South Charles, West Virginia in 1973. Air quality data on 2-4 hour sulfate measurements as well as H_2SO_4 aerosol determinations have not been made. Independent researchers have made limited measurements of both the 24-hour sulfate and peak 2-hour sulfate levels Based on Cass's measurements in the Los Angeles area of peak 2-hour levels being approximately 175% higher than the 24-hour averages, the above 24-hour sulfate level could have 2-hour peak levels of 280 $\mu g/m^3$.

Animal studies have revealed adverse pulmonary function effects to various levels of H_2SO_4 aerosol Previous studies showed this effect at concentrations $\geq$2000 $\mu g/m^3$. Recently, Amdur exposed guinea pigs for one hour to concentrations from 100 to 1000 $\mu g/m^3$ at particle sizes of 0.3 and 1 0 μm All exposures produced a significant increase in pulmonary flow resistance, which was dose-related. Pulmonary compliance decreased for all exposures, but was not significant for the 100 and 400 $\mu g/m^3$, 1.0 μm exposures.

Amdur et al. reported adverse effects (decreased flow rates) in human subjects exposed by face mask to relatively high concentrations of H_2SO_4 mist (350-500 $\mu g/m^3$ of 1 μm particle size for 5-15 minutes). Sim and Pattle reported symptoms of respiratory tract irritation and increased airway resistance in human subjects exposed to high concentrations of H_2SO_4 acid mist ($\geq$3000 $\mu g/m^3$, 1 μm for 10 minutes) in high humidity (90% RH).

More recently, Gardner et al. exposed healthy nonsmoking human subjects for 2 hours to 66, 100, or 195 $\mu g/m^3$, 0 055 μm MMD H_2SO_4 aerosol. The subjects exposed to the lowest concentration seemed to be the most sensitive, with significant decreases in FEV_2 and Raw and an increase in FRC. The group exposed to 100 $\mu g/m^3$ showed significant changes in FEV_2 and Raw, with no significant changes in pulmonary function associated with the subjects exposed to the highest concentration. No significant changes in respiratory rate or tidal volume were observed in this latter group

Avol et al reported no effects on pulmonary function in healthy, normal humans and subjects with asthma following exposure to 100 $\mu g/m^3$ H_2SO_4 for 2 hours, and Sackner et al. found no effects following exposure of normals and asthmatics to 100 and 1000 $\mu g/m^3$ for 10 minutes. Utell et al did find significant changes in flow rates and increased bronchial reactivity, following exposure to 1000 $\mu g/m^3$ H_2SO_4 aerosol for 16 minutes in normal subjects

The purpose of the Phase I investigation was to determine if exposure of human subjects to levels of H_2SO_4 aerosol anticipated in the near future, in a realistic time frame, would have an adverse effect upon respiratory function. The concentration used was 98 $\mu g/m^3$, with a particle size of 0.14 μm MMD Exposure duration was 4 hours.

Ozone — Phase II

Ozone is a photochemical oxidant pollutant formed by the ultraviolet energy of sunlight on the oxides of nitrogen and hydrocarbons primarily emitted from automobiles

Ozone may represent an occupational hazard for flight crews flying at high altitudes Young et al. reported estimated concentrations of 0.3 and 0.4 ppm ozone (rubber band cracking method) in the passenger and crew compartments of commercial jet airliners flying between 27,000 and 39,000 feet in altitude Jaffe and Estes described FAA test studies involving two KC-135 jet aircraft flying at 25,000 to 41,000 feet in altitude; maximum ozone concentration in the aircraft cabin measured 0.5 ppm using a Mast analyzer

In September 1979 Southern California experienced an episode of photo-

chemical pollution described as the worst Southern California smog seige in 25 years, with one-hour average concentrations of ozone exceeding 0 4 ppm and eight consecutive days with Stage II ozone ($\geq$ 0.35 ppm) episodes in the South Coast air Basin

Ozone, the major oxidant in photochemical smog, is a respiratory irritant that has been shown to produce decrements in pulmonary function following low level exposure (0 4-0 5 ppm) Kerr et al. found significant reductions in forced vital capacity (FVC) and specific airway conductance (SGaw), and increased total pulmonary resistance (R_L) following exposure to 0 5 ppm for 6 to 10 hours. Farrell et al found significant reductions in FVC and SGaw following exposure to 0.4 ppm ozone for 3 hours Animal studies had previously revealed the phenomenon of tolerance to the respiratory effects of ozone with repeated exposure More recently this phenomenon of adaptation was demonstrated in human subjects In a study by Hackney et al 5 to 6 subjects, exposed to 0 5 ppm for 2 hours per day for 4 consecutive days, showed decreases in pulmonary function on days 1, 2, and 3 that were largely reversed by the fourth day Farrell et al demonstrated that when nonsmoking human subjects were exposed to 0 4 ppm ozone for 3 hours per day for 5 consecutive days, decrements in FVC and SGaw occurred on the first two days, which returned to baseline levels by the fifth day despite continued exposure. Folinsbee and coworkers showed that repeated 2-hour exposures to ozone at 0.20 ppm produced no acute effects in pulmonary function, whereas, 2-hour exposures to 0 35 and 0.50 ppm repeated over 3 days produced significant changes in FVC, FEV_1, $FEF_{25-75\%}$. In all these human studies, the maximum decrement in function occurred on the second day of ozone exposure, indicating that there may be some enhancement of sensitivity from the initial ozone exposure. Symptoms generally correlated with decrements in pulmonary function

Increased bronchial reactivity, as measured by the response to histamine inhalation, has been demonstrated following exposure of normal nonsmoking subjects to 0 6 ppm O_3 for 2 hours, this exposure produced no significant changes in baseline airway resistance (Raw), suggesting that bronchial reactivity may be a more sensitive indicator than pulmonary function of changes in the airways following O_3 exposure The reactivity increase occurred immediately following O_3 exposure, becoming nonsignificant by 24 hours post-exposure In another study performed in their laboratory, nonatopic and atopic nonsmokers were also exposed to 0.6 ppm O_3 for 2 hours. In the nonatopic group, the increase in specific airway resistance (SRaw) produced by either histamine or methacholine aerosol after O_3 exposure was significantly greater than after the sham (air) exposure. For the atopic group inhaling histamine aerosol only, the SRaw increase following O_3 exposure was also significantly greater In each group, bronchial response was measured one hour after O_3 exposure, the observed increase returning to control 24 hours post-exposure. Baseline SRaw did not change significantly with O_3 exposure In both studies subjects were exposed while wearing nose clips, restricting O_3 exposure to oral inhalation only. Although these studies did not show a significant change in pulmonary function (Raw, SRaw), other studies have demonstrated significant decrements in pulmonary function with exposures to 0 4-0 5 ppm O_3 for 2-3 hours.

Sulfuric Acid Aerosol with Ozone Pre-Exposure — Phase II

Recent air pollution episode studies performed from 1975 through 1977 in the eastern half of the U S from the Great Lakes through the TVA region showed the co-existence of elevated ground-level concentrations of particulate sulfate and ozone as a regional and interstate phenomenon Maximum concentrations were >0 14 ppm ozone and 40 $\mu g/m^3$ sulfate.

During July 1971, over Southern England significantly higher than normal concentrations of ozone as well as oxidized sulfur dioxide in the form of sulfuric acid and sulfates were measured at ground levels Total sulfate reached levels of 70 $\mu g/m^3$, with the hydrogen ion concentrations expressed as H_2SO_4 aerosol peaking at 55 $\mu g/m^3$ Maximum O_3 levels were 0 10 ppm A close correspondence in concentration pattern and peaking occurred with the O_3 and H_2SO_4 levels, the H_2SO_4 aerosol also peaked at a lower level earlier in the day when the O_3 concentration was building up

Previous investigators have studied the combined exposure to ozone and sulfuric acid aerosol, sulfur dioxide or ambient total suspended particulate Using a mobile laboratory in Los Angeles County during the summer of 1978, Linn et al. demonstrated significant but very small losses in forced expiratory volumes and flows and total lung capacity with very mild clinical symptoms in "allergic" normal and asthmatic subjects exposed to ambient L A air of 0 22 ppm ozone and 200 $\mu g/m^3$ total suspended particulate The H_2SO_4 concentration was not determined Bedi et al. exposed nine young adult males to 0 40 ppm SO_2, 0 40 ppm O_3, and their combination, each for a 2-hour duration When exposed to SO_2 alone, no significant changes occurred in pulmonary function, whereas exposure to O_3 or O_3 plus SO_2 produced significant decreases in forced expiratory volumes and maximum expiratory flows Responses between O_3 alone and O_3 plus SO_2 were not significantly different, thus a synergistic effect was not demonstrated

Kleinman et al exposed normal human subjects for 2 hours to 0 37 ppm O_3, 0 37 ppm SO_2, and 100 $\mu g/m^3$, 0.5 μm H_2SO_4 aerosol The combined exposure showed small statistically significant decrements in forced expiratory function (volumes and flows) The increase in reported symptoms with exposure approached statistical significance The authors stated that the results did not support the hypothesis that H_2SO_4 aerosol markedly enhances respiratory irritance of other pollutants (O_3, SO_2), although, a modest degree of enhancement may have occurred compared to previous ozone exposure data

Last and Cross exposed normal rats to 0 4-0 5 ppm O_3, 1100 $\mu g/m^3$, 0 5 μm H_2SO_4 aerosol, and their combination for 3 and 14 days. Exposure effects were evaluated on conducting airway metabolism as rate of secretion of mucus glycoproteins by tracheal explants and on biochemical parameters in lung homogenates The authors stated that true synergism was observed in that the responses to the mixture of O_3 and H_2SO_4 aerosol exceeded the sum of the effects observed with the same concentration of O_3 and H_2SO_4 presented separately

Gardner et al. exposed female mice to 900 $\mu g/m^3$, 0 23 μm H_2SO_4 aerosol and 0 1 ppm ozone for 2 and 3 hours respectively, using an infectivity model for evaluating exposure effects Neither pollutant alone caused a significant increase in mortality with the infectious microorganism challenge as compared to filtered air controls With sequential exposures to the two pollutants, only

when the exposure to the oxidant gas immediately preceded that of the acid (not the acid preceding the ozone) was there a significant increase in respiratory infections, with the observed increased mortality equal to the additive effect of the individual pollutants A significant decrease in tracheal ciliary activity of hamsters was observed with the same sequential exposure to O_3 followed by H_2SO_4 as compared to the decrease (significant) observed with the H_2SO_4 exposure alone, the O_3 exposure alone resulted in no significant difference from air controls An additional experiment was conducted using 0.1 ppm O_3 and 500 $\mu g/m^3$ H_2SO_4 aerosol administered simultaneously for a period of 3 hours to female mice, also employing the infectivity model A significant increase in mortality over air controls was observed, with the acid alone showing no increase and the ozone, a nonsignificant increase in mortality.

As noted in the previous section, ozone appears to have the capability of producing a further decrease in pulmonary function with a second exposure A pre-exposure to this pollutant might have the potential of magnifying the response to respirable sulfuric acid aerosol exposure Both sulfuric acid aerosol and ozone are pulmonary irritants

The purpose of the Phase II investigation was to determine if pre-exposure to ozone at a level seen in the urban environment would produce a significant decrement in pulmonary function with an H_2SO_4 aerosol exposure previously shown not to decrease function Concentrations used were 0 3 ppm ozone and 100 $\mu g/m^3$, 0 13 μm sulfuric acid aerosol for 2 and 4 hours, respectively In addition, bronchial reactivity to inhaled methacholine was determined; these measurements appear not to have been made in any published studies

Conclusions

Phase I — Sulfuric Acid Aerosol

Single short-term (4-hour) exposure to low levels of respirable sulfuric acid aerosol (98 $\mu g/m^3$ of particle size 0.14 μm) with two 15-minute light-to-moderate exercise periods appears to have no adverse effects on pulmonary function in normal human subjects.

Phase II — Ozone and Sulfuric Acid Aerosol

Single short-term exposure to 0 3 ppm ozone for 2 hours with one 15-minute light-to-moderate exercise period showed no significant changes in pulmonary function or bronchial reactivity to methacholine in normal, nonsmoking human subjects Exposure to respirable sulfuric acid aerosol (100 $\mu g/m^3$, 0.13 μm H_2SO_4 for 4 hours) with the same light-to-moderate exercise also demonstrated no significant changes in pulmonary function or bronchial reactivity When the H_2SO_4 aerosol exposure was preceded by the O_3 exposure, no significant changes were seen in pulmonary function or bronchial reactivity We conclude that there are no readily apparent risks from sequential exposures of nonsmokers to these low levels of ozone and sulfuric acid aerosol at this exercise level.

Recommendations

Phase I — Sulfuric Acid Aerosol

No significant changes in pulmonary function were evident with this study, but longer or repeated exposures may produce function decrements. Exacerbations of chronic bronchitis are known to occur with exposure to high ambient levels of SO_2 and particulates, of which H_2SO_4 aerosol is a constituent.

Further studies should be undertaken to 1) evaluate the effects of longer or repeated exposures to H_2SO_4 aerosol; 2) evaluate the effects of H_2SO_4 aerosol on subjects with allergy, asthma and/or chronic bronchitis; 3) evaluate the effects of combinations of H_2SO_4 and other constituents of the SO_2/particulate complex on both normal subjects and subjects with allergy, asthma and/or chronic bronchitis. Investigation of the effects to higher H_2SO_4 concentrations would appear to have little relevance to the effects of air pollution, unless ambient levels increase markedly in the future

Phase II — Ozone and Sulfuric Acid Aerosol

In normal, nonsmoking human subjects, no significant changes in pulmonary function were observed with individual or sequential exposures to 0.3 ppm O_3 for 2 hours and 100 $\mu g/m^3$, 0 13 μm H_2SO_4 aerosol for 4 hours employing light-to-moderate exercise loads Bronchial reactivity to methacholine did not show a significant increase with any exposure; although, a substantial, nearly significant decrease occurred following the 4-hour exposure to respirable sulfuric acid aerosol.

Additional studies should be undertaken to: 1) evaluate the effects of ozone and respirable H_2SO_4 aerosol on subjects with allergy, asthma and/or chronic bronchitis; 2) further evaluate the decrease in bronchial reactivity to methacholine following exposure to respirable H_2SO_4 aerosol, i.e. expose additional subjects to 4 hours of 100 $\mu g/m^3$, 0.1-0 3 μm H_2SO_4 aerosol; and 3) evaluate the effects of these two air pollutants employing moderate-to-heavy exercise loads.

Thomas J. Kulle, H. David Kerr, Bernard P. Farrell, and Larry R. Sauder are with the University of Maryland School of Medicine, Baltimore, MD 21201; David L. Swift is with Johns Hopkins University, Baltimore, MD 21205.

***Edward D. Haak, Jr.**, was the EPA Project Officer (for current contact, see below).*

The complete report, entitled "Pulmonary Function and Bronchial Reactivity in Human Subjects with Exposure to Ozone and Respirable Sulfuric Acid Aerosol: An Environmental Chamber Study," (Order No. PB 82-255 126; Cost: $15.00, subject to change) will be available only from:

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Telephone: 703-487-4650

*The EPA contact, **W. F. McDonnell**, can be contacted at:*

Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

United States
Environmental Protection
Agency

Center for Environmental Research
Information
Cincinnati OH 45268

Postage and
Fees Paid
Environmental
Protection
Agency
EPA 335

Official Business
Penalty for Private Use $300

PS 0000329
U S ENVIR PROTECTION AGENCY
REGION 5 LIBRARY
230 S DEARBORN STREET
CHICAGO IL 60604