EFFECTS OF SULFUR DIOXIDE AND FORMALDEHYDE ON PARTICLE CLEARANCE IN THE RAT

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The effects of exposures to sulfur dioxide and formaldehyde atmospheres on the clearance of inhaled, insoluble tracer particles from the lungs of rats have been studied. The tracer particles employed were polystyrene latex microspheres radio-labeled with \(^{51}\)Cr. Following the deposition of the 1.9-µm activity median aerodynamic diameter (AMAD) particles, the rats were divided into 3 groups for a single 4-h exposure to purified air, 20 ppm sulfur dioxide, or 20 ppm formaldehyde. Early, presumably upper-respiratory-tract, clearance was monitored by analysis of radioactivity excreted in feces, while late, presumably deep-lung, clearance was followed by thoracic counting of the animals. Both the sulfur dioxide and formaldehyde atmospheres did significantly delay early clearance (p < 0.1, two-tailed t-test). However, the late clearance rates of the two pollutant-exposed groups of rats were not significantly different from that of the purified air-exposed group of rats. Although sulfur dioxide had numerically greater effects than formaldehyde, the differences were not statistically significant at the p < 0.1 level.

INTRODUCTION

Sulfur dioxide (SO\(_2\)) is an upper-respiratory-tract irritant and a common community and industrial air pollutant. The gas is often present in urban atmospheres as a result of the burning of sulfur-laden fossil fuels. Outdoor SO\(_2\) exposures in excess of the National Air Quality Standard of 0.14 ppm (24 h averaging time) have not been uncommon in the past (National Research Council, 1978). Indoor levels of SO\(_2\) have been observed to be on the order of 20 to 70% of the outdoor levels (Spengler et al., 1979). While a Federal air quality secondary standard limits short-term (3 h averaging time) community SO\(_2\) exposures to an annual...
maximum below 0.5 ppm, workers may be exposed to much higher levels of the gas. The Federal time-weighted average permissible exposure limit (PEL) for SO$_2$ is 5 ppm. Thus, workers may be exposed to 5 ppm for 8 h/d, 5 d/wk, for an entire career. Workers in a variety of industries, ranging from ore smelting and petroleum refining to paper and ice production, are potentially exposed to SO$_2$.

Formaldehyde (HCHO) is an upper-respiratory-tract irritant primarily recognized as an indoor air pollutant. Exposures to HCHO vapor occur in the workplace, as well as in residential and commercial settings. Atmospheric levels of HCHO near industrial outlets or in areas of heavy smog have been reported to range from less than 0.005 to 0.06 ppm (National Institute for Occupational Safety and Health, 1981). Formaldehyde is often present in homes and commercial buildings as a result of the emanation of the vapor from particle board (Andersen et al., 1975; Myers and Nagaoka, 1981), plywood (White, 1979), permanent press fabrics (Bourne and Seferian, 1959), and urea-formaldehyde foam insulation (Most et al., 1981; Williams et al., 1981). Cigarette smoke, a rather notorious pollutor of indoor air, contains up to 40 ppm of formaldehyde by volume (National Institute of Occupational Safety and Health, 1981). Indoor, residential HCHO concentrations have been reported to be as high as 8.1 ppm, which was measured in a Connecticut urea-formaldehyde foam-insulated home (Sardinas et al., 1979). Occupationally, the Federal time-weighted average PEL for HCHO is 3 ppm. However, concentrations up to 10 ppm are allowed for a maximum duration of 30 min. Anatomy, embalming, and wood preserving are typical of the occupations with significant HCHO exposure potential.

Several investigators have undertaken studies in order to determine the effects of SO$_2$ upon respiratory-tract clearance phenomena. A delay in the bronchial clearance of monodisperse Fe$_2$O$_3$ particles was observed in donkeys following an acute exposure (300 ppm SO$_2$, 30 min) by Spiegelman et al. (1968). The effects of 3 h exposures to 5 ppm SO$_2$ on tracheobronchial clearance in healthy, nonsmoking adults were investigated by Wolff et al. (1975). No significant alteration of the rate of mucociliary clearance occurred in the resting subjects, except for a small transient increase seen 1 h after exposure. Newhouse et al. (1978) reported an acceleration in bronchial clearance in healthy, nonsmoking adults following a 2-h exposure to 5 ppm SO$_2$ during intermittent exercise. Dalhamn (1956) studied changes in mucus transport rates and ciliary activity in the tracheae of rats exposed to 11.4 ppm of SO$_2$ for up to 67 d (approximately 5.5 h/d, 6 d/wk). The rate of mucus flow was considerably retarded by the gas. Ciliary activity was likewise significantly reduced in rats exposed for 18 d, while no such effect was discernible in rats exposed for longer periods of time. Oomichi and Kita (1974) developed a system to measure the in vitro ciliary activity of excised guinea pig tracheal specimens. An SO$_2$ concentration of 32 ppm was found to be quite toxic,
reducing the ciliary beat rate by half after 6.5 min of exposure. (In the same experiment, 32 ppm of HCHO had a corresponding "half reduction time" of 11.5 min.)

Studies to evaluate the potential effects of HCHO exposure on the respiratory system have also been performed. Kensler and Battista (1963) measured the transit time of tracer particles on sections of excised rabbit tracheae following exposures to cigarette smoke and its gas-phase components. HCHO was found to have appreciable ciliary-depressant activity. Dalhamn and Rosengren (1971) described an experiment in which in vitro tracheal ciliary activity was observed subsequent to HCHO exposure. The vapor was found to be a potent ciliostatic agent, with a marked rise in toxicity occurring between 10 and 50 ppm. Green and Carolin (1967) developed an in vitro quantitative phagocytic system in which HCHO was added to a mixture of rabbit alveolar macrophages and bacteria in tissue culture flasks. HCHO did not inhibit macrophage activity at concentrations which were in excess of its reported content in cigarette smoke.

The present study was performed in order to compare the effects of SO₂ and HCHO on the clearance of radioactive tracer particles in the rat. Since both substances are highly soluble in the mucus lining the upper airways (Morgan and Frank, 1977), the respiratory-tract deposition of the two gases would be expected to be quite similar. Both gases are eye, nose, and throat irritants, and each has a time-weighted average threshold limit value (TLV) of 2 ppm (American Conference of Governmental Industrial Hygienists, 1982). By exposing matched groups of rats to similar concentrations of each gas, significant differences in their effects might be detected.

MATERIALS AND METHODS

Animals

The barrier-reared Sprague-Dawley rats used in this study were purchased from Hilltop Lab Animals, Inc. (Chatsworth, Calif.). Male rats weighing approximately 200 g were delivered to the laboratory in filtered shipping boxes in order to minimize prior exposure of the animals to particulate pollutants. The rats were housed in a laminar air-barrier caging system in wire-bottom stainless-steel cages over a relatively dust-free sodium chloride litter for about 1 wk prior to the start of the experimental protocol. Microbiological assays, supplied by Hilltop Lab Animals, indicated that the animals' lungs were relatively free of respiratory infection sites; this fact was confirmed by quality-control histopathologic examinations at our laboratory.

Tracer Microspheres

The tracer particles were labeled at this laboratory (Hinrichs et al., 1978) with $^{51}$Cr (0.32 MeV gamma ray, 27.8 d half-life). These particles
were produced from commercially available monodisperse polystyrene latex microspheres (Duke Scientific Corp., Palo Alto, Calif.). Aerosols were generated from a 0.1% (by volume) aqueous suspension of the particles using a Lovelace-type laboratory compressed air nebulizer (Raabe, 1972) (ARIES, Inc., Davis, Calif.). The aerosol, sampled from the breathing zone of the rats using a calibrated seven-stage impactor (Mercer et al., 1970) (ARIES, Inc.), had an activity median aerodynamic diameter of 1.9 µm and a geometric standard deviation of 1.3. Less than 0.5% of the radioactivity was in the fine-particle fraction (diameter < 0.3 µm) collected on the fiberglass back-up filter in the impactor. The aerosol size distribution of the tracer microspheres was also determined by electron microscopic analysis of samples collected from the exposure unit using a point-to-plane electrostatic precipitator (Morrow and Mercer, 1964) (ARIES, Inc.). The size distribution was found to closely fit a log-normal function. In vitro and in vivo leaching studies demonstrated a leaching rate of $^{51}$Cr from the particles of less than 0.1%/d (Hinrichs et al., 1978). The specific activity of the particles was calculated to be 500 Ci/g.

The aerosolized particles were dried by heating and dilution with filtered air and passed through a $^{85}$Kr discharger (TSI Inc., St. Paul, Minn.) before entering the nose-only exposure chamber (Raabe et al., 1973). The airborne mass concentration of the tracer aerosol in the breathing zone of the rats was on the order of 2 µg/m$^3$. Fifteen rats were exposed simultaneously to the radioactive aerosol in this system (Fig. 1) for 20 min. The nose-only tubes that held the unanesthetized animals were constructed of perforated stainless steel in order to minimize thermal stress to the animals.

**FIGURE 1.** Nose-only inhalation system used to deposit tracer aerosols into the respiratory systems of rats.
Postdeposition Procedures

After the deposition of the tracer particles, the rats were removed from the system and their noses washed with wet cotton balls in order to reduce the amount of externally deposited radioactivity. The animals were then placed in plastic counting tubes and positioned beneath a collimated 3-in NaI(Tl) gamma-ray detection system shielded with lead. Each rat was counted for 100 s; if an animal moved forward or backward or twisted sideways in the tube while being counted, then it was recounted. The initial total amount of deposited radioactivity (defined as 100% for each rat) was thus determined before the rats went into either pollutant or control (purified air) atmospheres. The time between the end of particle exposure and counting the first and last animals ranged from 4 to 46 min, respectively. While there is some particle clearance during this time (an estimated 6% at 46 min, using the early clearance-rate data), the effect on the subsequent data analysis is minimized by using the midpoint of the group counting interval in the analysis.

At 1 h after exposure to tracer particles, the rats were divided into 3 groups and placed into individual compartments of 1⁄4-in mesh stainless-steel exposure cages. The cages were subsequently positioned on single levels of 1-m³ stainless-steel Rochester chambers for 4-h exposures to purified air, 20 ppm SO₂, or 20 ppm HCHO. For each pollutant exposure, purified air-exposed animals from the same supply batch were used as controls. All three chambers were supplied with air that had passed through coarse particulate filters, gas scrubbers, a cooler-drier, a humidifier, a heater, and a high-efficiency particulate filter. Temperature and humidity were controlled during all exposures. An exposure temperature of 70°F was selected for this study in order to ensure the thermal comfort of the animals. The relative humidity was approximately 40%, and chamber flow rates were on the order of 1.1 m³/min.

Pollutant Generation and Characterization

SO₂, obtained from a cylinder of research-quality gas (1% SO₂ in zero air), was monitored continuously at the breathing zone of the animals through Teflon tubing. The pulsed fluorescent SO₂ analyzer (Thermo Electron Corp., Hopkinton, Mass.) was calibrated using a conventional permeation tube system (CEA Instruments, Inc., Westwood, N.J.). The SO₂ concentration was recorded every 10 min during the study; the mean value was 20.1 ± 0.6 (SD) ppm.

HCHO was generated by metering filtered, monomeric HCHO vapor into the chamber inlet airstream. The vapor was produced by passing dry, purified nitrogen through purified-grade paraformaldehyde (Fisher Scientific Co., Fair Lawn, N.J.) held in an aluminum depolymerization chamber. Stable generator output was achieved by immersion of this chamber in a constant-temperature bath, and by careful control of the carrier-gas flow rate. Monomeric HCHO is reported to polymerize at
concentrations above 0.4% if water vapor or other impurities are present (Walker, 1975). Therefore, the nitrogen carrier flow rate was adjusted to keep the depolymerization chamber outlet concentration below this level.

The exposure-chamber HCHO was characterized using two independent methods. Continuous, quasi-real-time HCHO concentrations were obtained using a CEA 555 formaldehyde monitor. This automated wet-chemical analyzer employs the modified Schiff's test for aldehydes (Lyles et al., 1965) with an HCHO detection limit (0.01 ppm) well below the levels used in the present study. The monitor was calibrated every 10 h of use utilizing the conventional permeation tube system mentioned previously, with α-polyoxymethylene as the HCHO source. As a second check on the HCHO concentration, a modified chromotropic acid method (Altshuller et al., 1961) was used. At hourly intervals, chamber air samples were drawn at 1 l/min through two glass midget bubblers connected in series, each containing 9.4 ml of chromotropic acid in concentrated sulfuric acid. Then 1 ml distilled water was added to each bubbler, the solution was mixed, and 30 min allowed for full color development. The absorbance of sample and back-up bubbler solutions was measured at 580 nm against an absorbing reagent blank. Typically, 95% or more of the collected HCHO was found in the first bubbler. Calibration standards were prepared from sodium formaldehyde bisulfite, and the calibration curve was linear ($r = 0.99$) over the formaldehyde concentration range used (0-0.7 μg HCHO/ml). Analytical results from the two methods were generally concordant. The mean HCHO concentration (6 readings/h) obtained using the CEA 555 was 20.2 ± 0.9 (SD) ppm, while the chromotropic acid analysis yielded a mean value of about 21 ppm.

Clearance Measurements

After the rats were removed from the chambers following the 4-h exposure, their feces were collected at fixed intervals selected to allow for the determination of fecal activity excretion curves. Early clearance was characterized from these excretion curves because of the interference of early gastrointestinal tract activity with the thoracic counts. A total of 10 fecal collections from each rat were made during the first 50 h after the deposition of the tracer microspheres. Fecal collections were not performed after this time because levels of excreted radioactivity were negligible. Fecal excretion curves were subsequently fit to a log-normal function, and the time at which 50% of the total activity was excreted was determined for each rat. This time is referred to as the 50% clearance time ($T_{50\%}$) rather than a half-time because the early clearance phase was not strictly exponential. During the time interval of 50 to 400 h after the deposition of the tracer particles, 5 thoracic counts were performed on each animal using the plastic counting tubes. The percentages of these counts with respect to the initial total respiratory tract activity were calculated, plotted versus time, and fit to a single exponential function.
From this function, a biological half-time for late clearance \( T_L \) of the radioactive tracer particles, decay-corrected to the time of deposition, was computed for each rat. This late clearance phase was sufficiently fit by an exponential function to warrant the use of the half-time concept. Means and standard deviations were calculated for the 3 groups of rats, and the early 50% clearance times and the late clearance biological half-times were compared using two-tailed t-tests. (Animals that did not drink water and animals that did not defecate during three successive fecal sampling intervals were excluded from the early clearance study.)

As an independent measure of late clearance, the rats were sacrificed at 30 d postdeposition and their excised lungs were counted in a well counter in order to quantify the residual lung radioactivity. This was done because by this time the rats had outgrown the plastic counting tubes. The lung activity for each rat was corrected for decay of the \( ^{51} \text{Cr} \) back to 50 h postdeposition, and then normalized by dividing by the thoracic count obtained for the same rat at 50 h post deposition. This normalization, using two separate detection systems, was necessary in order to account for differences in the quantity of radioactivity deposited in the slow-clearing compartments of the individual rats. The resultant values constitute an index of late clearance, called the \( A_{30} \). Should the mean \( A_{30} \) value for a pollutant exposed group be larger than the corresponding value for the control group, this would indicate that a larger fraction of the radioactivity remained in the lungs of the exposed group. This would be identified as a delay in late clearance.

RESULTS

The effects of 4-h exposures to 20 ppm \( \text{SO}_2 \) and 20 ppm HCHO on the clearance of tracer particles were measured (Table 1). A significant delay in early clearance was detected for both pollutant-exposed groups using a preselected criterion of \( p < 0.1 \). However, no significant alteration of late clearance was observed in either the \( \text{SO}_2 \) or HCHO exposed groups. [Several years ago a decision was made to establish a 0.10 significance level (two-tailed t-test). This decision was based on computations in which the type II error could be maintained at a tolerable level (approximately 0.25) and the study could be conducted with a manageable number of animals. The actual \( p \) values have been stated for each test. In this way the reader is able to judge whether a statistically significant result was obtained.]

The effects of the \( \text{SO}_2 \) and HCHO exposures on early clearance are shown in Fig. 2. The difference between the group activity excretion curves (purified air minus pollutant-exposed) have been plotted versus time postdeposition. Calculations indicate that the time required for the \( \text{SO}_2 \)-exposed animals to excrete 50% of the total radioactivity excreted through the first 50 h postdeposition was 1.1 ± 0.6 (SE) h greater than the
time required by the control animals. Similarly, the $T_{50\%}$ of the HCHO exposed group was 0.8 ± 0.4 (SE) h greater than that of the control animals. Both of these early clearance delays were statistically significant.

The effects of exposures to the pollutants on late clearance are shown in Fig. 3. The radioactivity in the respiratory tract (as a percentage of the initial activity) is plotted versus time for each group of rats. The three lines have nearly identical slopes, and the calculated mean late clearance biological half-times for the pollutant exposed groups were not statistically different from that of the control group. The results of the $A_{30}$ analysis likewise indicated that neither pollutant affected the retained activity at 30 d post exposure.

Early clearance data were reanalyzed by several methods (Dixon and Massey, 1969). Similar results were obtained when analyses were performed on data transformed by taking logarithms. Nonparametric analysis based on ranks and a "trimmed $t$-test" showed the difference between HCHO exposed and control animals to be significant at the 0.05 level. These methods are known to be less sensitive than standard $t$-tests to data sets having extreme values. Late clearance data were similarly reanalyzed with results being essentially the same as those obtained originally (no

| TABLE 1. Effects of 20 ppm SO$_2$ and 20 ppm HCHO on Early and Late Clearance of Radiolabeled Tracer Microspheres$^a$ |
|---|---|---|---|---|
| Clearance | Atmosphere | Number | $T_{50\%}$ (h) | $\Delta T_{50\%} \pm SE$ (h) | $p^c$ |
| Early | Purified air | 27 | 9.0 ± 1.5 | - | - |
| | 20 ppm SO$_2$ | 29 | 10.1 ± 2.9 | 1.1 ± 0.6 | 0.08 |
| | 20 ppm HCHO | 26 | 9.8 ± 1.7 | 0.8 ± 0.4 | 0.06 |
| Late | Purified air | 30 | 533 ± 160 | - | - |
| | 20 ppm SO$_2$ | 30 | 587 ± 217 | 54 ± 49 | 0.27 |
| | 20 ppm HCHO | 30 | 555 ± 214 | 22 ± 49 | 0.65 |
| 30 d | Purified air | 30 | 20.7 ± 5.5 | - | - |
| | 20 ppm SO$_2$ | 30 | 22.1 ± 5.5 | 1.4 ± 1.4 | 0.32 |
| | 20 ppm HCHO | 30 | 20.6 ± 6.0 | -0.1 ± 1.5 | 0.95 |

$^a$Exposures were 4 h in length; $T_{50\%}$ = time required to excrete 50% of total activity excreted through 50 h post deposition; $T_L$ = late clearance biological half-time; $A_{30} = \text{index of residual lung radioactivity remaining at 30 d post exposure.}$

$^b$Eight rats were excluded from the early clearance data analysis for failure to meet established defecation criteria.

$^c$Two-tailed $t$-test.
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**FIGURE 2.** Difference in activity excretion curves (purified air minus pollutant exposed) as a function of hours postdeposition. Error bars represent ±1 standard error.

significant effect). When SO$_2$ and HCHO were compared with respect to their effects on clearance, no significant difference was observed.

**DISCUSSION AND CONCLUSIONS**

The purpose of this study was to determine the similarities and differences between the effects of SO$_2$ and HCHO using particle clearance endpoints. Both of these gases are highly soluble in the mucus lining the upper airways, and under normal conditions they would not be expected to penetrate in significant amounts to the deep lung (Frank et al., 1969; Egle, 1972). Therefore, one might suspect that clearance in the upper respiratory tract (primarily mucociliary clearance) could be affected by exposure to these gases, but that late clearance phenomena (macrophage
engulfment, solubilization, penetration through tissues), associated with the deep lung (respiratory bronchioles and more distal structures), would be unaffected.

The results of the study seem to support the above hypotheses. Early, presumably upper-respiratory-tract, clearance was significantly delayed by 20-ppm levels of SO\textsubscript{2} and HCHO, to roughly the same extent. Both of the endpoints used in characterizing late clearance ($T_L$ and $A_{30}$) were in agreement—neither the SO\textsubscript{2} nor HCHO significantly affected late, presumably deep-lung, clearance. Therefore, it appears that SO\textsubscript{2} and HCHO at the concentration studied have nearly identical effects upon particle clearance in the rat.

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