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# Factors Affecting the Response of Lung Clearance Systems to Acid Aerosols: Role of Exposure Concentration, Exposure Time, and Relative Acidity

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**The ability of the lungs to clear deposited material is essential for maintenance of lung homeostasis. Acid aerosols have been shown to alter the efficiency of this process. This paper assesses the role of acid aerosol exposure concentration (*C*), exposure time (*T*), and relative acidity in producing changes in clearance from both the tracheobronchial tree and respiratory region of the lungs of rabbits. The response was found to be due to total exposure, i.e., some combination form of $C \times T$, and was also related to relative acidity.**

## Introduction

The respiratory tract maintains an array of defenses that serve to prevent or reduce damage to the tract itself and absorption of noxious materials into the circulation (*1*). One component involves the physical removal of inhaled particles that contact and deposit upon epithelial surfaces. This process is known as clearance, and the rapidity and degree to which particles are removed frequently plays a role in determining the biological effects of these particles.

Clearance processes are not the same throughout the respiratory tract, with regional differences in both mechanisms and kinetics (*2*). In the conducting airways of the lungs, i.e., the tracheobronchial tree, clearance occurs via mucociliary transport, whereby a mucous blanket that overlies the epithelium is moved by the coordinated beating of cilia toward the oropharynx. Insoluble particles that deposit in this region are generally cleared within 24 to 48 hr.

Clearance from the respiratory (alveolated) region of the lungs occurs via a number of mechanisms and pathways, but the major one involves alveolar macrophages. These freely moving cells actively phagocytize deposited particles and are then removed from the gas-exchange region primarily via the mucociliary system, after reaching the distal terminus of the mucous blanket.

There is accumulating evidence that inhaled acid sulfate aerosols, in particular, sulfuric acid ($H_2SO_4$), may alter the efficiency of lung clearance mechanisms (*3*); such changes have implications for the ultimate handling of the offending agent itself, as well as other materials that may be concurrently or subsequently inhaled. Furthermore, changes in clearance may have pathogenic consequences (*2,3*).

Although acid aerosols may affect clearance function, a number of important factors upon which the response depends have yet to be totally resolved. This paper discusses three of these, namely the roles of exposure concentration, exposure duration, and the relative acidity of the inhaled aerosol.

## Methodology

The studies reported involved use of male, New Zealand White, specific pathogen-free (*Pasteurella multocida*) rabbits (3.0–3.5 kg), an animal model developed and successfully employed in this laboratory for the study of pollutant effects on lung clearance. The animals were individually housed in stainless-steel cages in rooms maintained at temperature and relative humidity levels of 20°C and 50%, respectively. Food (Purina Rabbit Chow-HF) and water were provided *ad libitum*.

Clearance patterns are obtained by measuring the retention of radioactively tagged tracer microspheres by external scanning techniques employing paired, collimated NaI scintillation detectors coupled to a pulse height analysis system (*4,5*); clearance is observed as the progressive decline in radioactivity retained in the

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lungs within specific measurement periods. Mucociliary clearance from the tracheobronchial tree is assessed by serial measurements of the retention of ferric oxide microspheres [4.5 μm, mass median aerodynamic diameter (MMAD)] tagged with $^{99m}Tc$. Retention measurements are performed every minute during the first 3 hr after tracer aerosol exposure, and once every 3 min during hour 4; an additional measurement is then performed 24 hr after exposure. The results of each clearance test are quantitatively described in terms of the parameter mean residence time (MRT). This represents the mean time, over the measurement period, that tracer particles that initially deposited in the tracheobronchial tree reside there. MRT is derived by computer integration of the clearance curve, i.e., the retention curve corrected for residual activity remaining at 24 hr post-tracer exposure.

Alterations in mucociliary clearance due to acid aerosol inhalation are assessed as follows. Each rabbit serves as its own control, and a mean control value for MRT is obtained for each animal based on a series of five clearance tests performed prior to any pollutant exposure. The mean MRT for the clearance tests conducted after pollutant exposure is obtained for each rabbit, and a value of %ΔMRT, i.e., the percentage change in MRT from mean preexposure control, is determined. A group mean percentage change, i.e., $\overline{\%\Delta MRT}$, is then obtained for the entire cohort for each specific exposure condition.

Clearance patterns from the respiratory region are assessed by measuring the retention of $^{85}Sr$-tagged 3.5 μm (MMAD) polystyrene latex microspheres by daily profile scanning. After inhaling the tracer particles, each rabbit is moved along a horizontal plane between the pair of collimated scintillation detectors, and counts are obtained at nine thoracic positions spaced 0.5 cm apart. At the end of each scan. the greatest measured lung activity among the nine positions is recorded for each animal as an index of total lung burden. Since studies in this laboratory are aimed at assessing the effect of pollutant exposure on the early phase of particle clearance from the respiratory region of the lungs, and previous work had demonstrated that the period from 2 to 14 days after tracer aerosol inhalation was representative of this phase in rabbits (*4*), respiratory region clearance is measured in terms of the percentage of tracer particles on day 2, i.e., 48 hr posttracer exposure, which was retained on each day through day 14.

To provide overall quantitation of the respiratory region clearance, the 2 to 14 day retention data for each test run were fit with a single exponential function using standard regression procedures, and a halftime ($t_{1/2}$) was obtained. Halftime data were then analyzed similarly to that for mucociliary clearance, except that in this case each rabbit did not serve as its own control. Rather, sham controls (exposure to temperature/humidity conditioned air only) were run at each exposure condition, and a mean control $t_{1/2}$ of the entire control group obtained. A $t_{1/2}$ for each rabbit at each pollutant exposure condition is obtained, and a value of $\%\Delta t_{1/2}$, i.e., the percentage change in $t_{1/2}$ from mean sham control, determined. A group mean percentage change, i.e., $\overline{\%\Delta t_{1/2}}$ is then obtained for the entire cohort at each pollutant exposure condition.

The acid aerosols used in these studies consisted of either $H_2SO_4$, ammonium bisulfate ($NH_4HSO_4$), or ammonium sulfate [$(NH_4)_2SO_4$]. The techniques for generating and monitoring these aerosols have been previously described in detail (*6*). Basically, submicrometer (0.3 μm, MMD) aerosols are produced by nebulizing aqueous solutions. The pollutant atmospheres are then equilibrated to the appropriate temperature and relative humidity in a mixing chamber and delivered to individual exposure ports via a manifold system. The size distribution of the $H_2SO_4$ aerosol is monitored with a cyclone sampler; mass concentration analyses for sulfate are performed by flame photometry. Inhalation of sulfate aerosol was via oral tube (for mucociliary clearance series) or nasal mask (for respiratory region clearance series).

## Relative Roles of Exposure Concentration and Exposure Time in Eliciting Response

The response to a toxicant is generally dependent upon dose. For inhaled materials, dose is a function of the amount retained, which is determined by both the concentration ($C$) of toxicant in the inhaled air and the duration of exposure ($T$). Many air pollutants demonstrate fluctuating concentrations during 1 day, or even within shorter time frames. This is especially true for those pollutants such as acid sulfates that are formed secondarily in the atmosphere and whose production is dependent upon both primary pollutant release and various other factors, such as meteorological conditions.

Unfortunately, little is known about the concentration-time-response relationship for acid sulfate effects on the respiratory tract; this information is needed to predict the severity of response under different ambient exposure conditions and to allow the evaluation of pollution measurements in terms of health end points. For example, in many cases, the time weighted average concentrations of atmospheric pollutants are obtained from monitoring stations, and this is then used for comparison to results of toxicologic or controlled clinical studies. Implicit in this analysis, however, is acceptance of Haber's Law, that is, that the product of $C \times T$ is proportional to the severity of response, and that all values of $C$ and $T$ that produce the same product will produce a response of the same magnitude. In the only previously reported examination of $C \times T$ relationships for acid aerosols, Amdur et al. (*7*) found that exposure for 72 hr to 8 mg/m$^3$ $H_2SO_4$ did not increase mortality percentages over those observed due to 8-hr exposures to the same concentration. Thus, lethality appeared to depend on actual concentration,

rather than on the duration of exposure. On the other hand, the extent of histological damage appeared to be related to cumulative exposure, in that guinea pigs exposed to 8 mg/m$^3$ $H_2SO_4$ for 72 hr [$C \times T$ = 576 (mg/m$^3$)·hr showed more extensive tissue damage than did those exposed at 20 mg/m$^3$ for 8 hr [$C \times T$ = 160 (mg/m$^3$·hr]. A series of studies have been performed in this laboratory to examine the concentration-time-response pattern for sulfuric acid aerosol in terms of altering clearance functions of the lungs.

## Mucociliary Clearance

Acute exposures to $H_2SO_4$ were carried out under various conditions of concentration and time (Table 1). This involved exposures (via oral tube) of one group of five rabbits for 2 hr, and another group of five rabbits for 4 hr, followed by inhalation of tracer aerosol. The results were compared with those previously reported by Chen and Schlesinger (*8*) and Schlesinger et al. (*9*) for 1-hr exposures.

Figure 1 shows the results of all exposures to $H_2SO_4$ as a function solely of exposure concentration ($C$). The statistical significance of $\overline{\%\Delta MRT}$ at each concentration for each of the three exposure series (i.e., 1 hr, 2 hr, or 4 hr) was assessed using ANOVA (after angular transformation of the data), followed by Dunnett's test for comparison of response at each concentration to a respective sham control exposure run at

**Table 1. $H_2SO_4$ exposure conditions for mucociliary clearance assays.**

| Exposure concentration ($C$), mg/m$^3$ [a] | Exposure time ($T$), hr [b] | $C \times T$, (mg/m$^3$) · hr |
|---|---|---|
| 0.1 (0.100 ± 0.005) | 1 [c] | 0.1 |
| 0.2 (0.198 ± 0.003) | 1 | 0.2 |
| 0.25 (0.262 ± 0.020) | 1 | 0.25 |
| 0.4 (0.409 ± 0.048) | 1 | 0.4 |
| 0.7 (0.693 ± 0.007) | 1 | 0.7 |
| 0.85 (0.828 ± 0.031) | 1 | 0.85 |
| 1.3 (1.270 ± 0.197) | 1 | 1.3 |
| 2.2 (2.155 ± 0.121) | 1 | 2.2 |
| 0.2 (0.196 ± 0.013) | 2 | 0.4 |
| 0.3 (0.284 ± 0.034) | 2 | 0.6 |
| 0.4 (0.407 ± 0.080) | 2 | 0.8 |
| 0.5 (0.502 ± 0.007) | 2 | 1.0 |
| 1.0 (1.043 ± 0.010) | 2 | 2.0 |
| 0.1 (0.101 ± 0.009) | 4 | 0.4 |
| 0.15 (0.145 ± 0.006) | 4 | 0.6 |
| 0.2 (0.207 ± 0.016) | 4 | 0.8 |
| 0.25 (0.247 ± 0.011) | 4 | 1.0 |

[a]Exposure atmospheres were maintained at 24°C, 75% relative humidity. Numbers in parentheses represent the actual concentrations obtained (mean ± SD of readings at 15-min intervals during each exposure).

[b]Each exposure time involved a different group of rabbits. The number per group was as follows: 1 hr, $n$ = 8; 2 hr, $n$ = 5; 4 hr, $n$ = 5. Tests within each group were performed randomly, at intervals of not less than 1 week between successive exposures. Control clearance tests were performed between each $H_2SO_4$ exposure to be sure that all animals had returned to baseline before the next exposure.

[c]1-hr exposure data are from Chen and Schlesinger (*8*) and Schlesinger et al. (*9*).

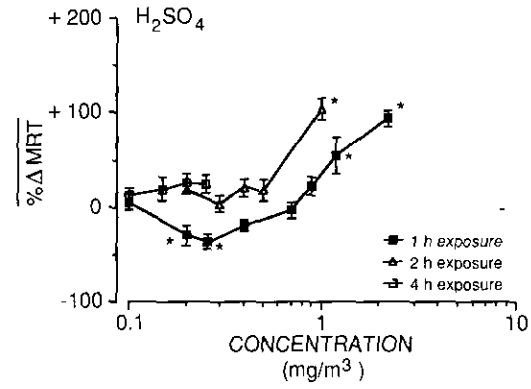


FIGURE 1. Change in mucociliary clearance of tracer particles due to single exposure to $H_2SO_4$ as a function of exposure concentration (measured as $SO_4^{2-}$). Each point represents the average change in MRT, i.e., $\overline{\%\Delta MRT}$ (± SE), for the entire group exposed at each condition. Changes in MRT in the positive direction indicate a slowing of clearance; changes in the negative direction indicate speeding. The shaded horizontal band represents the 95% confidence interval for $\overline{\%\Delta MRT}$ = 0 based on preexposure control clearance tests. Asterisk (*) indicates significant change from preexposure control ($p < 0.05$).

each of the three exposure times. If there was no interaction between $C$ and $T$, there should be no statistical difference in response when either parameter is varied, provided the product is constant. It is evident from Figure 1 that exposures at the same concentration, but for different durations, do not necessarily result in responses of the same magnitude.

A multiple regression analysis was then performed to assess the relative contribution of $C$ and $T$ to the observed response. The results are shown in Table 2. It is evident that both $C$ and $T$ are highly significant contributors to the change in mucociliary clearance induced by exposure to $H_2SO_4$, although the partial regression coefficients indicate that $C$ has a greater influence on the ultimate response than does $T$ and that $C$ is more important for a fixed level of $C \times T$. Figure 2 shows $\overline{\%\Delta MRT}$ plotted as a function of $C \times T$. It is now evident that there is no statistical difference in response between tests conducted at equivalent $C \times T$ values.

## Respiratory Region Clearance

The relative roles of $C \times T$ in eliciting changes in respiratory region clearance due to $H_2SO_4$ were assessed with repeated daily exposures (via nasal mask) of 1 to 4 hr duration for 14 days (Table 3) (Figs. 3 and 4). For these tests, the tracer aerosol was administered immediately after the first acid exposure. On subse-

**Table 2. Multiple regression analysis for mucociliary clearance.[a]**

| Parameter | Partial regression coefficient | $p$ |
|---|---|---|
| $C$ | 0.73 | 0.0001 |
| $T$ | 0.40 | 0.0007 |

[a]Coefficient of determination of multiple regression, $r^2$ = 0.7 ($p$ = 0.0001).

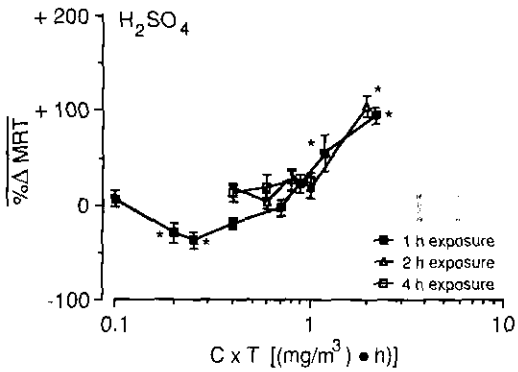


FIGURE 2. Change in mucociliary clearance of tracer particles due to single exposure to $H_2SO_4$ as a function of the product of exposure concentration. ($C$) and exposure time ($T$). Shaded band, error bars, and asterisk as in Fig. 1.

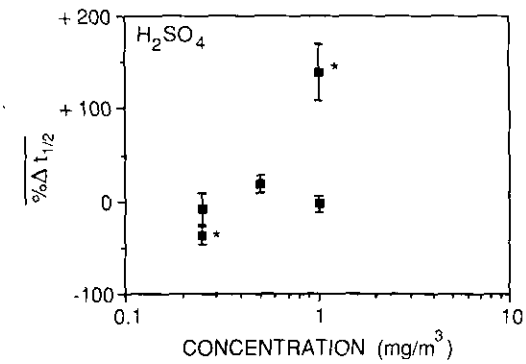


FIGURE 3. Change in halftime of early clearance of tracer particles from the respiratory region of the lungs due to intermittent exposures to $H_2SO_4$ as a function of exposure concentration (measured as $SO_4^{2-}$). Each point represents the mean change in $t_{1/2}$, i.e., $\overline{\%\Delta t_{1/2}}$ (± SE), for the entire group at each exposure condition. Changes in the positive direction indicate a slowing of clearance; changes in the negative direction indicate speeding. The shaded horizontal band represents the 95% confidence interval for $\overline{\%\Delta t_{1/2}} = 0$, based upon sham control exposures. Asterisk indicates significant change from control ($p < 0.05$).

quent days, retained activity was measured prior to that days' pollutant exposure. Figure 3 shows a plot of $\overline{\%\Delta t_{1/2}}$ versus concentration; it is evident that exposures to equivalent $H_2SO_4$ concentrations do not necessarily result in equivalent responses.

A multiple regression analysis was then performed using $C$, $\log T$, and $\%\Delta t_{1/2}$ as variables; $\log T$ was used because regression with $T$ was found to be not significant. Examination of the regression parameters (Table 4) shows that although both $C$ and $T$ are highly significant contributors to the response, the former is a greater contributor. This is consistent with the results of the mucociliary clearance tests discussed above. Figure 4 shows $\overline{\%\Delta t_{1/2}}$ plotted as a function of $C \times T$.

**Table 3. Acid sulfate exposure conditions for respiratory region clearance assays.**

| Acid sulfate | Exposure concentration, mg/m³[a] | Exposure duration, hr/day[b] | Daily $C \times T$, (mg/m³) · hr |
|---|---|---|---|
| $H_2SO_4$ | 0.25 (0.251 ± 0.014) | 1 | 0.25[c] |
| | 0.25 (0.255 ± 0.018) | 2 | 0.5 |
| | 0.25 (0.272 ± 0.088) | 4 | 1 |
| | 0.5 (0.513 ± 0.009) | 2 | 1 |
| | 1.0 (1.043 ± 0.232) | 1 | 1 |
| | 1.0 (1.056 ± 0.105) | 2 | 2 |
| $NH_4HSO_4$ | 0.5 (0.527 ± 0.071) | 2 | 1 |
| | 1.0 (1.020 ± 0.095) | 2 | 2 |
| | 2.0 (2.040 ± 0.127) | 2 | 4 |
| $(NH_4)_2SO_4$ | 2.0 (2.010 ± 0.297) | 2 | 4 |

[a]Exposure atmospheres were maintained at 25°C, 80% relative humidity. Numbers in parentheses represent actual concentration (mean ± SD of all daily exposures).
[b]Each exposure condition involved a different group of animals. Each group had $n = 5$, except for 0.25 at 1 hr, where $n = 4$.
[c]Data from Schlesinger and Gearhart (*14*).

**Table 4. Multiple regression analysis for respiratory region clearance.[a]**

| Parameter | Partial regression coefficient | $p$ |
|---|---|---|
| $C$ | 0.64 | 0.002 |
| $\log T$ | 0.49 | 0.014 |

[a]Coefficient of determination of multiple regression, $r^2 = 0.65$ ($p = 0.004$).

## $C \times T$: Conclusion

The results of studies conducted to examine the role of $H_2SO_4$ concentration and exposure time in eliciting changes in tracheobronchial and respiratory region clearance indicate that the response is due to some combination form of $C \times T$. However, these data do not allow for determination of the exact $C \times T$ relationship, although they suggest that both $C$ and $T$ have exponents lower than 1. To obtain a more rigorous solution, it would be necessary to do additional inhalations at a larger number of concentrations and exposure durations. Once known, the mathematical relationship between $C$, $T$, and response may be used to predict biological equivalent concentrations of $H_2SO_4$ in ambient air. Nevertheless, the initial studies presented here strongly suggest that, in terms of alterations in clearance function, time-weighted average concentra-

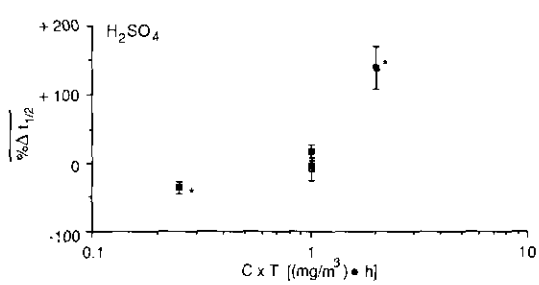


FIGURE 4. Change in halftime of early clearance of tracer particles from the respiratory region due to intermittent exposures to $H_2SO_4$ as a function of the product of exposure concentration ($C$) and exposure time ($T$). Shaded band, error bars, and asterisk as in Fig. 3.

tions of $H_2SO_4$ may be used to integrate exposure within the range of $C \times T$ currently examined. They also suggest that effects of time-variable concentration should be considered in estimating any environmental criteria for $H_2SO_4$, at least in terms of altering clearance function.

It should be kept in mind that the $C \times T$ relationship may not hold at extreme values of either parameter. For example, at very low acid aerosol concentrations, no response is likely to be found regardless of the exposure duration. In addition, the current data set does not allow for the definite prediction of a no effect level other than for 1-hr exposures with mucociliary clearance as the end point where the threshold in the rabbit model appears to be approximately 0.095 mg/m$^3$.

## Role of Relative Acidity in Eliciting Response

All of the major persistent sulfate species identified in ambient air, i.e., $(NH_4)_2SO_4$, $NH_4HSO_4$, and $H_2SO_4$, are acidic, although they vary greatly in acidity. Not surprisingly, studies that have examined their relative irritant potency in terms of altering pulmonary mechanics have found $H_2SO_4$ to be the most potent. Amdur et al. (*10*) ranked sulfates based upon their ability to change flow resistance in guinea pigs; $H_2SO_4$ was approximately 10 times more potent than $(NH_4)_2SO_4$, and approximately 33 times more than $NH_4HSO_4$. The greater irritancy of $(NH_4)_2SO_4$ as compared to $NH_4HSO_4$ was unexpected, because the latter has a lower pH in aqueous solution. On the other hand, Utell et al. (*11*) exposed healthy humans to $H_2SO_4$, $NH_4HSO_4$, $(NH_4)_2SO_4$ or sodium bisulfate ($NaHSO_4$) aerosols. None of these produced a significant change in specific airway conductance. However, when sulfate exposure was followed by a carbachol challenge aerosol (a parasympathomimetic agent), the bronchoconstrictor action of the carbachol was potentiated by the sulfates in rough relation to their acidity, i.e., $H_2SO_4 > NH_4HSO_4 > NaHSO_4 > (NH_4)_2SO_4$.

### Mucociliary Clearance

A previous study performed in this laboratory examined the role of relative acidity in altering mucociliary function (*12*). In this study, rabbits were exposed for 1 hr to submicrometer aerosols of $NH_4HSO_4$, $(NH_4)_2SO_4$ or sodium sulfate ($Na_2SO_4$) (Fig. 5). Exposure to 0.6 to 1.7 mg/m$^3$ $NH_4HSO_4$ produced a significant depression of clearance rate only at the highest level. No significant effects were observed with the other aerosols at levels up to 2 mg/m$^3$. When these results were compared to those obtained with 1-hr exposures to $H_2SO_4$ (*8,9*) (Fig. 1), the ranking of irritant potency was $H_2SO_4 > NH_4HSO_4 > (NH_4)_2SO_4$, $Na_2SO_4$; this strongly suggested a relation between the hydrogen ion ($H^+$) concentration and the extent of bronchial mucociliary clearance alteration. In another study, Schlesinger et al. (*13*) found bronchial clearance to be altered in donkeys exposed to $H_2SO_4$ for 1 hr at levels above 0.2 mg/m$^3$, while exposures to $(NH_4)_2SO_4$ at up to 3 mg/m$^3$ produced no response.

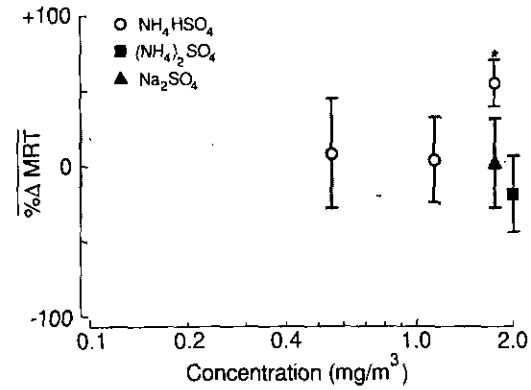


FIGURE 5. Change in mucociliary clearance (measured in terms of MRT) due to 1-hr exposure to sulfate aerosols as a function of exposure concentration (measured as $SO_4^{2-}$) Shaded band, error bars and asterisk as in Fig. 1. Modified from Schlesinger (*12*).

### Respiratory Region Clearance

There are no previously reported studies that examined the relative potency of acid sulfates in terms of altering respiratory region clearance. To begin to assess this, rabbits were exposed to $NH_4HSO_4$ and $(NH_4)_2SO_4$ for 2 hr/day (for 14 days) for comparison to similar exposures to $H_2SO_4$ (Table 3) (Figs. 3 and 4). The results for $NH_4HSO_4$ are shown in Figure 6. Although none of the individual exposures resulted in a statistically significant change in clearance, the entire data set strongly suggested a concentration-response relationship. Accordingly, linear regression analysis was performed for $\overline{\%\Delta t_{1/2}}$ versus log$C$, and a significant relation was found ($r = 0.7$, $p = 0.04$), indicating a trend of accelerating clearance with increasing $C$ for the 2-hr exposures. Exposure to $(NH_4)_2SO_4$ at 2 mg/m$^3$ for 2 hr resulted in no change in clearance (Fig. 6.)

### Relative Acidity: Conclusion

The results of studies aimed at assessing the role of relative acidity in altering clearance suggest a relation

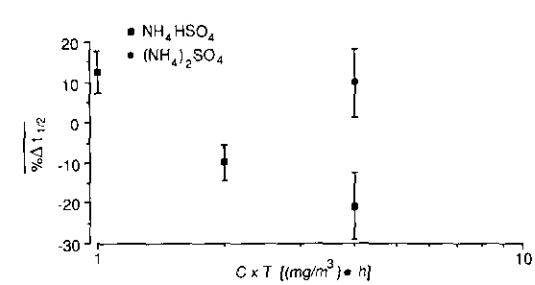


FIGURE 6. Change in halftime of early clearance of tracer particles from the respiratory region due to intermittent exposures to $NH_4HSO_4$ and $(NH_4)_2SO_4$. Shaded band and error bars as in Fig. 3.

between acid content of the sulfur oxide aerosol and response of both tracheobronchial and respiratory region clearance. Although the exposure regimes were different, the data also suggest that $NH_4HSO_4$ is more effective in altering mucociliary clearance than clearance from the respiratory region, since a daily exposure level of 4 $(mg/m^3)\cdot hr$ did not significantly alter clearance from the respiratory region. If the effect on respiratory region clearance was related directly to $H^+$, one would have expected some change at the highest $NH_4HSO_4$ level used (i.e., 2 $mg/m^3$, as sulfate), which should deliver (stoichiometrically) the same amount of $H^+$ as would $H_2SO_4$ at 1 $mg/m^3$ (for comparable 2-hr exposures), assuming relatively similar deposition patterns. Figure 7 shows $\overline{\%\Delta t_{1/2}}$ plotted as a function of $[H^+]$, i.e., total $H^+$ content. It is evident that $NH_4HSO_4$ is less than half as potent as $H_2SO_4$ with respiratory region clearance as the end point. Additional studies need to be done with mucociliary clearance to confirm whether this is also true with this clearance end point; the limited data presented in Figure 5 suggest that it may not be. The relation between $[H^+]$, specific sulfate species, and response has certain implications in terms of ambient monitoring, in that it is critical to determine whether the analysis of strong $H^+$ is adequate to assess the presence of material with potential biological effects, or whether it is exposure to the $H^+$ associated solely with $H_2SO_4$ that poses the greatest threat.

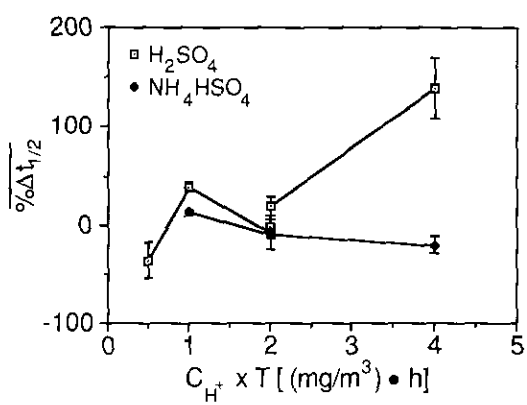


FIGURE 7. Change in halftime of early clearance of tracer particles from the respiratory region due to intermittent exposures to $H_2SO_4$ and $(NH_4HSO_4)$ as a function of total $H^+$ content of each chemical species. Shaded band, error bars, and asterisk as in Fig. 3.

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