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Effects of Inhaled Acids on Lung Biochemistry

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Effects of respirable aerosols of sulfuric acid, ammonium sulfate, sodium sulfite, and ammonium persulfate on lungs of rats are reviewed. The literature regarding interactions between ozone or nitrogen dioxide and acidic aerosols (ammonium sulfate, sulfuric acid) is discussed. An unexpected interaction between nitrogen dioxide and sodium chloride aerosol is also discussed. An attempt is made to identify bases for prediction of how and when acid aerosols might potentiate effects of inhaled gases.

Effects of Sulfuric Acid and Ammonium Sulfate Aerosols

By most of the conventional biochemical and histopathological criteria applied to the determination of lung injury, sulfuric acid (H_2SO_4) aerosol is a remarkably benign substance when inhaled by experimental animals, especially rats. Last and Cross (*1*) reported on the effects of exposure of rats to 1 mg/m^3 and higher concentrations of H_2SO_4 aerosol (nuclei mode, 0.02 μm CMD) on various parameters evaluated in lungs of rats exposed continuously for 3, 4, 7, or 14 days to up to 180 mg/m^3 of the aerosol. In the same study, a significant potentiation of the effects of exposure of rats to 0.4 ppm of ozone (O_3) (expressed as concentration determined by UV photometric analysis) by 1 mg/m^3 of H_2SO_4 aerosol, as evaluated by several parameters, was also reported. These observations have led us into various studies in the last 10 years that have mainly focused on the following questions: (a) What are the apparent no-effect levels for O_3 and H_2SO_4 in the positive interaction we have observed between them by various biochemical and morphological assays? (b) Can we develop a systematic data base by which we might generalize what specific properties of O_3 and of H_2SO_4 give rise to their synergistic interaction? (c) Can we begin to understand the mechanisms underlying interaction between pollutants in the centriacinar region of the lung, thereby allowing predictions of potential interactions between compounds prior to their testing in animal exposures? and (d) Can we develop sensitive quantitative assays that can be performed on acutely exposed animals that are predictive of (sub)chronic effects upon the lung?

To approach the first question, we have done extensive dose-response (more correctly, exposure-concentration response) experiments to characterize minimal response levels for the oxidant gases O_3 and nitrogen dioxide (NO_2) and for the acid aerosols ammonium sulfate [$(NH_4)_2SO_4$] and H_2SO_4, alone and in binary combinations of oxidant gases and acid aerosols. We have examined several biological end points, including lung collagen synthesis rate determined in explant cultures, protein content of lung lavage fluid, and total protein and DNA content of lung tissue. An important aspect of our work has been to examine various assays for quantifying the response of rat lungs to exposure to O_3. We then selected for further use those methods that were sensitive indicators of response at low concentrations of O_3 and that also showed proportional exposure (dose)-response behavior over a range of O_3 concentrations. This approach requires a systematic optimization of each assay for dose/time response before challenging animals at different concentrations of pollutants. For example, protein content of lung lavage fluid shows peak elevations above control values after 1 day of exposure of rats to 0.63 ppm O_3, but only after 2 days of exposure of rats to 0.20 ppm O_3 (*2*).

Guth et al. (*3*) showed significant exposure concentration-related increases in the total protein content of whole lung lavage fluid from rats exposed for 2 days to either 0.12 or 0.19 ppm O_3. Several other assays performed on lung lavage fluid were less sensitive indicators of response to O_3. Activities of lactate dehydrogenase, acid phosphatase, and *N*-acetyl-β-D-glucosaminidase were not affected by O_3 at these concentrations. Minimal effective concentrations of O_3 with

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respect to increased enzyme activity in lung lavage fluid by these assays were 0.66, 0.40, and 0.40 ppm O_3, respectively. Transport of a tracer molecule, [^{3}H]albumin, from blood to lavage fluid was also increased by exposure of rats to concentrations of O_3 of 0.40 ppm and above. Warren and Last (*4*) examined concentration-response relationships between O_3 and H_2SO_4 aerosols; Warren et al. (*2*) studied similar concentration-response relationships between O_3 and $(NH_4)_2SO_4$ aerosols. These papers extended earlier studies with O_3 and $(NH_4)_2SO_4$ or H_2SO_4 aerosols (*5*) performed at relatively high concentrations of O_3. These last three papers used the assays of lung lavage fluid described above, plus lung collagen synthesis rate and selected morphometric indices of lung inflammation or structural change, as quantifiable responses of the lung to exposure. The collagen synthesis rate assay and the protein content of whole lung tissue and of lung lavage fluid are the three most sensitive indicators of lung response to exposure to oxidants that we have, so these indicators were taken as the standard for attempts to define apparent no-effect levels in this series of studies.

Since well-controlled dose-response exposures to binary mixtures and their constituents are expensive and tedious experiments to perform, it was clear at the outset that it would be impossible to examine every possible combination and permutation of binary mixtures of oxidant gas and acid aerosol potentially of interest. We therefore initially focused on concentration-response relationships between O_3 and $(NH_4)_2SO_4$ aerosol.

We found in this study (*2*) that there was a significant increase in lung collagen synthesis rate and in protein content of lung lavage fluid in rats exposed for 7 or 2 days, respectively, to 0.2 ppm of O_3. A significant increase in both parameters over the values observed in rats exposed to 0.2 ppm of O_3 alone was found for rats exposed to 0.2 ppm of O_3 plus 5 mg/m^3 of $(NH_4)_2SO_4$ aerosol. We could, therefore, conclude that O_3-$(NH_4)_2SO_4$ synergy could be demonstrated at concentrations of O_3 as low as 0.2 ppm [with 5 mg/m^3 of $(NH_4)_2SO_4$]. We found in subsequent studies an apparent no-effect level at 1 mg/m^3 of $(NH_4)_2SO_4$ (0.20 and 0.64 ppm O_3 were used in these combined exposures) by the criterion of potentiating the response to O_3 in the panel of assays performed above (*2*). Thus, all of our subsequent experiments have been performed with H_2SO_4 aerosols, alone and in combination with O_3.

We also examined whether acidity of the aerosol or its sulfate (SO_4) content was the important determinant of interaction with oxidant gases (*6*). We quantitated lung collagen synthesis rate and whole lung protein content after 7 days of exposure of rats to 0.96 ppm O_3 ± 5 mg/m^3 $(NH_4)_2SO_4$, Na_2SO_4, or NaCl aerosols. By both of the criteria tested, exposure of rats to O_3 increased values significantly as compared with control rats breathing filtered air. The animals exposed to O_3 plus $(NH_4)_2SO_4$ aerosol showed significant increases above the values seen with rats exposed to O_3 in both assays [for example, collagen synthesis rate was 150% of the values observed with rats exposed to 0.96 ppm O_3 alone for the animals exposed to the mixture of O_3 and $(NH_4)_2SO_4$. These results may be contrasted with the findings for rats exposed to O_3 plus Na_2SO_4 or NaCl aerosols, where there was no difference as compared to values observed with rats exposed to O_3 alone. Morphometric analysis of volume of lung lesion and of fibroblast accumulation in lung lesions gave results consistent with the biochemical analyses. We concluded that acidity, not SO_4 content, of an aerosol is the determinant of its potential to interact synergistically with O_3.

Interaction of Ozone and Sulfuric Acid Aerosol

The response of rat lungs to exposure of animals to O_3 for 1 or 2 days is proportional to concentration of O_3 between 0.12 and 0.96 ppm (*3*). Elevations of lung collagen synthesis rates are proportional to exposure concentrations between 0.12 and 1.2 ppm of O_3 for 7 days (*2,5*). We thus titrated the response of rats to H_2SO_4 aerosols using low (0.12 or 0.20 ppm) and high (0.64) ppm concentrations of O_3 as standard regimens. We found synergistic interaction between O_3 and H_2SO_4 aerosols upon exposure of rats to 0.20 ppm O_3 plus 100, 500, or 1000 μg/m^3 of acid after 3 days of exposure by the criterion of significant increases in total lavagable protein (*4*). A small (not significant) increase in this parameter was observed in rats exposed to 0.20 ppm O_3 plus 40 μg/m^3 H_2SO_4 aerosol. H_2SO_4 aerosol alone provoked no significant response by this assay (95 or 107% of control values for 100 or 1000 μg/m^3 of acid aerosol alone, respectively). Synergistic interaction was also observed by the criterion of increased lung protein content (7- and 9-day exposures to ozone plus acid aerosol) in rats exposed to 0.2 ppm O_3 plus 40, 100, or 500 μg/m^3 H_2SO_4 aerosol (*4*). Recent unpublished experiments have also shown significant increases in lung protein content in rats exposed for 9 days to 0.2 ppm O_3 plus 20 μg/m^3 H_2SO_4 aerosol. An apparent no-effect level as defined by this assay (whole lung protein content) was observed (with a trend to slightly elevated values above those with O_3 alone) in preliminary experiments with rats exposed for 9 days to 0.2 ppm O_3 plus 5 μg/m^3 H_2SO_4 aerosols.

Lung collagen synthesis rates were significantly elevated in rats exposed to 0.64 ppm O_3 in this study (*4*), with synergistic interaction observed between 0.64 ppm O_3 and 200, 500, and 1000 μg/m^3 H_2SO_4 aerosol. A synergistic interaction was also observed between 0.20 ppm O_3 and 40, 100, 500, and 1000 μg/m^3 H_2SO_4 in this study. Also of interest was the apparent interaction between 0.12 ppm O_3 and 500 μg/m^3 H_2SO_4 aerosol observed with this assay (*4*). O_3-exposed rats had lung collagen synthesis rates that were 115% of control values (not significantly elevated); rats exposed to 0.12 ppm O_3 plus 500 μg/m^3 H_2SO_4 had rates that

were 132% of control values, a significant increase.

Two aspects of this study deserve special mention. First, interaction of O_3 and H_2SO_4 aerosols seems to be an all-or-nothing response. That is, there is no apparent dose-response relationship between concentration of acid aerosol in the exposure chamber and extent of increase over values observed with O_3 alone in any of the assays we have performed. Second, we have examined the relationship between H_2SO_4 aerosol mass concentration added to the chambers and pH of eluates of sample filters (*4*). There is no evidence in our experiments for neutralization of H_2SO_4 by chamber NH_3 (putatively arising from microbial action on animal excretia or from the rats themselves), at least down to values of 100 $\mu g/m^3$ of H_2SO_4 aerosol, by this criterion. That is, plots of aerosol concentration versus pH of filter eluates have a linear correlation of 0.98 between 100 and 1000 $\mu g/m^3$ H_2SO_4 aerosol. The biological response of rat lungs to exposure to 0.20 ppm O_3 plus 40 or 20 $\mu g/m^3$ H_2SO_4 aerosol suggests that any putative neutralization of H_2SO_4 by NH_3 is of little or no consequence at concentrations of acid at or above 20 $\mu g/m^3$.

Finally, it should be emphasized that the interaction between O_3 and H_2SO_4 or $(NH_4)_2SO_4$ is clearly one in which the damaging effects of O_3 on the centriacinar region of the lung are enhanced; that is, the acid aerosol potentiates the effects of O_3 and not vice-versa (*7*). We have suggested a biochemical mechanism involving extension of the lifetime of active oxygen species (free radicals) at sites of O_3 interaction with the deep lung in more acidic environments as one potential mechanism to explain this effect (*7*). Clearly, other mechanisms are also possible, including altered patterns of breathing affecting sites of deposition of O_3, or altered mucociliary clearance affecting removal of mediators or products of cell damage. It remains to be proven what the actual mechanism underlying the synergistic interaction between oxidant gases and acidic aerosols may be.

Interaction of Nitrogen Dioxide and Sulfuric Acid Aerosol

Rats were exposed for 7 days to 10, 5, or 2 ppm of NO_2. Elevations of lung collagen synthesis rate as compared with control animals exposed to filtered air were 210, 120, and 99%, respectively. The values at 5 and 10 ppm NO_2 were significantly increased as compared with the controls. Thus, there was a reasonable concentration-response relationship by this assay, with an apparent no-effect level at 2 ppm NO_2. This is not an unexpected finding: Using the relationship that the ratio of toxicity of NO_2:O_3 = 18 (*5*), we would estimate that 2 ppm NO_2 is equivalent in biological effect to 0.11 ppm O_3, while 5 ppm NO_2 is equivalent to 0.28 ppm O_3.

Protein content of lung tissue after 7 days of exposure was significantly increased to 122% of control values at 10 ppm NO_2. Values observed at 5 and 2 ppm were, respectively, 98 and 109% of controls; neither value was significantly different from the controls. Thus, an apparent no-effect level, as defined by this assay, was observed at 5 ppm NO_2.

Protein content of lung lavage fluid was quantified after 3 days of exposure. Values observed were 225, 175, and 106% of control for 10, 5, and 2 ppm, respectively; the first two values (at 10 and 5 ppm) were significantly greater than the controls. Enzyme activities quantified in the lavage fluid from the rats exposed to 5 ppm NO_2 included lactate dehydrogenase, acid phosphatase, and *N*-acetyl-β-D-glucosaminidase, none of which were significantly different than control values.

Thus, good concentration-response behavior was observed by the criteria of the lung collagen synthesis rate and the total lavagable protein content assays for rats exposed to 2 to 10 ppm NO_2, with an apparent no-effect level at 2 ppm. With this background information, we examined the response of rats by these assays to exposure to mixtures of NO_2 and H_2SO_4 aerosol.

Rats were exposed for 1, 3, or 7 days to 5 ppm NO_2 ± 1 mg/m^3 H_2SO_4 aerosol. As discussed above, response of rats to 5 ppm NO_2 alone as quantified by the collagen synthesis rate assay (7 days) and by the protein content of lung lavage fluid (3 days) was significant, whereas protein content of lung lavage fluid after 1 day of exposure was indistinguishable from control values. The protein content of lung lavage fluid from rats exposed to NO_2 plus H_2SO_4 aerosol was significantly elevated to 215 and 180% of control values, respectively, for assays after 1 and 3 days exposure. The elevation at 1 day was significantly greater than that observed with NO_2 alone; the value at 3 days was comparable to that observed with NO_2 alone (175% of controls). These results illustrate the importance of considering the optimal time-response behavior of rats as a function of pollutant concentration in this assay when designing the experiment. Protein content of lavage fluid for rats exposed for 3 days to the acid aerosol alone was not significantly different from control values (113% of controls). For rats exposed for 3 days to 2 ppm NO_2 plus H_2SO_4 aerosol, lavagable protein content was increased to 132% of control values.

The rats exposed for 7 days to 5 ppm NO_2 plus acid aerosol had lung collagen synthesis rates of 145% of control values, significantly greater than the controls or values from rats exposed to 5 ppm NO_2 alone (120% of control values). The rate of collagen synthesis for lungs of rats exposed to H_2SO_4 aerosol alone was indistinguishable from control values (98% of controls). Rats exposed to 2 ppm NO_2 plus H_2SO_4 aerosol had lung collagen synthesis rates (129% of controls) significantly higher than rats exposed to either 2 ppm NO_2 (99% of controls) or to filtered air.

We conclude that there is a synergistic interaction between 1 mg/m^3 of H_2SO_4 aerosol and 2 or 5 ppm NO_2 by two independent assays of response of rat lungs to exposure to these agents.

Effects of Other Aerosols Containing Sulfur Oxide Anions

We exposed rats to respirable aerosols of sodium sulfite (Na_2SO_3) over a concentration range of 0.1 to 15 mg/m^3, equivalent to concentrations of sulfur dioxide (SO_2) of 0.02 to 2.7 ppm, for 3 days (24 hr per day). Additional groups of rats were exposed to 10 mg/m^3 Na_2SO_4 and to the addition product of Na_2SO_3 and formaldehyde (sodium hydroxymethane sulfonate) at 6 mg/m^3 (*8*). Aerosols had MMADs of 0.8 to 1.2 μm and were essentially SO_4- and SO_2-free. We measured various parameters of lung response to exposure, of which the most sensitive (in this study) was an increase in the wet to dry weight ratio of whole lung tissue. We interpret this assay as indicative of changes related to pulmonary edema and/or inflammation. Significant dose-related increases in lung wet to dry weight ratio were observed in rats exposed to 1, 6, and 14 mg/m^3 of Na_2SO_3 aerosol, with nonsignificant trends toward increased wet to dry weight observed in the groups exposed to 0.1 mg/m^3 Na_2SO_3 aerosol and to 6 mg/m^3 sodium hydroxymethane sulfonate. No response was observed by this criterion in lungs of rats exposed to 10 mg/m^3 sodium sulfate (Na_2SO_4) aerosol.

We have also exposed rats to 1 to 20 mg/m^3 of respirable (0.8–1.3 μm MMAD) aerosols of ammonium persulfate [$(NH_4)_2S_2O_8$] for 7 days (*9*). Rats inhaling 4 to 20 mg/m^3 of the persulfate aerosol lost body weight and had significantly increased lung wet weight, total lung protein content, and lung DNA content. We interpret these changes as indicative of changes related to pulmonary edema and/or inflammation. Small, not significant, increases in all of these parameters were observed in the lungs of rats exposed to 1 mg/m^3 of persulfate aerosol. In the same study, we also exposed a group of rats to a 5 mg/m^3 aerosol $(NH_4)_2SO_4$ (0.8 μm MMAD) containing 0.7 mg/m^3 of gaseous hydrogen peroxide (H_2O_2), equivalent in oxidizing capacity to 5 mg/m^3 $(NH_4)_2S_2O_8$ aerosol, to examine whether a highly soluble gaseous oxidant (H_2O_2) plus a sulfate aerosol gave comparable effects to the persulfate aerosol. No response was observed to the H_2O_2-sulfate combination by any of the assays used in this study.

Even though the concentrations of sulfite or persulfate aerosols required to elicit responses in these studies were very high as compared to realistic exposures likely to be encountered by humans, these results are suggestive that acid aerosols other than H_2SO_4 and/or HSO_4 could be potential toxicants in occupational or environmental atmospheres.

Effects of Sodium Chloride Aerosols

There is no observable interaction between O_3 (0.96 ppm) and respirable aerosols of 5 mg/m^3 NaCl under conditions identical to those that we demonstrated had elicited a synergistic interaction in our experiments with O_3 and $(NH_4)_2SO_4$ aerosols (*6*).

In an earlier study (*5*), we exposed rats to aerosols of 5 mg/m^3 $(NH_4)_2SO_4$, alone or in combination with 5, 10, 15, 20, or 25 ppm of NO_2. There was an approximate doubling of the lung collagen synthesis rate in rats exposed to the binary mixtures as compared with NO_2 alone at all concentrations tested; $(NH_4)_2SO_4$ aerosol alone had no effect on the rats in these studies. In later work (Last and Warren, unpublished data), we have examined responses of rats to 2, 5, or 10 ppm of NO_2 by most of the assays described above, observing an apparent no-effect level at 2 ppm NO_2 (discussed above). Based upon these experiments we exposed rats to 5 ppm NO_2 with and without 1 mg/m^3 H_2SO_4 or of NaCl aerosol (*10*).

Rats exposed to 5 ppm NO_2 for 7 days showed a significant increase in lung collagen synthesis rate (120% of control values). Groups of rats exposed to 5 ppm NO_2 and 0.9 mg/m^3 H_2SO_4 aerosol had lung collagen synthesis rates of 145% of the control values, i.e., rats exposed to filtered air, values significantly greater than those observed with the rats exposed to NO_2 alone. Of interest here, however, is the response of rats exposed for 7 days to 5 ppm NO_2 plus 1.1 mg/m^3 NaCl aerosol. These animals showed a lung collagen synthesis rate of 165% of the values observed with controls exposed to filtered air. In control experiments we found values of 98 and 95% of control for rats exposed to H_2SO_4 aerosols and NaCl aerosols alone, respectively, by this assay.

We also quantified the protein content of the lung lavage fluid from rats exposed for 3 days to 5 ppm NO_2, with and without either 1 mg/m^3 H_2SO_4 or NaCl aerosol. As compared with filtered air controls, we found values of 175% of controls in the rats exposed to NO_2 alone, 180% of controls in rats exposed to NO_2 + H_2SO_4 aerosol, and 210% of controls in rats exposed to NO_2 + NaCl aerosol. The increase in values for the NO_2 + NaCl group was significant as compared to those observed in rats exposed to NO_2 alone.

We interpret these results as suggesting that a reaction product of NO_2 and NaCl is responsible for the interaction observed in these experiments, since no interaction was observed between NaCl and O_3, which do not react chemically. We hypothesize that the interaction between NO_2 and NaCl is due to their reaction to form nitrosyl chloride (NOCl), the mixed anhydride of hydrochloric, nitrous, and nitric acids, which could give rise to strong acids in the centriacinar region of the lung upon hydrolysis. The possibility of acid aerosols (or acidogenic aerosols) arising in the atmosphere from sources other than SO_2 or direct dissolution of NO_2 to give nitric and nitrous acids opens some very interesting vistas toxicologically.

Summary and Conclusions

To return to the four questions asked at the beginning of this paper, we can attempt to answer them as

follows: (a) Apparent no-effect levels for O_3 and H_2SO_4 aerosol interactions: As of our present assays and data base, the apparent no-effect concentration value for O_3 is at or below 0.12 ppm, while that for H_2SO_4 aerosol (at 0.20 ppm of O_3) is below 20 $\mu g/m^3$. (b) Properties of O_3 and H_2SO_4 responsible for their interaction: The combination of a relatively insoluble oxidant gas and a respirable-sized acidic (or acidogenic) aerosol, such that significant deposition and interaction can occur in the centriacinar region of the lung, seem to be the critical properties that are predictive for interactions to occur. (c) Interactions between pollutants: On a phenomenological level, synergistic interaction seems to occur between oxidant gases and acids. We do not yet understand on a mechanistic level what are the controlling factors underlying such interactions (i.e., what are the rules?). (d) Development of sensitive, quantitative assays predictive of chronic effects: Until now, essentially all of our work on O_3 (or NO_2)-acid aerosol interaction has been done with acute experiments (1–9 days of exposure), so we know little or nothing about possible chronic effects upon the lung of inhalation of such mixtures. We have one hint that the synergistic interaction between 0.4 ppm O_3 and 1 mg/m^3 H_2SO_4 persists for at least 50 days of continuous exposure (*5*), but far more work remains to be done in this area to define the nature and extent of any chronic interactions. A panel of sensitive assays for studying effects on acutely exposed animals discussed in this paper remain to be validated for their ability to predict chronic effects upon the lung.

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