A MATHEMATICAL MODEL OF TRANSPORT AND REMOVAL OF OZONE IN MAMMALIAN LUNGS

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ABSTRACT

MILLER, FREDERICK JOHN. A Mathematical Model of Transport and Removal of Ozone in Mammalian Lungs. (Under the co-direction of HENRY L. LUCAS and ROBERT J. MONROE).

A unified approach for evaluating the pulmonary toxicity of ozone (O$_3$) is formulated which involves experimental laboratory animal studies and mathematical modeling analyses. The applicability of the model is illustrated by examining the similarity between man and laboratory animals in regional pulmonary deposition of O$_3$.

The experimental phase of this investigation concerned the determination of nasopharyngeal removal of O$_3$ in rabbits, guinea pigs, and rats. Experimental estimates of nasopharyngeal pollutant removal serve to determine boundary conditions, when using convective-diffusion equations to model pollutant gas transport in the lung.

The tracheal O$_3$ concentration in anesthetized rabbits and guinea pigs was markedly similar and was linearly related to the concentration of O$_3$ (196 - 3920 μg/m$^3$) drawn through the isolated upper airways of these animals. Exposures of guinea pigs to O$_3$ concentrations between 3920 and 5880 μg/m$^3$ showed that, at these higher concentrations, relatively more of the pollutant is removed by the nasopharynx. Investigations on the isolated upper airways of rats were not successful.

A lower airway mathematical model was developed which incorporates species anatomical differences and chemico-physical properties of O$_3$ as parameters. Chemical reactions of O$_3$ with various components of mucus were included in an analysis which allowed for the effects on gas
transport of convection, axial diffusion, and radial diffusion. The
effects of both molecular diffusion and eddy diffusivity were
considered. Respiration was assumed to be sinusoidal.

After examining the biochemical composition of mucus and surfac-
tant, specific components of the mucus layer were identified which
undergo an irreversible instantaneous reaction with O₃. The airway
lumen O₃ concentration was found to determine the location in the
mucous layer of the reaction plane between O₃ and the mucous reaction
components. This led to characterizing the removal of O₃ from an
airway by considering three reaction regimes. These regimes were:
1) surface-controlled, 2) inner-regime with reaction plane located
within the mucus, and 3) inner-regime with penetration of O₃ to the
tissue. The model formulation for airways lined with surfactant
considered no chemical reactions between O₃ and surfactant.

The predicted pulmonary O₃ dose curves obtained by model analysis
of the transport and removal of O₃ in the lungs of guinea pigs,
rabbits, and man indicate a general similarity exists between these
species in the shape of the dose curves. The model predicts that the
respiratory bronchioles receive the maximum O₃ dose. For exposures
corresponding to tracheal O₃ concentrations greater than 100 μg/m³
(0.05 ppm), the predicted respiratory bronchiole dose for rabbits was
found to be twice that for guinea pigs and 80% of that for man. The
roles of inspiratory duration and tidal volume in the determination
of O₃ uptake in man were also examined.

Model sensitivity analyses, with respect to the average rate of
production per unit area of mucous reaction components and the thick-
ness of the mucous layer, show that considerable differences in the
data base are needed to affect the model predicted doses. Even then, only the relative location on the dose-axis and the shape of the conducting airways portion of the dose curves would be changed.

The consistency and similarity of the dose curves for the three species lend strong support to the validity of extrapolating to man the results obtained on animals exposed to this pollutant.
A MATHEMATICAL MODEL OF TRANSPORT AND REMOVAL OF OZONE
IN MAMMALIAN LUNGS

by

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Co-chairman of Advisory Committee

Co-chairman of Advisory Committee
BIography

Frederick J. Miller was born October 16, 1945 in Sheridan, Wyoming. He received his elementary and secondary education in Sheridan, graduating from Sheridan High School in 1963. He attended the University of Wyoming at Laramie from 1963-1968, receiving a Bachelor of Science degree (high honor) with a double major in mathematics and statistics in 1967 and a Master of Science degree in statistics in 1968. While attending the university, he married the former Miss Lana Darlene Nicholson.

In 1968 he was commissioned in the officer corps of the United States Public Health Service and was assigned to the National Air Pollution Control Association in Cincinnati, Ohio. From that time until the fall of 1971 he was involved in the design and analysis of controlled laboratory animal studies on the health effects related to exposure to environmental air pollutants.

In 1971 he was selected to participate in an extramural training program and began a course of study for a Ph.D. in statistics at North Carolina State University at Raleigh. Since 1973 he has been a biostatistician with the Environmental Protection Agency, assigned to the research center at Research Triangle Park, N. C.

The author and his wife have three children--Todd, Ross, and Darcie.
ACKNOWLEDGMENTS

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For the many informative discussions with Dr. John H. Overton on various aspects of the model development, the author is grateful. Dr. David L. Coffin and Dr. Donald E. Gardner were instrumental in providing the necessary funding and personnel for the experimental portion of this study. The technical assistance of Mr. Chris A. McNeal was vital to the completion of the nasopharyngeal studies. Helpful suggestions on the organizational format of the manuscripts were received from Dr. Donald E. Gardner and Ms. Judith A. Graham. The author also thanks Mrs. Joanne W. Freeland for her excellent typing of the manuscripts.

Finally, special recognition is due the author's wife, Lana, for her encouragement and sacrifice, and his children, Todd, Ross, and Darcie, for their patience during the course of this study.
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Nasopharyngeal Removal of Ozone in Rabbits, Guinea Pigs, and Rats

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Laboratory Animal Upper Airway Removal of $O_3$

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Abstract

In estimating pollutant concentrations responsible for observed pulmonary effects, nasopharyngeal removal of the pollutant must be taken into account. Experimental estimates of nasopharyngeal removal provide boundary conditions for mathematical models which examine pulmonary transport and removal of $O_3$. The nasopharyngeal removal of ozone ($O_3$) in anesthetized rabbits of both sexes, male guinea pigs, and male rats was determined by drawing $O_3$ through the isolated upper airways at a constant flow rate which approximated the animal's respiratory minute volume. The tracheal $O_3$ concentration in rabbits and guinea pigs was markedly similar and was linearly related to the chamber concentration of $O_3$ (196 - 3920 µg/m$^3$). Regression analyses showed that $O_3$ removal in the nasopharyngeal region is approximately 50% in both species. Both rabbit sexes responded similarly over the concentration range studied. Exposures of guinea pigs to $O_3$ concentrations between 3920 and 5880 µg/m$^3$ showed that, at these higher concentrations, relatively more $O_3$ is removed by the nasopharynx. Investigations on the isolated upper airways of rats were not successful.
Introduction

The degree to which environmental air pollutants can directly affect the lung is a function of the amount of pollutant and reaction products reaching the lower airways. Removal of the pollutant in the nasal-pharyngeal region serves to lessen the insult to the lung. Thus, in estimating pollutant concentrations responsible for observed pulmonary effects, upper airway (nasal-pharyngeal) removal must be taken into account.

Various factors influence the rate of removal of foreign material in the upper airways and lead to differences between pollutants in the major location of action or absorption. Among these factors are: 1) the chemical and physical properties of the pollutant, 2) the route of breathing, 3) the depth and rate of airflow, 4) the nasal geometry of the animal, and 5) the biochemical composition and amount of mucus present. Previous upper airway studies on ozone (O$_3$) (6,7,11,15,18), sulfur dioxide (SO$_2$) (2,3,14,17), and nitrogen dioxide (NO$_2$) (17) are illustrative of these factors.

Utilizing a theoretical approach, their own empirical data, and information available from the literature (2,18), Aharonson et al. (1) examined the effect of respiratory airflow rate on nasal removal of soluble vapors. They demonstrated conclusively that the uptake coefficient (R), which defines the average flux of soluble vapor into the nasal mucosa per gas-phase unit partial pressure, increases with increasing airflow rate, provided the rate of uptake is proportional to the pressure of the vapor in the gas
phase. When comparing uptake at different flow rates, not expressing retention data on the basis of $R$ has led to overlooking this flow-dependent relationship $(2, 4, 5, 7)$ or to incorrect conclusions for the relationship between uptake and flow $(18)$.

The geometry of the upper airways is very complex. The air deflecting channels of the posterior nares cause impaction of large airborne particles and create turbulent air flow conditions, making mathematical modeling of local transport and removal of air pollutants in the nasopharyngeal region correspondingly difficult. Although determination of the average uptake coefficient of gaseous pollutants in the upper airways is straightforward, the tracheobronchial tree at present is relatively inaccessible to the local measurement of uptake of highly reactive gases, such as $O_3$.

Experimental estimates of nasopharyngeal pollutant removal serve to determine boundary conditions, when using convective-diffusion equations to model pollutant gas transport in the lower airways. Extensive lower airway morphometric data on human beings $(16)$, guinea pigs, rabbits, and rats $(10)$ and the technical inability of obtaining local lower airway $O_3$ uptake data for these species, make mathematical modeling the method of choice for examining $O_3$ uptake in the deep lung. Therefore, the combination of upper airway empirical studies and lower airway mathematical models provides a unified approach to evaluating the toxicity of environmental air pollutants, such as $O_3$. Towards that goal, this study examines the nasal-pharyngeal removal of $O_3$ in rabbits and guinea pigs over a
concentration range of 196 - 3920 \( \mu g \, O_3/m^3 \) (0.1 - 2.0 ppm \( O_3 \)).
Similar investigations of the isolated upper airways of rats were not successful.

Methods

Anesthesia and Surgical Preparation of Animals

Guinea pigs and rats were obtained from Charles Rivers Breeding Laboratories, Wilmington, Mass., and rabbits from Pel-Freez Farms, Rogers, Ark. The average weight of the guinea pigs (male, Hartley strain) was 0.425 kg with a standard error (SE) of 0.005 kg. Uptake experiments on rabbits (New Zealand, white) utilized both sexes, with an average weight of 2.784 kg ± 0.075 SE. Male rats (COBSR CDR (SD)BR) weighing 0.217 kg ± 0.01 SE were also used.

Rabbits were anesthetized by intravenous injection into the marginal ear vein of a 36-40 mg/kg body weight dose of sodium pentobarbital (Nembutal, Abbott Labs, Chicago, Ill.). Some animals required a supplemental dose (3.5-11.1 mg/kg body weight) to allow completion of the surgical procedure and effective restraint in the exposure chamber. A respiratory frequency of 27.5 breaths/min ± 1.7 SE was observed under anesthesia.

An intramuscular (IM) injection of 0.88 ml/kg body weight of droperidol-fentanyl (Inovar-Vet, Pitman-Moore, Washington Crossing, N.J.) was used initially to anesthetize the guinea pigs (12), and this was followed 15 min later by an intraperitoneal (IP) injection of pentobarbital sodium (12.5 mg/kg body weight
dose). The droperidol-fentanyl provided the desired state of anesthesia and analgesia, while the sodium pentobarbital prevented the rigidity usually associated with droperidol-fentanyl. After surgical preparation of the guinea pigs, a 0.1-0.15 ml supplemental injection of droperidol-fentanyl was given. Respiratory frequency averaged 14.8 breaths/min ± 0.6 SE.

Using the doses given by Garcia et al. (8), rats were anesthetized in the same manner as guinea pigs. First an IM injection of 0.45 ml/kg body weight of droperidol-fentanyl was given. Fifteen minutes later, the animal received IP sodium pentobarbital (15 mg/kg body wt.). A supplemental injection of 0.04-0.07 ml droperidol-fentanyl was given following completion of the operative procedure. With this anesthetic procedure, the average respiratory frequency of the rats was 59.8 breaths/min ± 3.7 SE.

An anesthetized animal was placed ventral side-up on a stainless steel rack, and its limbs were secured using strips of Teflon tape. The animal's head was held in place by means of a Teflon strap, which had been sutured to the underside of the chin. Before operating on the rabbits, the fur was trimmed around the incision area. Then the trachea was exposed and elevated slightly by placing a small tube underneath it. An incision was made towards the distal end of the trachea to allow insertion of a tube to ventilate the lungs. Another incision was made towards the proximal end of the trachea and a glass tube inserted to a position just caudal to the distal end of the larynx. The glass tube was siliconized with a 1% solution
of silicald (Clay Adams, Parsippany, N.Y.) to reduce surface tension and aid in draining any condensation that might form. Tests showed these treated tubes did not react with O₃. In order to prevent any airflow through the buccal cavity, the lips were tightly sutured using sterile surgical gut (Ethicon, Chromic 4-0, Somerville, N.J.).

**Exposure System**

All O₃ exposures were conducted in a 0.322 m³ stainless steel chamber (9). The chamber flow rate was equal to one chamber volume/min. Oxygen at a flow rate of 1.0 l/min was partially converted to O₃ in a neon tube ozonator. By varying the voltage applied to the electrodes, the O₃ concentration was adjusted to the desired level.

A schematic diagram of the method used to expose the isolated nasal-pharyngeal region is given in Fig. 1. The rack on which the animal was secured, was inclined on a chamber shelf at an angle of 20⁰ for rabbits, 30⁰ for rats, and 30-45⁰ for guinea pigs. Inclination assisted drainage of secretions and condensation and reduced tension on the upper tracheal cannula by allowing for the angle at which the trachea entered the chest cavity in these species. Teflon tubing was connected to this cannula, and this line was extended to a trap, which removed any secretions and prevented excessive moisture from being drawn into the line leading to the O₃ analyzer (Fig. 1). The volume of the trap was 155cc for rabbits and 40cc for guinea pigs and rats.

Teflon tubing led from the trap to a three-way glass and Teflon stopcock. A chamber sampling line was connected to the
second port of the stopcock. The remaining stopcock port attached a Teflon line from the chemiluminescent $O_3$ analyzer (Bendix, Model 8003, Ronceverte, W.Va.). Proper positioning of the stopcock permitted monitoring of the chamber $O_3$ concentration or the animal's tracheal $O_3$ concentration, but not both simultaneously (Fig. 1). The flow rate of the air pulled through the animal's nasal-pharyngeal region (1.0 l/min for rabbits, 0.16 l/min for guinea pigs, and 0.1 l/min for rats) was approximately equal to the respiratory minute volume for the given species. A mass flowmeter (Technology/Versatronics, Model NL-01-2P, Yellow Springs, Ohio) was used to maintain the proper airflow. All tubing connections were wrapped with Teflon tape to prevent leaks in the gas flow system. The transnasal pressure drop was monitored in some guinea pigs using a magnehelic differential pressure gage (Dwyer, Model 2001, Michigan City, Ind.).

**Experimental Regimen**

At the beginning of any given exposure, the animal was placed in the chamber and the $O_3$ concentration monitored until it stabilized at the desired pre-selected concentration. The time to stabilization was a function of $O_3$ concentration, flow rate, and exhaust load of the exposure facilities, but the time required to stabilize the chamber $O_3$ concentration never exceeded 15 min. Then the stopcock was positioned so that $O_3$ was drawn in through the animal's nares and exhausted from the animal via the upper tracheal cannula. Exposure of the nasal-pharyngeal region was continued
until a constant tracheal O₃ concentration was maintained for approximately 15 min. Completion of this phase of the regimen required from 25-50 min., depending upon the chamber O₃ concentration. After the nasopharyngeal removal profile was obtained, the O₃ generator was shut off and the chamber O₃ concentration monitored until an ambient level was reached. The animal was then removed from the chamber and sacrificed.

The effect of secretions and condensation in the tracheal cannula upon the removal of O₃ between the larynx and the O₃ analyzer was assessed. O₃ was again generated and the chamber concentration of O₃ (C) allowed to stabilize at a level slightly greater than was monitored as the nasopharyngeal equilibrium value (E). Then O₃ was drawn through the animal tubing system (now minus the animal) and the concentration determined (A).

Since all components of the sampling line were Teflon or glass, any O₃ loss between the larynx and the O₃ analyzer was presumed due to secretions or condensation present in the line. The concentration of O₃ that the trachea would have received, had the cannula been absent, was determined as

\[ T = CE/A \]

Regression analysis was then used to examine the relationship between the inspired O₃ concentration and the resulting tracheal concentration.

A complete record of the O₃ concentrations for the various phases of the experimental regimen was obtained using a strip
chart recorder (Hewlett Packard, Model 680, Pasadena, Calif.). The chamber temperature and relative humidity during the exposure of rabbits averaged $24.9^\circ C \pm 0.4$ SE and $58.3\% \pm 1.3$ SE respectively. For guinea pigs, these same parameters averaged $25.2^\circ C \pm 0.2$ SE and $65.2\% \pm 1.1$ SE.

Results

Of the 35 rabbits exposed to 196 - 3920 $\mu g O_3/m^3$ (0.1-2.0 ppm $O_3$), there were 14 females and 19 males, while the sex of 2 rabbits was not recorded. Condensation and secretions did not substantially contribute to the removal of $O_3$ in the tracheal sampling line (i.e. T/C = $0.87 \pm 0.02$ SE, where 1.0 represents complete absence of any secretions or condensation). The nasopharyngeal removal of $O_3$ was examined using a regression model which considered the chamber $O_3$ concentration and sex of rabbit as independent variables, with the dependent variable being the tracheal $O_3$ concentration.

The results of this analysis are presented in Table 1. There is a highly significant linear relationship between the $O_3$ concentration drawn in through the nares (chamber concentration) and the concentration of $O_3$ observed at the trachea. Both sexes responded similarly over the concentration range studied, as indicated by "sex" not being significant in Table 1. Hence, sex was ignored in obtaining the regression shown in Fig. 2.
This linear regression model accounted for 88% of the variability inherent in the data. The model's adequacy for characterizing the nasopharyngeal removal of O₃ is demonstrated by the nonsignificance of the test for "Model lack of fit" (Table 1).

Exposure of guinea pigs to O₃ concentrations as high as 5880 μg O₃/m³ (3.0 ppm O₃) were conducted. However, in conjunction with comparing the responses of guinea pigs with those of rabbits, linear regression analysis of the data on guinea pigs was restricted to the same concentration levels as those for rabbits. The results of this analysis are given in Table 2.

The linear dependence of the tracheal concentration of O₃ on the inspired O₃ concentration is, again, highly significant (p=.0001). Approximately 93% of the total variation about the average tracheal concentration was explained by the regression, and the test for the lack of fit of the model was not significant (Table 2). The prediction equation and the 95% confidence intervals for the mean tracheal concentration, for a given chamber O₃ concentration, are given in Fig. 3. Comparison of Fig. 2 and 3 reveals that tracheal O₃ values predicted in guinea pigs and rabbits are markedly similar for exposures to 196 - 3920 μg O₃/m³, as evidenced by a slope of 0.478 and 0.492 for guinea pigs and rabbits, respectively.

The data resulting from exposures of guinea pigs to O₃ concentrations between 3920 and 5880 μg O₃/m³ (2.0 and 3.0 ppm O₃) are given in Table 3. Ozone tracheal concentrations were consistently 10 - 15% below those that would be predicted using the regression
equation given in Fig. 3. This result suggests that, with exposure to higher levels of O$_3$, there is relatively more of the gas removed by the nasopharynx. To characterize the dependence of tracheal concentrations upon inspired concentrations between 196 - 5880 µg O$_3$/m$^3$ (0.1 - 3.0 ppm O$_3$), a quadratic regression equation ($\hat{Y} = -0.052 + 0.543 X - 0.041 X^2$) was sufficient to explain 95% of the total variation.

Removal of O$_3$ in the tracheal sampling line by condensation and secretions resulted in an average trachea to chamber sampling line concentration ratio of $0.82 \pm 0.02$ SE for guinea pigs. The transnasal pressure change averaged 0.635 cm H$_2$O $\pm 0.13$ SE. There was no correlation between transnasal pressure changes and the concentration of O$_3$ measured at the trachea.

Attempts to expose the isolated upper airways of anesthetized rats were not successful, due to "serous like" secretions occluding the end of the tracheal cannula. A wide variety of methods, all unsuccessful, were used to attempt to block or reduce these secretions. Among these were: 1) injection by various routes of atropine sulfate, atropine methyl nitrate, and scopolamine over a wide concentration range, 2) different combinations of initial and supplemental dosages of the aforementioned agents, 3) alterations in the positioning of the animal in the exposure chamber, and 4) extending the tongue from the mouth and suturing the tongue to the lips to facilitate better drainage of the secretions.

The secretions were nonspecific to O$_3$ exposure, since animals exposed only to filtered air gave a similar response. However,
exposure of a dead animal was successful without the use of secretion inhibiting drugs and yielded a tracheal $O_3$ concentration which was lower than the concentration observed with anesthetized rabbits and guinea pigs.

Discussion

With a constant flow rate, removal of $O_3$ in the nasopharyngeal region of rabbits and guinea pigs was markedly similar over a concentration range 196 - 3920 $\mu g$ $O_3/m^3$. The tracheal $O_3$ concentration in these anesthetized animals was linearly related to the concentration of $O_3$ drawn through the isolated upper airways. This implies that the absorption of $O_3$ into the nasal mucosa is proportional to the partial pressure of $O_3$ in the air. Hence, the data conclusively show that $O_3$ satisfies the condition necessary for using the theoretical model approach of Aharonsen et al. (1), when studying the effect of respiratory airflow rate on removal of $O_3$ by the upper airways.

Frank and co-workers (7) found that removal of 2620 and 26,200 $\mu g/m^3$ (1.0 and 10.0 ppm) of radioactive sulfur dioxide ($^{35}SO_2$) by the upper airways of dogs was nearly complete when administered nasally at a continuous flow of 3.1 l/min; uptake dropped only slightly when flow was increased 10-fold. At comparable concentrations, uptake by the mouth exceeded 95% at a flow of 3.5 l/min, but decreased to less than 50% when flow was increased 10-fold. Studies on rabbits (3) and humans (14) also indicate that $SO_2$ is removed to a greater extent when breathing nasally, as compared
to orally. Also, the nasal uptake of SO$_2$ has been shown to exceed that of NO$_2$ (17).

Vaughan et al. (15) exposed the isolated upper airways of beagle dogs to O$_3$ at a continuous flow of 3.0 l/min and collected the gas just below the larynx in a plastic (Mylar) bag. They found essentially 100% uptake of O$_3$ for concentrations below 784 µg O$_3$/m$^3$ (0.4 ppm O$_3$). However, in a similar study where the tracheal gas was sampled directly through Teflon tubing, Frank et al. (6) observed 60-70% uptake by the upper airways. In a subsequent study on the respiratory uptake of O$_3$ in dogs, Yokoyama and Frank (18) repeated the procedure of Vaughan et al. (15) and found that some O$_3$ was lost due to adsorption on the bag wall, even if the bag had been "pre-conditioned" with O$_3$.

From a modeling viewpoint, the results of Moorman et al. (11) on the decomposition of ozone in the nasopharynx of acutely versus chronically exposed dogs are pertinent. Dogs chronically exposed (18 mo) to 1960 - 5880 µg O$_3$/m$^3$ (1-3 ppm O$_3$), using various daily exposure regimens, were shown to have significantly higher mean tracheal concentrations of O$_3$ than animals tested after one day of exposure to the corresponding regimens. These investigators postulated that the differences were likely due to physiochemical alterations of the mucosal lining in the chronically exposed animals.

Between animals chronically exposed to 1960 µg O$_3$/m$^3$, those exposed for 8 hrs. per day had significantly lower tracheal values than those continuously exposed. However, the acutely exposed
animals' average concentration was not different from the 8 hr/day chronic exposure group, but was significantly different from the 24 hr/day chronic group (19.6 vs 44.1 µg O₃/m³). Accounting for the sensitivity of the Mast ozone meter used to measure the responses, this latter difference would not represent a significant treatment difference, unless the Mast ozone meter had been modified. Moorman et al. (11) did not state what modifications, if any, were performed.

Nevertheless, in view of the small difference observed with exposure to 1960 µg O₃/m³ (1.0 ppm O₃), it is likely that chronic exposure to lower levels would not result in tracheal O₃ concentrations significantly greater than those observed with acute exposure. Thus, at lower concentrations it is probably reasonable to use the results of acute exposure studies on nasopharyngeal removal of O₃ when modeling lower airway transport and removal. However, the investigations of Moorman et al. indicate that modeling lower airway chronic exposures to higher concentrations should account for greater concentrations of O₃ reaching the trachea.

A major goal of environmental toxicological studies on animals involves the eventual extrapolation of the results to man. The validity of such extrapolations is largely a function of the extent to which the animal species studied mimic the human response. The likelihood that the human response is mimicked will be much greater if the animal metabolizes and detoxifies the test substance
in the same way as does man, and if the route of exposure and the effective dose delivered to the target site are similar.

The influence of particle size upon respiratory dust retention in guinea pigs, monkeys, and man was examined by Palm et al. (12). Total respiratory retention and the relative proportion of retained dust deposited in the upper respiratory tract and in the alveoli changed markedly with particle size. A particle size of 1μ was found to be most favorable for alveolar deposition in guinea pigs and monkeys, a result comparable to that for man. Also, the alveolar percentage deposition was similar for the three species. Increased upper respiratory retention caused alveolar deposition to decline more abruptly in the guinea pig than in man when particle size was increased above 1μ.

The degree of similarity of aerosol particle deposition in the lung between guinea pigs, rabbits, rats, and man was examined by Kliment (10). Respiratory tract morphometric data and physical characteristics of the species and of the aerosol particles were combined by means of a dimensional analysis to obtain non-dimensional similarity criteria. Kliment showed that the degree of similarity is high (analogous to a correlation coefficient of 0.81 - 1.0) and allows the transfer of deposition information when comparing these species.

In view of Kliment's work on aerosol deposition, there is a need for the same type of analysis applied to the factors affecting
gaseous deposition. It is likely that such an analysis for non-reactive gases would yield analogous results. Possible species differences in mucous thickness and composition of possible reaction components could lead to a lack of similarity of respiratory tract deposition and removal for highly reactive gases, such as O₃. However, results for the nasopharyngeal removal of O₃ obtained in this study lead one to speculate on the possible similarity between these species and man.
References


Table 1.
Regression Analysis Summary for Nasopharyngeal Removal of Ozone in Rabbits

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Table 2.
Regression Analysis Summary for Nasopharyngeal
Removal of Ozone in Guinea Pigs

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<td>3.6342</td>
<td>612.06</td>
</tr>
<tr>
<td>Residual error</td>
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<td>.0059</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model lack of fit</td>
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<td>.0077</td>
<td>1.38</td>
<td>.24</td>
</tr>
<tr>
<td>Pure error</td>
<td>37</td>
<td>.0056</td>
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Table 3.
Tracheal O$_3$ Concentrations in Guinea Pigs
Exposed to Various O$_3$ Levels

<table>
<thead>
<tr>
<th>Ozone (ppm)</th>
<th>Chamber</th>
<th>2.25</th>
<th>2.50</th>
<th>2.75</th>
<th>3.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachea*</td>
<td>0.93 ± 0.11</td>
<td>1.04 ± 0.05</td>
<td>1.06 ± 0.03</td>
<td>1.24 ± 0.05</td>
<td></td>
</tr>
</tbody>
</table>

*mean values ± standard error for 3 animals at each level
Figure 1. Schematic diagram of the method used to expose the isolated nasopharyngeal region.
Figure 2. Nasopharyngeal removal of ozone in rabbits.
Figure 3. Nasopharyngeal removal of ozone in guinea pigs.
A Mathematical Model for Pulmonary Deposition of Ozone

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Transport and Removal of $O_3$ in the Lung

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Abstract

Difficulty in assessing the pulmonary effects of ozone (O₃) centers around the problem of comparing experimental results obtained using different animal species and pollutant concentrations and of extrapolating these results to man. A mathematical model for the uptake of O₃ in the lung is presented. Species anatomical differences and chemico-physical properties of O₃ are incorporated as model parameters in an analysis based upon the binary convective-diffusion equation for gas transport in the lung. Chemical reactions of O₃ with components of the mucous layer are included. Model solutions are obtained using a multi-step procedure involving mass balance expressions in finite difference form. Convection is simulated by instantaneously moving a small gas volume during each time step. The effects on axial diffusion of both molecular diffusion and eddy diffusivity are considered by relating, in each airway generation at any given time, the diffusion coefficient to the mean axial gas velocity. Radial diffusion is coupled with a scheme for incorporating chemical reactions to account for the removal of O₃ from the airway lumen.
Introduction

During the past twenty years many studies have been conducted on the toxicity of ozone (O₃), a major air pollutant in many sectors of the world. References cited in photochemical oxidant documents by the Environmental Protection Agency (1970), NATO (1974), and the National Research Council (1976) attest to the wide range of concentrations, exposure regimens, animal species, and biological parameters which have been examined. Environmental toxicologists are confronted with the formidable task of interpreting the manifold results and assessing their relevance and implications concerning pollutant levels to which human beings are exposed. They must also design new studies to fill gaps in the current data base so that mechanism of action hypotheses may be formulated and tested.

Currently, the major restriction in assessing the pulmonary effects of O₃ centers around the problem of comparing experimental results obtained using different animal species and pollutant concentrations and of extrapolating these results to man. While the nasal-pharyngeal removal of O₃ has been experimentally determined in several species (Yokoyama and Frank, 1972; Vaughan et al., 1969; Moorman et al., 1973; Miller, 1977), the lower airways are presently inaccessible to the measurement of pollutant uptake. This paper describes a mathematical model for the uptake of O₃ in the lung which allows a unified approach to evaluating O₃ toxicity. Species anatomical differences are accounted for via morphometric input parameters. Chemical reactions of O₃ with the mucous lining are included in an analysis based upon the binary convective-diffusion
equation for gas transport in the lung. A brief description of the
physical model on which the mathematical model is based follows.

With respect to assessing gaseous pollutant exposure effects, it
is reasonable to hypothesize that the extent of damage or injury
observed at any particular level in the lung is a function of the
rate of delivery and of the cumulative pollutant mass per unit sur-
face area transported to the tissue. The amount of pollutant acting
on a given level of the lung is reflected by its airway concentration
at that level. Of course, the pollutant does not immediately strike
the airway wall, but rather, must first come in contact with the
mucous or surfactant layer lining the airway, depending upon which
level of the lung the pollutant has reached. The gas must then
diffuse through this layer in order to reach the tissue. Chemical
reactions with components in these layers may occur, thereby increas-
ing the total absorption of the gas, but may also reduce the quantity
of pollutant reaching the tissue. Thus, the biochemical composition
of the mucous and surfactant layers dictate the manner in which the
model should account for chemical reactions.

Numerous studies have been conducted on the qualitative and
quantitative properties of mucus. Potter and co-workers (1963)
showed that human pulmonary secretions contain approximately one gram
each of lipid, protein, and carbohydrate per 100 grams of secretion.
Characterization of the lipid fraction in human bronchial mucus by
Lewis (1971) showed variable amounts of neutral lipids and a more
constant amount of phospholipids. Previously, Baxter et al. (1968)
analyzed the lung phospholipids in a variety of vertebrates and found remarkably similar composition. In lung surfactant, Bondurant and Miller (1962) found predominately phosphatidyl choline (lecithin) among phospholipids of which dipalmitoyl lecithin (DPL) is the dominant species (Brown, 1962; Abrams, 1966).

In comparison to the detailed quantitative data available on the lipid composition of tracheobronchial secretions, the data on carbohydrate and protein composition is sparse, and when present, more qualitative in nature. The glycoproteins of mucins have been reviewed by Marshall (1972), who points out that normal human tracheobronchial secretions are difficult to obtain because intubation causes inflammation.

The amino acid composition of human nasal mucus has been characterized by Hilding and co-workers (1973). They found, compared to other types of mucus, a relatively high proline content and a relatively low content of threonine and serine. Earlier, Levine et al. (1969) quantified the amino acids present in human parotid glycoprotein, as well as some of the sugars. Proteins in human bronchial mucus have been identified and characterized using crossed immunoelectrophoresis (Laine and Hayem, 1976). However, the techniques they employed did not allow retention of acid mucins. The carbohydrate constituents of sputum from persons with chronic bronchitis were examined by Atassi et al. (1959). Also, they qualitatively examined the amino acids present in the mucoprotein fraction.
Current knowledge and theories regarding $O_3$ chemical mechanisms of action in biological systems have been unified by Menzel (1976). The data available on the composition of mucus and surfactant, in conjunction with these chemical mechanisms of action, can be combined to estimate the concentration of $O_3$ reactants present in the protective layers (mucus and surfactant). The rate of production of these reactants for a given animal species can be estimated from data on mucous flow rates. Reactions of $O_3$ with the protective layer reaction components are shown to be irreversible and instantaneous.

To date, McJilton et al. (1972) are the only investigators who have proposed a model to predict ozone uptake in the lung. Their work was presented at the American Industrial Hygiene Conference in San Francisco in May, 1972, but has never been published in the open literature. Therefore, a general description of their approach follows.

Their model uses mass balance expressions in finite difference form for convective and diffusion components of fluid flow in conjunction with the general equation which describes the spatial and temporal concentration of a gas in an airway. Using their technique, Weibel's (1963) airway system was partitioned into 25 finite segments. Airway dimensions were assumed fixed throughout each time step of a sinusoidal breathing cycle. Other major assumptions involved ascribing to mucus the chemical and physical properties of water. Chemical reactions were not considered and diffusional back-flow from the tissue was assumed to be negligible.
Since nonreactivity of $O_3$ with the mucous layer was assumed, McJilton et al.'s model is really more useful for estimating lower airway uptake of water soluble and relatively water insoluble gases that are nonreactive with the mucous layer than it is for estimating the uptake of $O_3$. Thus, the McJilton et al. model probably underestimates conducting airway uptake of $O_3$ and overestimates respiratory airway uptake.

Dubois and Rogers (1968), on the other hand, developed a different model for estimating the rate of uptake of inhaled gases. Using Weibel's (1963) morphometric data on the human lung, the rate of absorption for each generation of the conducting airways was expressed as a function of the partial pressure of the gas in the lumen, the diffusion coefficient of the gas in tissue, solubility of the gas in blood, the rate of blood flow, and the thickness of the air-blood barrier. The objective in their study was to examine the role of respiratory factors in determining the tissue concentrations of inhaled toxic substances. From their analyses, Dubois and Rogers concluded that, unless the inhaled substance is extensively altered in the tissue, respiratory factors are not important after long periods of inhalation.

In view of the limited previous work concerning uptake models for gaseous pollutants, it would seem appropriate to include a review of research which has examined such topics as: gaseous convection and diffusion in the airways, approximating the lung with various geometrical models, pulmonary gas transport, and incorporating morphometric and
chemico-physical data in analyzing pulmonary responses. As such, this review is not intended to be an exhaustive one. Instead, the objective is an elucidation of the factors affecting the uptake of gases in the lung.

Several research workers have examined the role of gaseous diffusion in the airways of the human lung in an attempt to resolve conflicting theories regarding the slope of the alveolar plateau in the single-breath nitrogen washout test. In this test a subject takes a deep breath of pure oxygen and then exhales steadily. The alveolar plateau refers to the gradual rise in the concentration of nitrogen associated with the latter portion of expired air. Krough and Lindhard (1914) thought that gas mixing was slow enough to produce a gradient of nitrogen within the lungs after inspiration, and hence, that the alveolar plateau was due to stratified inhomogeneity.

This view was widely held until Rauwerda's (1946) investigations into the rate of gaseous diffusion showed that diffusion in the lungs was sufficiently rapid as to rule out a measurable concentration gradient within a terminal airways unit one second after establishment of the gaseous interface. Later, Otis et al. (1956) proposed regional inhomogeneity as an alternative explanation for the shape of the alveolar plateau.

Cumming et al. (1966) criticized Rauwerda's models since they were closed at both ends, while the terminal airways of the lung are open proximally. They examined seven geometrical models in conjunction with various boundary conditions and solved the appropriate
diffusion equations. Among the models examined were a finite cylinder and conical segments of a hollow sphere and of a hollow cone. As a result of their studies, they postulated that the single breath test measures mainly stratified inhomogeneity, while the nitrogen clearance curve measures mainly regional inhomogeneity.

La Force and Lewis (1970) examined this same problem using finite difference techniques in a dichotomously branched model of the human lung. They considered only the last 13 of the 23 generations described by Weibel (1963). Possible radial diffusion contributions were ignored so that the problem could be treated as a one-dimensional one. Their analysis led them to the conclusion that no significant concentration gradient exists between gas in the terminal bronchioles and gas distal to this point during normal respiration.

Prior to 1971, the inclusion of flow simultaneously with longitudinal diffusion had not been attempted. Then Cumming et al. (1971) published work where they solved the classic static diffusion equation approximating convective flow by instantaneously moving an interface 100 ml after every 150 msec period during which diffusion occurred. Paiva (1972, 1973) and Scherer et al. (1972) also considered this problem. In deriving a differential equation for simultaneous diffusion and convection, they treated the alveoli as reservoirs through which no diffusion occurred. All of these researchers examined the existence of concentration stratification and its possible contribution to the sloping alveolar plateau.

Chang and Farhi (1973) reviewed the work of Rauwerda (1946), Cumming et al. (1966, 1971) and La Force and Lewis (1970). Based on
the physical model and its mathematical representation, the method of solution, and the results obtained, comparisons were made among these various analyses. These authors also carefully examined the seven assumptions common to these models: 1) rigid airways with constant volumes, 2) neglecting the flux across the alveolar wall, 3) ignoring convection with respect to gas mixing in the alveolar region, 4) stationary diffusion front, 5) an initially uniform concentration over the cross section of the diffusion front, 6) only axial diffusion significant, and 7) a binary diffusion process.

The same authors (Chang et al., 1973) conducted a model study of gas diffusion in alveolar sacs in which individual alveoli were represented and radial diffusion included. Their analyses led them to the conclusion that stratification of alveolar air during quiet breathing is a definite possibility.

Simulation of single-breath nitrogen washout was conducted by Baker et al. (1974) using finite difference solutions of the differential diffusion equation. Simultaneous diffusion was incorporated and an exponentially varying equation for inspiratory and for expiratory flow was employed. Of major interest in their work were the effects of variations in conducting airway geometry upon the washout data. The volumes of generations 18-23 were lumped together into a single alveolar compartment, which was assumed to be well-mixed. The conducting airways were assumed to be non-distensible, and convective mixing processes were ignored.

Their model estimate of 270 ml for anatomic dead space is considerably greater than experimentally determined values which
range from 140 ml (Shepard et al., 1957) to 190 ml (Bartels et al., 1954). Agreement with trends in existing data was obtained when physiological conditions were varied. Also, model simulations, which varied airway geometries, predicted no contribution to gas transport in the first four generations by longitudinal diffusion. However, in the lower 13 airway generations, longitudinal diffusion was significant.

A consideration of the influences of convection and diffusion in the equations governing gas transport was presented by Wilson and Lin (1970) in a discussion of the design of airway geometry. Utilizing two dimensionless parameters, pure convection was shown to be the dominate mechanism of gas transport through the 7th generation of branching in the human lung. Between the 8th and 12th generations, the main transport mechanism is Taylor diffusion (Taylor, 1953). Thus, radial diffusion and axial convection are coupled to produce an effective block flow with axial diffusion. Block flow convection with axial diffusion dominates in generations beyond the 12th. The human bronchial tree was shown to be nearly optimal for providing a given alveolar ventilation with minimum metabolism of the respiratory muscles.

The work of Davidson and Fitz-Gerald (1974) on the transport of \( O_2 \) through the respiratory region of the lung represents the most complete mathematical modeling of the relative importance of diffusion and convection in the alveolated airways that has thus far been attempted. They modeled a typical pathway by a cylinder, closed at
one end, having a length of 5 respiratory units placed in series, with partitions defining individual alveoli. Pedley's (1970) one-dimensional trumpet model was used to connect the conducting airways to this model pathway. The numerical solution for the nondimensional velocities in an expanding respiratory unit is given. Davidson and Fitz-Gerald's analysis showed that with normal respiration, convection is only about 0.4% as important as diffusion in the alveolar regions. Even with a flow rate 10-15 times greater than that needed for normal respiration, convection is merely 12% as important as diffusion.

Most gas transport models assume fully developed laminar flow in the lungs, although it is well known that turbulence is present in larger airways during certain periods of the respiratory cycle and with increased ventilatory rates. Using large scale symmetrical models of typical junctions of the human bronchial tree, Schroter and Sudlow (1969) studied a wide variety of flow patterns and rates. For both inspiration and expiration and irrespective of entry profile form, they observed secondary flows at all flow rates in their single bifurcation model.

When a second bifurcation was added a short distance downstream of the first, the entering flow profile was found to influence the resulting flow patterns. Also, different results were obtained depending upon the plane in which the second bifurcation was located, relative to the first bifurcation. After examining conditions necessary to assume quasi-steady state flow, they concluded that their steady state findings can be applied to the unsteady flow situation in the lungs.
Yu (1975) examined longitudinal diffusion in gas transport models which consider the airways as a variable cross-sectional channel along which the gas moves in and out. Nonhomogeneous ventilation distributions in the lungs and the interaction of nonuniform velocity and concentration profiles necessitate adding an apparent longitudinal diffusion term to the usual molecular diffusion term.

Although explicit knowledge of individual airway velocity and concentration profiles is required to determine this apparent diffusion coefficient, the author introduced certain assumptions for concentration and velocity profiles. These assumptions permitted an analysis of the relative contribution to gas transport in the conducting airways of Taylor diffusion and of apparent longitudinal diffusion. Yu's results clearly show that apparent diffusion due to nonhomogeneous distribution of ventilation is everywhere much larger than both molecular diffusion and Taylor diffusion, and hence, dominates the diffusion process in the upper airways.

The work of Scherer et al. (1975) provides experimental measurements for the effective axial diffusivity for laminar flow of a gas in the bronchial airways. They analyzed benzene vapor dispersion in a five-generation glass tube model of the bronchial tree which maintained geometric similarity with Weibel's (1963) lung morphometric data. Separate equations for inspiration and expiration are derived which relate linearly effective axial diffusivity and the mean axial gas velocity. Increased radial mixing at bifurcations during expiration is postulated as the reason that diffusivity during expiration is about one-third of that for inspiration. Modeling applications of
their results, obtained using steady flows, requires the assumption of quasi-steady flow. Such can be considered the case in human airways, provided the flow rate is greater than 0.1 l/sec (Jaffrin and Kesic, 1974).

Diffusion in the lungs has always been assumed to be binary in the mathematical development of gas transport models, although, in fact, diffusion in the lungs normally involves at least oxygen, carbon dioxide and nitrogen. Ternary diffusion in the lung has been examined by Chang and co-workers (1975), who used a simple gas film model to compare differences between binary and ternary diffusion.

The behavior of ternary gas mixtures was shown to involve three diffusion phenomenon: 1) diffusion barrier - when a component gas diffusion rate is zero even though its concentration gradient is not zero, 2) osmotic diffusion - when a component gas diffusion rate is not zero even though its concentration gradient is zero, and 3) reverse diffusion - when a component gas diffuses against the gradient of its concentration. Their results indicate that for air breathing under normal conditions, gas transport diffusion problems in the lungs may be examined using binary laws. However, their ternary diffusion model studies suggest that significant errors may occur, if binary laws are used to examine diffusion involving gases, such as helium, or high pressures.

Various investigators, such as Mead (1961), have proposed lung models in which conducting airways are considered resistance elements and alveoli are identified as being mainly compliant in order to
examine various pulmonary function measurements. This model approach yields the usual types of resistance - capacitance (R-C) networks and the corresponding circuit equations which govern them. Flow and pressure can be identified with the computed time response of current and potential, respectively.

Blesser (1969) expanded this model approach to include three types of elements: 1) resistance elements to represent the upper airways with low extensibility, 2) resistors with intermediate capacitors to represent the more flexible lower airways, and 3) capacitors to represent the elastic single port elements, the alveoli. This model was extended by Trezek (1973) to consider the separate pathways after the carina.

It should now be evident that a variety of approaches have been used in examining transport and uptake of gases in the lung. The real physical model is extremely complex and requires making various assumptions to translate the phenomenon governing gas transport into a mathematical model. The development of better models hopefully will lead to a greater understanding and insight about the biological mechanisms and anatomical functional relationships present in the lung and indicate areas in which additional experimental research is needed.

**General Gas Transport Equation**

The mammalian lung represents an interface between an animal's internal homeostatic processes and the environment in which it lives. As such, the main functions of the lungs are to provide sufficient oxygen to the circulatory system and to eliminate carbon dioxide.
Inspired gas enters the lung through the trachea and is transported through a varying number of generations of branching tubular airways, depending upon the species of animal, before reaching the alveolar region of the lung, where gas exchange occurs. Convection and diffusion processes combine to facilitate gas transport.

The composition of inspired air normally involves nitrogen, oxygen, carbon dioxide, and other trace gases, but environmental pollution can result in ozone, as well as other gases, being present. Previous gas transport models have simplified this multicomponent system and have dealt with binary diffusion only. The validity of this assumption was studied by Chang et al. (1975), who concluded that binary laws may be used for normal respiration, unless gases such as helium are used or high pressures are studied. Thus we shall examine the transport of $O_3$ in the lung utilizing the binary convective-diffusion equation

$$\frac{\partial C}{\partial t} + \nabla \cdot (UC) = D_{mol} \nabla^2 C + S^*$$

where the concentration of $O_3$ is $C$, time is $t$, the bulk flow velocity vector is $U$, the vector operator "del" (Hildebrand, 1962) is $\nabla$, the molecular diffusion coefficient of $O_3$ in air is $D_{mol}$, and the source term in the mass balance equation is $S^*$. Basically, eq. (1) states that convection and diffusion of $O_3$ into a given volume from nearby volumes, in conjunction with the rate of production or loss of $O_3$ due to chemical reactions, are responsible for the rate of change of $C$. For modeling purposes, the volumes under consideration will refer to the sequence of individual airway generations or to partitions of them.
The components of the velocity vector are not known everywhere in the lung, and as noted by Chang and Fahri (1973), even if they were known, implementation of eq. (1) for mammalian systems is not practical. Further assumptions or modifications are necessary to render the problem more tractable.

The flow rate in most of the conducting airways is low because the total air flow is divided among thousands of tubes. However, eddy formation may occur at bifurcations (Schroter and Sudlow, 1969), with the resultant pressure required for flow being approximately the same as for turbulent flow. Eddy dispersion occurs when air is mixed by turbulence. Under these conditions, the flux is generated by individual fluid elements transporting the gas.

Convection (bulk fluid motion), represented in eq. (1) by the term involving UC, can be decomposed into the physically separable processes of advection and eddy dispersion (Butcher and Charlson, 1972). This involves treating the velocity vector as the sum of an average velocity and a random variable (the deviation from the average velocity) and treating concentration in a similar manner:

\[ U = \bar{U} + U' \]
\[ C = \bar{C} + C' \]

After simplification, the average flux density becomes:

\[ \bar{U}C = \bar{U}\bar{C} + \bar{U}' \bar{C}' \]

where the terms on the right hand side of eq. (2) represent advection and eddy dispersion, respectively. In many atmospheric diffusion problems, dispersion has been effectively represented as:
(3) \[ \mathbf{U}' \mathbf{C}' = -D_{ed} \nabla \mathbf{C} \]

where \( D_{ed} \) represents the diffusion coefficient associated with this phenomenon (Pasquill, 1974). This form will also be used here.

Consider \( \mathbf{C}, \mathbf{U}, \) and \( \mathbf{S}^* \) to represent animal species averaged population concentration, velocity, and source term values, respectively, in a given airway at a specified location and time. Then eqs. (2) and (3) may be used to express eq. (1) as

\[ \frac{\partial \mathbf{C}}{\partial t} + \nabla \cdot (\mathbf{U} \mathbf{C} - D_{ed} \nabla \mathbf{C}) = D_{mol} \nabla^2 \mathbf{C} + \mathbf{S}^*. \]

Collecting terms and assuming that \( D_{ed} \) is constant within a given airway yields

(4) \[ \frac{\partial \mathbf{C}}{\partial t} + \nabla \cdot \mathbf{U} \mathbf{C} = (D_{mol} + D_{ed}) \nabla^2 \mathbf{C} + \mathbf{S}^*. \]

Equation (4) is a general equation in vector form and is valid in any coordinate system.

Calculation of \( D_{ed} \) still requires more information on the velocity and concentration profiles in individual airways than is available. By including only molecular diffusion, previous lung models have greatly underestimated diffusional effects on gas transport in the conducting airways (Yu, 1975). Based upon the work of Scherer et al. (1975), the net effects of \( D_{ed} \) and \( D_{mol} \) can be estimated. The manner in which this was done will be discussed in greater detail later.

Model Assumptions Involving Convection and Diffusion

Assuming that the effects of turbulence and secondary flows may be accounted for by appropriately increasing the diffusion coefficient, the radial and circumferential average velocity components are
considered to be negligible. If the analogy is made that gas transport in the lung is like that in tubes, transforming to cylindrical coordinates and incorporating these assumptions allows eq. (4) to be written as:

\[
\frac{\partial C}{\partial t} + \frac{\partial U_x C}{\partial x} = \left( D_{\text{mol}} + D_{\text{ed}} \right) \left( \frac{\partial^2 C}{\partial r^2} + \frac{1}{r} \frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial x^2} + \frac{1}{r^2} \frac{\partial^2 C}{\partial \theta^2} \right) + S_x
\]

where \( r, \theta \) and \( x \) represent the radial, azimuthal, and axial coordinates respectively, and \( U_x \) represents the average axial gas velocity.

The axial velocity profiles of Schroter and Sudlow (1969) show that even within four diameters of a bifurcation, the change of axial velocity with distance is small (Pedley et al., 1970). The length to diameter ratio is usually less than four in the conducting airways of humans, rats, rabbits, and guinea pigs (Weibel, 1963; Kliment, 1973). Thus, \( U_x \) will be assumed constant within an individual airway. If, in addition, the usual assumption of symmetry about the \( x \)-axis is invoked, then \( C \) does not depend on \( \theta \) and eq. (5) reduces to

\[
\frac{\partial C}{\partial t} + U_x \frac{\partial C}{\partial x} = \left( D_{\text{mol}} + D_{\text{ed}} \right) \left( \frac{\partial^2 C}{\partial r^2} + \frac{1}{r} \frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial x^2} \right) + S_x.
\]

Equation (6) will be used to study the transport and uptake of \( O_3 \) in the lung, as a function of convection, axial and radial diffusion, and chemical reactions.

**Structure of the Mathematical Model**

A model which predicts the absorption of \( O_3 \) in each generation of the tracheobronchial tree is desired. The model formulation requires extensive use of lung morphometric data, such as is available for humans (Weibel, 1963) and for rabbits, guinea pigs, and rats (Kliment, 1973). Airway generations are partitioned to form model segments and
a multi-step procedure involving mass balance expressions in finite difference form is used to obtain solutions of eq. (6).

Convection is simulated by instantaneously moving a small gas volume during each time interval. Within each model segment a new airway concentration is obtained for this same time interval. Next, concentration profile changes due to axial diffusion are determined. Radial decay follows, during which radial diffusion enables mass transport of \( \text{O}_3 \) to the fluid layer lining the airway, where its removal can be increased due to chemical reactions. The airway concentration is again determined and the entire sequence is repeated for the next time increment. Respiration was assumed to be sinusoidal.

Mass Changing by Convection

Convection changes only the position of a gaseous "plug" volume. The character of the distribution does not change, except to conform to the physical boundaries of the system. In the \( n \)th model segment during a time interval, \( \Delta t \), complete transfer out of the \( n \)th model segment into upstream model segments occurs whenever \( \overline{U}_x(n)\Delta t = L(n) \), where \( L(n) \) denotes the length of the \( n \)th model segment. Partial removal of the plug from the \( n \)th model segment occurs whenever \( \overline{U}_x(n)\Delta t < L(n) \). To preserve mass continuity, a necessary model restriction is that \( \overline{U}_x(n)\Delta t \) never be greater than \( L(n) \). In other words, during any time step the total mass removed cannot exceed that which was originally present.

Convection was simulated by instantaneously moving a small gas volume during each time step. Since a constant volume increment, \( V_k \),
was added during inspiration (removed during expiration) from the beginning of the airway system during each time step, the sinusoidal flow pattern required using a different time increment for each step in the breathing cycle. The ratio of the tidal volume, \( V_T \), to \( V_k \) determines the total number of time steps, \( N_t \), needed to simulate inspiration or expiration.

The gas volume flow rate, \( Q(t) \), is defined as:

\[
(7) \quad Q(t) = \frac{\pi}{T} V_T \sin \left( \frac{2\pi}{T} t \right) \text{ for } 0 < t < T
\]

where \( T \) is the length of the respiratory cycle. The time at which a volume of gas equal to \( NV_k \) has been added to the airways, \( t_N \), may be found by integrating eq. (7) from zero to \( t_N \) and solving the resulting equation to give:

\[
(8) \quad t_N = \frac{T}{2\pi} \cos^{-1} \left( 1 - \frac{2NV_k}{V_T} \right) \text{ for } N = 1, 2, \ldots, N_t
\]

Thus, the time increment needed for the convection phase during the \( N \)th time step is \( t_N - t_{N-1} \).

Using the above scheme, a set of convection equations for inspiration and another set for expiration were formulated to move the pollutant plug through the airways. The model segments volumes exceeded \( V_k \) in the respiratory airways and towards the end of the conducting airways. Thus, some degree of mixing in each model segment in these regions was assumed to occur during the convection phase. However, it does appear that mixing occurs in these regions (Altshuler et al., 1959). The bulk of increased lung volume due to inspired gas is associated with respiratory units. In this study the
additional gas volume due to \( V_k \) was divided equally among the respiratory region model segments at each time step.

**Mass Changing by Axial Diffusion**

Axial diffusion refers to diffusion in the longitudinal (axial) direction of the airway ducts. In this study, the model representation for axial diffusion will consider the airways as an expanding cross-sectional channel. This approach has been used by a number of other investigators (Davidson and Fitz-Gerald, 1974; Paiva, 1973; Pedley, 1970; Scherer et al., 1972; Yu, 1975). In this approach, all pathways from the trachea to the alveoli are combined into one effective pathway whose cross-sectional area, \( A(x) \), is equal to the summed cross-sectional area of all bronchial tubes at a distance \( x \), with respect to the trachea. Model parameters needed to characterize this process are depicted in Fig. 1.

With respect to model segments \( n \) and \( n-1 \), the concentration gradient is established over the length between their midpoints, \( L_m(n-1, n) \). The cross-sectional area defining the channel through which diffusion can occur is defined by the boundary area between the model segments, \( A_b(n-1, n) \). The volume of the \( n \)th model segment, \( V_g(n) \), is the product of its length, \( L(n) \), and midpoint cross-sectional area, \( A_m(n) \).

The finite difference expression of mass balance during axial diffusion is obtained by considering the following. The mass present in the \( n \)th model segment at time \( t + \Delta t \) is equivalent to the mass present in the \( n \)th model segment at time \( t \) minus the mass exchanged with model segments \( n-1 \) and \( n+1 \). This can be expressed as:
\[
C(n,t+\Delta t)V_{g}(n) = \bar{C}(n,t)V_{g}(n) - (D_{mol} + D_{ed})A_{b}(n-1,n)
\]
\[
\frac{[\bar{C}(n,t) - \bar{C}(n-1,t)]\Delta t}{L_{m}(n-1,n)} - (D_{mol} + D_{ed})A_{b}(n,n+1)[\bar{C}(n,t) - \bar{C}(n+1,t)]\Delta t
\]
\[
\frac{L_{m}(n,n+1)}{L_{m}(n-1,n)}
\]

where the airways have been assumed to be rigid. Although during the breathing cycle there is a diffusional distance change in the lung of approximately 5%, the net effects on gas transport of the above assumption are not expected to be great (Chang and Fahri, 1973).

Solving for \( \bar{C}(n,t+\Delta t) \) in eq. (9) gives:

\[
\bar{C}(n,t+\Delta t) = \bar{C}(n,t) - (D_{mol} + D_{ed}) \left( \frac{A_{b}(n-1,n)}{V_{g}(n)} \left[ \frac{[\bar{C}(n,t) - \bar{C}(n-1,t)]}{L_{m}(n-1,n)} \right]
\right.
\]
\[
\left. + \frac{A_{b}(n,n+1)\Delta t}{L_{m}(n,n+1)} \right)
\]

Usually \( A_{m}(n) \) equals \( A_{b}(n, n+1) \) so that eq. (10) could be further simplified. However, alterations associated with various diseases can be studied easier using eq. (10).

The use of eq. (10) requires estimating the joint effects of molecular and eddy diffusivity. Using a five-generation glass tube model, Scherer and co-workers (1975) have empirically determined values for effective axial diffusivity, \( D_{x} \), for laminar flow of a gas in the conducting airways. Their method of determining \( D_{x} \) in effect replaces five generations by a single one which has an average axial velocity and cross-sectional area equal to those of the initial generation. Importantly though, the effects of bifurcations, turbulence, and secondary flows are retained. Separate equations for inspiration and expiration were obtained which relate \( D_{x} \) to the average axial gas velocity. Their results were:
\( D_x = D_{mol} (1 + \gamma N_{pe}) \)

where \( \gamma \) equals 1.08 for inspiration and 0.37 for expiration, and \( N_{pe} \) refers to the Peclet number of that region of the airways where \( D_x \) applies.

Since the model segments used in the current study are partitions of individual airway generations rather than a characterization over five-generations, modification of \( D_x \) is necessary. The method used was to consider the \( j \)th generation as the focal point of these five-generation simplifications by computing an average diffusion coefficient in the \( j \)th airway generation at each time step as:

\[
D = D_{mol} \left[ 1 + \gamma \sum_{i=j-2}^{j+2} \frac{2R(i)\bar{U}_x(i)}{D_{mol}} \right]
\]

\[
= D_{mol} + \frac{2\gamma}{5} \sum_{i=j-2}^{j+2} R(i)\bar{U}_x(i)
\]

where \( R(i) \) and \( \bar{U}_x(i) \) represent the radius and average axial gas velocity in the \( i \)th generation, respectively. Although replacing \( D_{mol} + D_{ed} \) in eq. (10) by \( D \) defined in eq. (12) is not precisely correct, the desired result of increasing the diffusion coefficient is achieved. As such it represents a substantial improvement over using only the molecular diffusion coefficient to characterize the effects of diffusion in the airways.

Subsequent sections characterize the radial diffusion process and then present the model development associated with 1) the chemical reactions of \( O_3 \) with the mucous layer lining the conducting airways, and 2) the nonreactive surfactant layer lining the transitory and respiratory airways. A three-compartment structure is employed which
in involves the following: 1) the gas-phase lumen concentration profile, 2) the fluid layer lining the airways, and 3) the tissue surrounding the airways. In contrast to the expanding cross-sectional area geometry used for axial diffusion, the appropriate geometry to use in examining radial diffusion is that of the lumen, which has a decreasing radius proceeding distally from the trachea.

**Radial Diffusion in the Lumen**

The time rate of change of $\bar{C}$, convective, and axial diffusion components in eq. (6) are equivalent to providing a source, $S$, to any given model segment. Radial diffusion then is represented as

$$-D \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial \bar{C}}{\partial r} \right) = S$$

where $r$ is with reference to the radial direction for mass transport. During the respiratory cycle $S$ may vary, but it is assumed constant during a given time increment $\Delta t$. Using the center of the lumen as the radial coordinate origin, eq. (13) may be integrated from zero to $r$ to represent the radial rate of change in average $O_3$ concentration as:

$$\frac{\partial \bar{C}}{\partial r} = -\frac{rS}{2D}$$

The solution of eq. (14) gives a parabolic radial concentration profile in each model segment for $\bar{C}$ as a function of $r$

$$\bar{C}(r) = \bar{C}(0) - \frac{r^2 S}{4D} \text{ for } 0 < r < R(n)$$

where $R(n)$ denotes the radius of the lumen of the $n$th model segment and defines the position of the gas-liquid interface.

Radial diffusion accounts for the mass transport of $O_3$ to the fluid layer lining the airways and is reflected by the current, $J(r)$,
where J(r) denotes the quantity of mass transported per unit area per unit time. Also, J(r) is a function of the loss of O₃ from the lumen due to either chemical reactions or to physical absorption. Several expressions are now given which relate the interfacial current to the lumen concentrations of O₃. They are valid for any model segment, and hence, reference to a particular model segment is temporarily suspended. These relationships are later combined with various reaction modes to obtain solutions to differential equations for the concentration of O₃ in the lumen and in the protective layer lining the airways.

The expression for current is defined by

\[ J(r) = -D \frac{\partial \overline{c}}{\partial r} \]  

The current at the gas-liquid interface, J(R) can be obtained from eq. (16) after evaluating eq. (14) at r=R as

\[ J(R) = \frac{RS}{2} \]  

In addition, J(R) can also be represented in terms of \( \overline{c}(0) \) and \( \overline{c}(R) \) by evaluating eq. (15) at r=R, then introducing J(R) defined by eq. (17), and solving the resultant expression to yield

\[ J(R) = k_g (\overline{c}(0) - \overline{c}(R)) \]  

where

\[ k_g = \frac{2D}{R} \]  

Finally, J(R) is also defined as a function of \( \overline{c}(0) \) and \( \overline{c}_a \), where \( \overline{c}_a \) denotes the result of spatially averaging over the values of \( \overline{c}(r) \). Upon assuming circular cross-sections, \( \overline{c}_a \) is determined as

\[ \overline{c}_a = \frac{1}{\pi R^2} \int_0^R \left[ \overline{c}(0) - \frac{r^2S}{4D} \right] 2\pi r dr \]

\[ = \overline{c}(0) - \frac{R^2S}{8D} \]
Then using eq. (17) and (19), in conjunction with eq. (20), gives

\[ J(R) = 2k_g (\bar{C}(0) - \bar{C}_a) \]

Equations (17), (20), and (21) will be used in formulating model solutions, after establishing the manner in which reactions of O\(_3\) with the protective layer will be treated.

**Biochemical Composition of Mucus and Surfactant**

The model framework for incorporating chemical reactions of O\(_3\) into the radial decay process must be based upon the biochemical composition of the fluid layer lining the airways. Also, the nature of reactions between these components and O\(_3\) must be included. Any gaps in this joint data set affect the extent to which the current model can treat chemical reactions.

On the average, human pulmonary secretions contain the following non-water constituents per 100 g of secretion: 1.13g ash, 0.03g DNA, 0.95g carbohydrate, 1.00g protein, and 0.84g lipid (Potter et al., 1963). Lewis (1971) has extensively characterized the lipid fraction in human bronchial asthmatic mucus. He obtained the percent composition of neutral lipids and phospholipids, as well as the fatty acid composition of the major lipid components. Also, Lewis concluded that the lipid composition of asthmatic mucus appears to be typical of bronchial mucus, since the same qualitative lipid composition was observed in bronchitic mucus.

As stated previously, the data on carbohydrate and protein composition of tracheobronchial secretions is sparse and usually qualitative in nature. The amino acids found in human parotid glycoproteins have been characterized by Levine et al. (1969). Other mucin sources
for which similar glycoprotein data exists represent still greater differences in location, with respect to pulmonary secretions. In view of this, the data of Levine and co-workers was used to approximate the amino acid composition of glycoproteins in bronchial mucus. Also, carbohydrate compositional data of bronchial mucus is not sufficiently detailed to permit model analysis.

Although respiratory surface area differs greatly among various vertebrate species, Clements et al. (1969) showed that the amount of surfactant correlates well with the amount of dipalmitoyl lecithin (DPL) in lung parenchyma and with alveolar surface area. Subsequent studies on fractional rabbit alveolar lavage fluid have found DPL to constitute 90-95% of the recoverable lipid (Ballis et al., 1970; Hurst et al., 1973). Thus, the alveoli are normally lined with saturated lecithin and are mostly free of other lipids, protein, and carbohydrate.

Oxidation of Biologically Active Compounds by Ozone

The chemical mechanisms of action of $O_3$ in biological systems have been extensively reviewed by Menzel (1976). Olefins are especially susceptible to oxidation by $O_3$. In view of available data, Menzel postulates that the reaction of $O_3$ with olefins involves a combination of two reactions:

1) an initial reaction of $O_3$ with the olefin to form the zwitterion (Criegee, 1962), and possibly ozonide, and then

2) a reaction involving the peroxidation of the remaining unreacted olefins. A four-step reaction scheme for the autoxidation of polyunsaturated fatty acids can be
formulated which involves an initiator free radical, an alkyl free radical, a peroxyl free radical, a fatty acid hydroperoxide, and a phenolic antioxidant.

Thiols are also easily oxidized by \( \text{O}_3 \). Mudd and co-workers (1969) examined the reaction of \( \text{O}_3 \) with amino acids in aqueous solutions. The amino acids studied displayed the following order of susceptibility to oxidation by \( \text{O}_3 \): cysteine, methionine, tryptophan, tyrosine, histidine, cystine, and phenylalanine. Oxidation was found to be pH dependent for tyrosine and histidine. \( \text{O}_3 \) did not affect the other amino acids found in proteins. Menzel (1971) has shown that glutathione and the thiol groups of proteins are oxidized to the corresponding disulfide and other products.

The initiation of the reactions of \( \text{O}_3 \) with olefins involves a direct attack of \( \text{O}_3 \) upon the double bonds of the fatty acid. This reaction can be treated as irreversible (Menzel, 1976). Under ordinary conditions, the reaction of the zwitterion and aldehyde does not regenerate \( \text{O}_3 \) and can be considered irreversible (Murray and Suzi, 1973). In addition, since the reactions of \( \text{O}_3 \) with olefins and amines proceed at a diffusion-controlled rate (Menzel, 1976; Criegee, 1962), they are characterized by an instantaneous-reaction regime.

The case of absorption accompanied by an instantaneous reaction is an example of a chemical absorption process for which the concentration distribution of the liquid-phase reactant influences the overall absorption rate. Only the instantaneous-reaction regime allows a finite absorption rate when the interface value of the absorbing gas
falls to zero (Astarita, 1967). Such is the case if the resistance to mass transfer in the gas-phase cannot be neglected.

Since surfactant consists almost entirely of saturated lecithin, the above formulation dictates that the mathematical model assumes no chemical reaction of O$_3$ with the surfactant layer. However, various instantaneous-reaction regimes, which are a function of the gas-phase partial pressure of O$_3$, must be considered for the reactions of O$_3$ with the mucous lining during various stages of the breathing cycle. Model solutions can now be obtained to complete the characterization of the radial decay process.

Model Structure for Radial Decay in Transitory and Respiratory Airways

Since surfactant lines the transitory and respiratory airways, no chemical reactions occur between O$_3$ and the protective layer lining these airways. Expressions for the mass flow rate of O$_3$ from the gas volume into the surfactant layer and from the surfactant layer into the surrounding tissue are first derived. Then solutions to differential equations for the concentration of O$_3$ in the lumen and in the surfactant layer are obtained.

Let $X(r)$ denote the liquid-phase concentration of O$_3$, as a function of $r$. The model structure for radial decay in the transitory and respiratory airways is illustrated in Fig. 2. For simplicity, a linear liquid-phase concentration profile was assumed, which is equivalent to assuming a steady-state profile during any given time step. With respect to the radial direction, the end of the surfactant layer is denoted by ES, and the surfactant concentration of O$_3$ at the gas-surfactant interface is given by $X(R)$. Since most experimental
concentrations of $O_3$ are very low in biological studies, Henry's law can be used to relate the gas-phase and liquid-phase interfacial concentrations. That is,

$$\overline{c}(R) = HX(R)$$  \hspace{1cm} (22)

where $H$ represents the Henry's law constant for $O_3$. Since the solubility of $O_3$ in mucus or in surfactant is not known, the Henry's law constant for $O_3$ in water will be used.

From Fig. 2 it is obvious that the average liquid-phase $O_3$ concentration in the radial direction, $\overline{X}_a$, is

$$\overline{X}_a = \frac{X(R) - X(ES)}{2}$$  \hspace{1cm} (23)

and that the interfacial current, $J(R)$, expressed as a function of $X(R)$ and $X(ES)$, is

$$J(R) = k_1 [X(R) - X(ES)]$$  \hspace{1cm} (24)

where $k_1$ represents the liquid-phase mass transfer coefficient.

Equations (23) and (24) can be used to obtain

$$X(R) = \overline{X}_a + \frac{J(R)}{2k_1}$$  \hspace{1cm} (25)

and

$$X(ES) = \overline{X}_a - \frac{J(R)}{2k_1}$$  \hspace{1cm} (26)

At the beginning of the radial decay step, the average gas-phase concentration of $O_3$ in the radial direction is assumed equal to $\overline{c}$. Thus, an expression relating the interfacial current to $\overline{C}_a$ and $\overline{X}_a$ can be used to represent a model segment, with respect to the mass flow rate of $O_3$ into the surfactant layer. Equation (18), in conjunction with eq. (22) gives

$$J(R) = k_g [\overline{C}(0) - HX(R)]$$  \hspace{1cm} (27)
Using eq. (25) to substitute for $X(R)$ in eq. (27) and collecting terms yields

$$ J(R) [k_1 + Hk_g] = k_g k_1 [C(0) - HX(ES)] $$

First solving for $C(0)$ in eq. (21), next substituting in eq. (28) for $C(0)$ and for $X(ES)$, as defined by eq. (26), and then simplifying gives

$$ J(R) = K_G [C_a - HX_a], $$

where

$$ K_G = \frac{2k_g k_1}{k_1 + Hk_g} $$

As given in eq. (30), $K_G$ is a function of the gas-phase and liquid-phase mass transfer coefficients, $k_g$ (eq. (19)) and $k_1$, respectively, where $k_1 = D_L/r_m$. Here $D_L$ is the liquid-phase diffusivity of $O_3$ and $r_m$ is the midpoint of the surfactant layer and defines the length over which the concentration gradient is established between the tissue and surfactant layer. Since $D_L$ for $O_3$ in surfactant is not known, the diffusion coefficient of $O_3$ in water will be used for $D_L$.

Explicit forms for the mass flow rates relating to the three-compartment model structure can now be obtained. The mass flow rate of $O_3$ from the lumen of the $n$th model segment into the protective layer is

$$ \frac{3M_l}{3t} = K_G A_S(n) [C_a(n,t) - HX_a(n,t)] $$

where $A_S(n)$ represents the surface area of the $n$th model segment. Since large amounts of lipids are contained in lung tissue, it is reasonable to assume that $O_3$ is instantaneously converted by chemical reaction when it reaches the tissue. Thus the mass flow rate of $O_3$
from the surfactant layer of the n-th model segment into the surrounding tissue is given by

\[ \frac{\partial M_2}{\partial t} = k_1 A_s(n) \bar{Y}_a(n, t) \]

In view of the three-compartment structure assumed (airway lumen, protective layer, and tissue), mass is lost from the lumen, while in the protective layer, mass is lost to the tissue and gained from the lumen. Thus, eqs. (31) and (32) can be used to formulate a general set of two simultaneous linear differential equations for the concentration of \( O_3 \) in the lumen and in the surfactant layer. They are

\[ \frac{\partial C_a(n, t)}{\partial t} = - \frac{\partial M_1}{\partial t} / V_g(n) \]
\[ \frac{\partial \bar{X}_a(n, t)}{\partial t} = \frac{\partial M_1}{\partial t} / V_1(n) - \frac{\partial M_2}{\partial t} / V_1(n) \]

where \( V_g(n) \) and \( V_1(n) \) represent the gas-phase and liquid-phase volumes, respectively, of the n-th model segment. Since a linear liquid-phase concentration profile was assumed and since the tissue corresponds to an infinite sink, eq. (34) is not needed in this instance. However, the general solutions of eqs. (33) and (34) are given in Appendix A and are necessary if other concentration profiles are examined.

Model Structure for Radial Decay in Conducting Airways

The conducting airways are lined with mucus. Previous sections have shown that the model structure for these airways should be based upon an instantaneous-reaction regime. Inherent in the instantaneous-reaction scheme is the concept that the absorbing component and the liquid-phase reactant cannot coexist in the same region of the liquid. This leads to considering the liquid as essentially being comprised of
two layers (Astarita, 1967). Diffusion of the absorbing component occurs in the first layer, while diffusion of the liquid-phase reactant takes place in the second layer. The boundary between these two layers defines the "reaction plane." At the reaction plane the concentrations of both the absorbing component and the liquid-phase reactant are zero. In this study, O$_3$ is the absorbing component, while the data on the biochemical composition of mucus can be used to assess collectively the available liquid-phase reactants.

Three cases, which are a function of the lumen O$_3$ concentration, are needed to characterize radial decay in the conducting airways. These various cases, illustrated in Fig. 3, result in establishing the reaction plane, $\lambda$, anywhere from the gas-mucus interface to a position equivalent to O$_3$ penetrating to the tissue. At the reaction plane, the diffusional fluxes of O$_3$ and the liquid-phase reactants must satisfy the stoichiometry of the reaction. This requirement can be expressed as

$$-qD_1 \frac{\partial X(r)}{\partial r} = D_2 \frac{\partial B(r)}{\partial r}$$

where $D_1$ is the diffusion coefficient of O$_3$ in mucus, $D_2$ is the diffusion coefficient of the mucous reaction components, $X(r)$ is now the concentration of O$_3$ in the mucus, $B(r)$ is the concentration of the mucous reaction components, and $q$ is the number of moles of mucous reactants consumed per mole of O$_3$ (Astarita, 1967). $D_1$ for O$_3$ in mucus is not well defined, but is probably less than that for O$_3$ in water. However, ciliary activity effectively increases the diffusion coefficient, and so $D_1$ will be assumed to be that of O$_3$ in water.
Let $K$ denote an effective rate of production per unit area at the airway wall of the components of mucus with which $O_3$ will react. Using eq. (35) and the appropriate boundary conditions, it can be shown (Appendix B) that the location of the reaction plane in the mucous layer is

$$\lambda = R + \frac{qD_1}{K} X(R),$$

while the mucous radial concentration profiles of $O_3$ and of the reactants are, respectively,

$$X(r) = K \frac{D_1}{q} (R-r) + X(R) \quad \text{for } r<\lambda$$

$$B(r) = K \frac{D_2}{q} (r-\lambda) \quad \text{for } r>\lambda$$

The different instantaneous-reaction regimes evolve when determining whether $\lambda$ is located at the gas-mucus interface or somewhere beyond the interface.

The concentration of mucous components that will react with $O_3$ may far exceed the interface concentration of $O_3$, so that the rate-controlling step is the diffusion of these components towards the interface. This corresponds to when resistance to $O_3$ mass transfer in the lumen (gas-phase) can not be neglected. The current, $J(r)$, can be defined in terms of the liquid-phase $O_3$ concentration as

$$J(r) = -D_1 \frac{2X(r)}{2r}$$

After evaluating the first derivative of eq. (37) at $r=R$, substitution in eq. (39) yields

$$J(R) = \frac{K}{q}$$
After solving for \( \overline{C}(0) \) in eq. (21) and substituting this result in eq. (18), the interfacial current is also given by

\[
(41) \quad J(R) = 2k_g [\overline{C}_a - \overline{C}(R)]
\]

The greatest gas-phase mass transfer of \( O_3 \) occurs if the interface concentration of \( O_3 \) becomes zero (Astarita, 1967). Thus, from eqs. (40) and (41), it is apparent that \( 2k_g \overline{C}_a > K/q \) is necessary for the reaction plane to be located within the mucous layer. In terms of \( \overline{C}_a \), this is

\[
(42) \quad \overline{C}_a > \frac{K}{2qk_g}
\]

- case a: surface-controlled regime, \( \lambda = R \)

If \( \overline{C}_a \) is such that eq. (42) does not hold, the reaction is surface controlled and radial decay can be depicted by case a in Fig. 3. Then \( \overline{C}(R) = 0 \) and the absorption rate expressed by eq. (41) reduces to

\[
(43) \quad J(R) = 2k_g \overline{C}_a
\]

The rate of change of \( O_3 \) concentration in the lumen of the \( n \)th model segment is thus

\[
(44) \quad \frac{\partial \overline{C}_a(n,t)}{\partial t} = -\frac{\partial M_1}{\partial t} / V_g(n) = -2k_g \omega \overline{C}_a
\]

where

\[
(45) \quad \omega = \frac{A_S(n)}{V_g(n)}
\]

The solution of eq. (44) and expressions for the mass lost to the mucus and tissue are given in Table 1.

- case b: inner-regime, \( r < \lambda < EM \)

If the lumen concentration is sufficiently large such that eq. (42) holds, the gas-phase is able to transfer enough mass to meet the
requirements of chemical absorption, and so the reaction plane is no longer located at the gas-mucus interface. Case b, as illustrated in Fig. 3, represents when \( \lambda \) is located within the mucus layer, but not at the end of this layer (EM).

Henry's law has been assumed to relate the gas-phase and liquid-phase interfacial concentrations of \( O_3 \). Equation (41) defines the relationship between \( C_a \) and the gas-phase interfacial \( O_3 \) concentration. As long as the liquid-phase interfacial concentration of \( O_3 \) is such that \( R < \lambda < EM \), the current is given by eq. (40), and there can be no \( O_3 \) transferred to the tissue. Hence, it follows that

\[
(46) \quad \frac{\partial C_a(n,t)}{\partial t} = \frac{\partial M}{\partial t} / V_g(n) = \frac{-K_0}{q}
\]

Table 1 gives the solution of eq. (46), as well as the mass lost to the mucus for this reaction regime.

**case c: inner-regime, \( \lambda = EM \)**

When the concentration of \( O_3 \) in the lumen is such that it implies that \( \lambda \) is beyond the end of the mucous layer, penetration of \( O_3 \) to the tissue results. This situation is depicted in Fig. 3 by case c. The dashed line indicates where the reaction plane would be using eq. (36), if the mucous layer were deep enough. However, the solid line is imposed by the restriction that \( O_3 \) is instantaneously converted by chemical reactions when it reaches the tissue (i.e. the \( O_3 \) concentration must be zero at the tissue surface and so \( \lambda = EM \)).

It is clear from Fig. 3 that in this case eq. (39) leads to

\[
(47) \quad J(R) = -D_1 \frac{X(R)}{R - EM}
\]
Using eq. (22) to first substitute for $X(R)$, and then using eq. (41) to eliminate $\overline{C}(R)$ allows eq. (47) to be written as

$$J(R) = \frac{D_1}{H(EM-R)} \left( \overline{C}_a - \frac{K}{2qk_g} \right)$$

For this regime, the rate of change of $O_3$ concentration in the lumen of the $n$th model segment is then

$$\frac{\partial \overline{C}_a(n,t)}{\partial t} = -\frac{\partial M_1}{\partial t} / V_g(n) = -\alpha \overline{C}_a(n,t) + \beta$$

where

$$\alpha = \frac{D_1 \omega}{H(EM-R)} \quad \text{and} \quad \beta = \frac{K \omega}{2qk_g}.$$  

The solution of eq. (49) and expressions for the mass lost to the mucus and tissue may be found in Table 1.

Summary of Model

The model developed in the previous sections characterizes the transport and uptake of $O_3$ within model segments that are partitions of individual airway generations. The effects on gas transport of convection, axial diffusion, and radial diffusion are included in the model, as well as the chemical reactions of $O_3$ with various components in the fluid layer lining the airways. A multi-step procedure involving mass balance expressions in finite difference form was presented which can be used to examine the transport and removal of $O_3$. Respiration was assumed to be sinusoidal.

Convection was simulated by instantaneously moving a small gas volume during each time step. With this scheme, the sinusoidal flow pattern required determining a different time increment for each step. Eddy diffusivity and molecular diffusion were included in describing
the effects of axial diffusion in the airways. This was done by relating, in each airway generation at any given time, the diffusion coefficient to the mean axial gas velocity. Radial diffusion was coupled with a scheme for incorporating chemical reactions to account for the removal of O$_3$ from the lumen of an airway.

After examining the biochemical composition of mucus and surfactant, specific components of the mucous layer were identified which undergo an irreversible instantaneous reaction with O$_3$. Within a given airway, the lumen O$_3$ concentration was found to determine the location of the reaction plane between O$_3$ in the mucous layer and the reaction components of the mucus. This led to characterizing the removal of O$_3$ from the airway by considering three reaction regimes. These regimes were: 1) surface-controlled, 2) inner-regime with reaction plane located within the mucus, and 3) inner-regime with penetration of O$_3$ to the tissue. The appropriate model formulation for airways lined with surfactant considered no chemical reactions between O$_3$ and surfactant.

A computer program has been written which utilizes all features of the mathematical model to study the transport and removal of O$_3$ in the lungs of human beings, rabbits, and guinea pigs. Specific details concerning number of model segments and time steps, convection volume increments, etc. will be presented in other papers forthcoming, which will illustrate the applicability of the model and its usefulness in studying O$_3$ toxicity.
References


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<table>
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<th>Expression</th>
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<th>Case b</th>
<th>Case c</th>
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<td>( C_a(n, t) - \omega \Delta t )</td>
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Table 1: Change in Lumen O\(_3\) Concentration and O\(_3\) Lost to Mucus and Tissue During \( \Delta t \) for Various Irreversible Instantaneous-reaction Regimes

- Case a: surface-controlled, \( \lambda = R \)
- Case b: inner, \( R < \lambda = EM \)
- Case c: inner, \( \lambda = EM \)
Figure 1. Schematic representation of geometry used for axial diffusion (for illustration, one model segment per generation).
Figure 2. Radial decay in transitory and respiratory airways.
Figure 3. Instantaneous-reaction regimes which characterize radial decay in the conducting airways.
Appendix A

Model Solutions for Airways Lined with Surfactant

We present here the details of the general solutions of eqs. (33) and (34). Using eqs. (31) and (32), a matrix-form representation of eqs. (33) and (34) is

\[
\frac{\partial \bar{C}_a(n,t)}{\partial t} = \begin{bmatrix}
-\frac{K_g A_S(n)}{V_g(n)} & \frac{HK_g A_S(n)}{V_g(n)} \\
\frac{K_g A_S(n)}{V_1(n)} & -\left( -\frac{K_g A_S(n)}{V_1(n)} + \frac{k_1 A_S(n)}{V_1(n)} \right)
\end{bmatrix} \begin{bmatrix}
\bar{C}_a(n,t) \\
\bar{X}_a(n,t)
\end{bmatrix}
\]

(A-1)

To simplify notation we define the following variables

\[
A = -\frac{K_g A_S(n)}{V_g(n)}, \quad B = -AH, \quad E = \frac{K_g A_S(n)}{V_1(n)}, \quad \text{and} \quad F = -(EH + \frac{k_1 A_S(n)}{V_1(n)})
\]

(A-2)

Using eq. (A-2), we have eq. (A-1) as

\[
\frac{\partial \bar{C}_a(n,t)}{\partial t} = \begin{bmatrix}
A & B \\
E & F
\end{bmatrix} \begin{bmatrix}
\bar{C}_a(n,t) \\
\bar{X}_a(n,t)
\end{bmatrix}
\]

(A-3)

Define the 2 x 1 vector comprised of \( \bar{C}_a(n,t) \) and \( \bar{X}_a(n,t) \) as \( \mathbf{P}(t) \) and the right-hand side 2 x 2 matrix of constants in eq. (A-3) as \( \mathbf{W} \). With this notation eq. (A-3) can be represented as

\[
\frac{\partial \mathbf{P}(t)}{\partial t} = \mathbf{W} \mathbf{P}(t)
\]

(A-4)

The solution of the differential equation represented by eq. (A-4) is well known and is given by

\[
\mathbf{P}(t) = e^{(t-t_0)\mathbf{W}} \mathbf{P}_0
\]

(A-5)
where \( P(t_0) = P_0 \) defines the initial conditions. We let \( \Delta t = t-t_0 \) and evaluate \( e^{\Delta t W} \) by using \( e^{\lambda} = \alpha_0 + \alpha_1 \lambda \), where \( \lambda \) is an eigenvalue of the matrix \( \Delta t W \). Thus, we have

\[
\begin{align*}
\lambda_1 &= \alpha_0 + \alpha_1 \lambda_1 \\
\lambda_2 &= \alpha_0 + \alpha_1 \lambda_2
\end{align*}
\]

This solution for \( \alpha_0 \) and \( \alpha_1 \) in the set of equations defined in eq. (A-6) can be shown to be

\[
\alpha_0 = e^{\lambda_1} - \frac{\lambda_1 (e^{\lambda_2} - e^{\lambda_1})}{\lambda_2 - \lambda_1}
\]

\[
\alpha_1 = \frac{e^{\lambda_2} - e^{\lambda_1}}{\lambda_2 - \lambda_1}
\]

Next we determine \( e^W = \alpha_0 I + \alpha_1 W \) as

\[
(A-8) \quad e^W = \begin{bmatrix} \alpha_0 & 0 \\ 0 & \alpha_0 \end{bmatrix} + \begin{bmatrix} \alpha_1 A & \alpha_1 B \\ \alpha_1 E & \alpha_1 F \end{bmatrix} = \begin{bmatrix} \alpha_0 + \alpha_1 A & \alpha_1 B \\ \alpha_1 E & \alpha_0 + \alpha_1 F \end{bmatrix}
\]

From eq. (A-8) it can thus be seen that \( e^{\Delta t W} \) is

\[
(A-9) \quad e^{\Delta t W} = \begin{bmatrix} (\alpha_0 + \alpha_1 A) e^{\Delta t} & \alpha_1 B e^{\Delta t} \\ \alpha_1 E e^{\Delta t} & (\alpha_0 + \alpha_1 F) e^{\Delta t} \end{bmatrix}
\]

Since the initial conditions can be expressed as

\[
(A-10) \quad P(t_0) = \begin{bmatrix} P_1 \\ P_2 \end{bmatrix} = \begin{bmatrix} \overline{c}_a(n,t_0) \\ \overline{x}_a(n,t_0) \end{bmatrix},
\]

the product of equations (A-9) and (A-10) yields the general solution as

\[
(A-11) \quad P(t) = \begin{bmatrix} P_1(\alpha_0 + \alpha_1 A) e^{\Delta t} + P_2\alpha_1 B e^{\Delta t} \\ P_1\alpha_1 E e^{\Delta t} + P_2(\alpha_0 + \alpha_1 F) e^{\Delta t} \end{bmatrix}
\]
Appendix B

Characterization of the Instantaneous Reaction Inner-regime

We present here the details needed to obtain eqs. (36)-(38), which characterize the instantaneous reaction inner-regime. At the reaction plane, \( \lambda \), the diffusional fluxes of the two reactants must satisfy

\[
\text{(B-1)} \quad -qD_1 \frac{\partial X(r)}{\partial r} = D_2 \frac{\partial B(r)}{\partial r}
\]

Since the liquid-phase reactant is being produced at the rate \( K \), it follows that when \( r = EM \)

\[
\text{(B-2)} \quad -D_2 \frac{\partial B(r)}{\partial r} = -K
\]

The linear profiles of \( X(r) \) and \( B(r) \) can be expressed as

\[
\text{(B-3)} \quad B(r) = A_1 r + A_2
\]

and

\[
\text{(B-4)} \quad X(r) = A_3 r + A_4
\]

where \( A_i, i=1,2,3,4 \) need to be determined for the appropriate boundary conditions. Evaluating (B-4) at the gas-mucus interface and solving for \( A_4 \) yields

\[
\text{(B-5)} \quad A_4 = X(R) - A_3 R,
\]

Differentiating eq. (B-4) gives

\[
\text{(B-6)} \quad \frac{\partial X(r)}{\partial r} = A_3
\]

and so eq. (B-1) may be rewritten using eq. (B-6) and eq. (B-2) to give

\[
\text{(B-7)} \quad A_3 = -\frac{K}{qD_1}
\]

Equation (B-7) can be used to substitute for \( A_3 \) in eq. (B-5) so that

\[
\text{(B-8)} \quad A_4 = X(R) + \frac{KR}{qD_1}
\]
Then eqs. (B-7) and (B-8) can be used to substitute for $A_3$ and $A_4$, respectively, in eq. (B-4) to give

(B-9) \[ X(r) = \frac{K}{qD_1^2} (R-r) + X(R) \]

which verifies eq. (37).

Now since $\partial B(r)/\partial r = A_1$, eq. (B-2) implies

(B-10) \[ A_1 = \frac{K}{D_2} \]

Also, since $B(r)=0$ at the reaction plane, $r=\lambda$, it follows from eq. (B-3) and (B-10) that

(B-11) \[ A_2 = \frac{K}{D_2} \lambda \]

Equations (B-10) and (B-11) now can be used to rewrite eq. (B-3) as

(B-12) \[ B(r) = \frac{K}{D_2} (r-\lambda) \]

which verifies eq. (38). Since $X(r)=0$ at the reaction plane, evaluating eq. (B-9) at $r=\lambda$ and solving for $\lambda$ gives

(B-13) \[ \lambda = R + q \frac{D_1}{K} X(R) \]

which verifies eq. (36).
Similarity Between Man and Laboratory Animals in Regional Pulmonary Deposition of Ozone

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Model for Pulmonary Deposition of $O_3$

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Abstract

Predicted pulmonary ozone \((O_3)\) dose curves obtained by model analysis of the transport and removal of \(O_3\) in the lungs of guinea pigs, rabbits, and man indicate a general similarity exists between these species in the shape of the dose curves. An overview is presented of the major features of the lower airway mathematical model utilized. The model predicts that the respiratory bronchioles receive the maximum \(O_3\) dose. For exposures corresponding to tracheal \(O_3\) concentrations greater than 100 \(\mu g/m^3\) (0.05 ppm), the predicted respiratory bronchiole dose for rabbits was found to be twice that for guinea pigs and 80% of that for man. Sensitivity analyses are presented for model parameters relating to the treatment of the chemical reactions of \(O_3\) with the mucous layer. The roles of inspiratory duration and tidal volume in the determination of pulmonary uptake of \(O_3\) in man is examined. The consistency and similarity of the dose curves for the three species lend strong support to the validity of extrapolating to man the results obtained on animals exposed to this pollutant.
Model for Pulmonary Deposition of O$_3$ - Miller

Introduction

The assessment of adverse human health effects associated with exposure to environmental air pollutants involves the toxicological evaluation of results obtained from epidemiologic, clinical, and animal studies. One of the strong points of epidemiologic and clinical studies is that the information obtained is directly related to the human experience. Also, sub-groups of the general population can be selected for study which correspond to sensitive individuals. Likewise, industrial workers represent a group for study who are routinely exposed to pollutant levels significantly greater than those found in the ambient air. Inability to control exposure levels, the mobility of the population, and difficulty in accurately determining previous exposure history and important concomitant variables are uncertainties in epidemiologic studies.

In human clinical trials exposure levels can be adequately controlled, but the types of biological parameters which can be studied must usually be limited to those for which non-invasive measurement techniques are available. As a result of these limitations, and others, the vast majority of toxicological studies are conducted using laboratory animals. In contrast to clinical studies, animal experimentation offers the choice of a wide range of concentrations, exposure regimens, animal species, chemical agents, and biological parameters that can be examined. From these studies, the environmental toxicologist must make judgments concerning the validity of extrapolating the results to man. In addressing the likelihood that the animals studied mimic the human response, an important consideration must be to estimate the effective
dose delivered to the target organ. Differences between man and experimental animals in the ratio of effective dose to exposure concentration must also be considered.

To achieve these objectives, greater emphasis must be placed upon developing mathematical models for pollutant target organs. These models should incorporate species anatomical differences and chemico-physical properties of the pollutant as parameters and should be based upon the physical laws which govern transport and removal of the pollutant. McJilton et al. (1972) have proposed a model for predicting the uptake of ozone ($O_3$) in the lung. Since chemical reactions of $O_3$ with components of the mucous layer were not included, their model underestimates conducting airway uptake of $O_3$ and overestimates respiratory airway uptake. Thus, the model of McJilton et al. is more useful for determining the uptake of nonreactive gases than it is for estimating the uptake of $O_3$.

An approach for evaluating $O_3$ toxicity has been presented which empirically accounts for nasopharyngeal removal of $O_3$ and mathematically models the chemical reactions associated with the transport and removal of $O_3$ in pulmonary airways (Miller, 1977). This model has been utilized to examine the similarity in regional pulmonary deposition of $O_3$ between man and laboratory animals.
Model for Pulmonary Deposition of O\textsubscript{3} - Miller

Materials and Methods

Transport Equation for Ozone in a Lower Airway Model

Since a detailed account of the mathematical model used in this study is presented elsewhere (Miller, 1977), only a summary of the major features of the model will be given here. The transport and removal of O\textsubscript{3} in the lung was studied using the binary convective-diffusion equation

\[
\frac{\partial \overline{C}}{\partial t} + \overline{U} \frac{\partial \overline{C}}{\partial x} = (D_{mol} + D_{ed}) \left( \frac{\partial^2 \overline{C}}{\partial r^2} + \frac{1}{r} \frac{\partial \overline{C}}{\partial r} + \frac{\partial^2 \overline{C}}{\partial x^2} \right) + \overline{s}^* 
\]

where \( \overline{C}, \overline{U}, \) and \( \overline{s}^* \) represent species averaged population concentration, velocity, and source term values, respectively, in a given airway at a specified location and time. In eq. (1) \( x \) and \( r \) represent distance in the axial and radial directions, respectively, \( t \) represents time, the molecular diffusion coefficient of O\textsubscript{3} in air is \( D_{mol} \), and \( D_{ed} \) represents the diffusion coefficient associated with the phenomenon of eddy dispersion. Simply stated, eq. (1) asserts that the transport and removal of O\textsubscript{3} in the lung is a function of convection, axial and radial diffusion, and chemical reactions.

The amount of O\textsubscript{3} acting on a given level of the lung is reflected by the airway lumen concentration at that level. Ozone does not immediately strike the airway wall; instead, it must first come in contact with the mucous or surfactant layer lining the airway, depending upon which level of the lung the gas has reached. Chemical reactions with components in these layers may occur, thereby increasing the total absorption of O\textsubscript{3}, but may also reduce the amount of O\textsubscript{3} reaching the tissue. Thus, it is clear that the biochemical
composition of the mucous and surfactant layers dictate the manner in which chemical reactions should be treated.

Biochemical Composition of Mucus and Surfactant

Clements and co-workers (1969) showed that, among various vertebrate species, the amount of surfactant correlates well with the amount of dipalmitoyl lecithin (DPL) in lung parenchyma and with alveolar surface area. DPL constitutes 90-95% of the recoverable lipid in fractional rabbit alveolar lavage fluid (Balis et al., 1970; Hurst et al., 1973). Hence, the alveoli are normally lined with saturated lecithin and are mostly free of other lipids, protein, and carbohydrate.

The lipid fraction in human bronchial asthmatic mucus has been extensively characterized by Lewis (1971). Since the same qualitative lipid composition was observed in bronchitic mucus as was found in asthmatic mucus, Lewis concluded that the lipid composition of asthmatic mucus is typical of bronchial mucus. Potter et al. (1963) determined the non-water constituents per 100g of human pulmonary secretions as: 1.13g ash, 0.03g DNA, 0.95g carbohydrate, 1.00g protein, and 0.84g lipid. To date, detailed biochemical analysis has not been performed on the protein and carbohydrate components of bronchial mucus.

Model Treatment of Chemical Reactions

Recently, Menzel (1976) reviewed the chemical mechanisms of action of O₃ in biological systems. Olefins are especially susceptible to oxidation by O₃. The reaction of O₃ with olefins likely involves an initial reaction with the olefin to form the zwitterion (Criegee, 1962), and possibly ozonide, and then a reaction involving the
peroxidation of the remaining unreacted olefins. Mudd et al. (1969) have determined the order of susceptibility of amino acids in aqueous solutions to oxidation by O₃.

A direct attack of O₃ upon the double bonds of the fatty acid is involved in the initiation of the reaction of O₃ with olefins. This reaction is irreversible (Menzel, 1976). Moreover, since the reactions of O₃ with amines and olefins are diffusion controlled (Criegee, 1962; Menzel, 1976), they can be characterized by an instantaneous-reaction regime.

Basic to the instantaneous-reaction scheme is the concept that the absorbing component, in this instance O₃, and the liquid-phase reactant cannot coexist in the same region of the liquid. Hence, the liquid can be considered as essentially being comprised of two layers (Astarita, 1967). In the first layer, diffusion of O₃ occurs, while diffusion of the liquid-phase reactant takes place in the second layer. The reaction plane, λ, is defined to be the boundary between the two layers. At the reaction plane the concentrations of both O₃ and the liquid-phase reactant are zero.

It can be shown (Miller, 1977) that three cases are needed to characterize removal of O₃ via chemical reactions in airways lined by mucus. These cases are a function of the lumen O₃ concentration and are depicted in Fig. 1. As the lumen O₃ concentration in a given airway rises and falls during the breathing cycle, the reaction plane may be established anywhere from the gas-mucus interface (case 1) to a position equivalent to O₃ penetrating to the tissue (case 3). The dashed line in case 3 indicates where the reaction plane would be if
Model for Pulmonary Deposition of O₃ - Miller

the mucus layer were deep enough. However, the solid line is imposed by the restriction that O₃ is instantaneously converted by chemical reactions when it reaches the tissue.

In the lung, the conducting airways are lined with mucus, while the transitory airways (respiratory bronchioles) and respiratory regions are lined with surfactant. Since surfactant consists almost entirely of saturated lecithin, no chemical reactions of O₃ with the surfactant layer were assumed. Hence, chemical reactions with the layer lining the airways were considered only for conducting airways.

The data of Lewis (1971) was used to determine the number of mole equivalents represented by the double bonds of the unsaturated fatty acids of the major lipid components of human bronchial mucus (Table 1). The amino acids found in human parotid glycoproteins were used to approximate the amino acid composition of glycoproteins in bronchial mucus (Levine et al., 1969). Of the amino acids present, histidine was the only one susceptible to oxidation by O₃ (Mudd et al., 1969). For histidine, the number of mole equivalents of O₃ given in Table 1 can be determined using Table 6 (for the moles of histidine/mole glycoprotein) from Marshall (1972) and the estimate of 1.0g protein/g mucus from Potter et al. (1963). Hence, the concentration of O₃ reactants present in mucus are collectively assessed by the data in Table 1.

Structure of the Model

The model formulation requires extensive use of lung morphometric data. For man, the regularized dichotomously branched lung data of Weibel (1963) was used, while for rabbits and guinea pigs, the
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morphometric data was based upon the work of Kliment (1973). Each
airway generation or morphometric zone was partitioned to form a
sequence of model segments, and a multi-step procedure involving mass
balance expressions in finite difference form was used to obtain solu-
tions of eq. (1). Respiration was assumed to be sinusoidal.

Convection was simulated by instantaneously moving a small gas
volume (approximately 1/200th of the normal tidal volume) during each
time interval. Within each model segment a new lumen concentration was
obtained for this same time interval. Changes in the lumen profile due
to axial diffusion were determined next, followed by radial decay,
during which radial diffusion accounted for mass transport of O₃ to the
fluid layer lining the given model segment, where removal of O₃ from
the airway occurs. The lumen concentration was again determined and
this entire sequence repeated for the next time increment. The number
of model segments for each species and the use of 200 time steps for
numerical analysis were obtained as a result of convergence testing.
The data which characterizes the model segments used for each species
are given in Tables A.1 - A.3 of Appendix A.

The joint effects of molecular and eddy diffusivity, \((D_{mol} + D_{ed})\)
of eq. (1), were estimated based upon a modification of the results of
Scherer and co-workers (1975). These investigators determined empiri-
cally values for effective axial diffusivity, \(D_x\), for laminar flow of a
gas in the conducting airways and obtained

\[
D_x = D_{mol}(1 + \gamma N_{pe})
\]

where \(\gamma\) equals 1.08 for inspiration and 0.37 for expiration, and \(N_{pe}\)
refers to the Peclet number of that region of the airways where \(D_x\)
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applies. By definition, $N_{pe} = 2R U_x / D_{mol}$, where $R$ is the airway radius. The method used to determine $D_x$ effectively replaced five generations by a single one which had an average axial velocity and cross-sectional area equal to those of the initial generation. However, the procedure of Scherer et al. retained the effects of bifurcations, turbulence, and secondary flows.

Since predictions of $O_3$ absorption in each generation of the tracheobronchial tree were desired in the current model study, $D_x$ was modified by considering the $j$th generation as the focal point of these five-generation simplifications. An average diffusion coefficient was computed in the $j$th airway generation at each time step as

$$D = D_{mol}(1 + \frac{\gamma}{5} \sum_{i=j-2}^{j+2} \frac{2R(i)U_x(i)}{D_{mol}})$$

$$= D_{mol} + \frac{2\gamma}{5} \sum_{i=j-2}^{j+2} R(i)U_x(i)$$

where $R(i)$ and $U_x(i)$ represent the radius and average axial gas velocity in the $i$th generation, respectively. Although replacing $(D_{mol} + D_{ed})$ in eq. (1) by $D$ defined in eq. (3) is not precisely correct, it represents a substantial improvement over previous models which considered only molecular diffusion in characterizing the effects of diffusion in the airways.

The model structure for radial decay in the conducting airways involves the effective rate of production per unit area, at the airway wall, of the components of mucus with which $O_3$ will react (Miller, 1977). Since the morphometric data for rabbits and guinea pigs is only available by "zone," while the data for man is given by dichotomously
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branched generation, "mucous production zones" were formed for humans by considering which generations had drained the same percentage of mucus-lined airway surface area as had a given morphometric zone in rabbits and guinea pigs (Appendix A, Table A.1). Goblet cell density, expressed as number of goblet cells per 5 high-power microscopic fields, has been shown in rats to decrease between the trachea and distal airways (Reid, 1970). In the present study, the effective rate of production of mucous reaction components per unit area was assumed to decrease linearly, with respect to mucous zone, from a maximum value at the trachea to zero at the beginning of the respiratory bronchioles (see Appendix B).

Results

Using the model approach described in previous sections, transport of $O_3$ in the lungs of man, rabbits and guinea pigs was studied. Subsequent sections illustrate physiological and toxicological comparisons that can be obtained and examine the sensitivity of the results with respect to some of the parameters of the model.

Predicted Dose Curves with Normal Respiration

Model estimates for the dose of $O_3$ delivered to the tissue in various generations of the human lung are shown in Fig. 2. Independent of the inhaled tracheal concentration of $O_3$, the model predicts that the first generation of respiratory bronchioles (generation 17) receives the maximum dose of $O_3$. While the model predicts uptake of $O_3$ by respiratory airway tissue for all tracheal concentrations studied, penetration of $O_3$ to the tissue in airways lined by mucus (generation 16 and above) is not predicted for inhaled tracheal concentrations less
than 125 μg/m³ (0.06 ppm). Presumably, at these low exposure levels, the concentration of O₃ reactants and the thickness of the mucous layer combine to deplete all of the O₃ absorbed in the conducting airways. However, as the inhaled tracheal concentration is increased from 250 to 4000 μg/m³, the tissue deposition pattern in the conducting airways becomes smoother, greater in magnitude, and includes more airways. Irrespective of tracheal concentration, alveolar (generations 20-23) O₃ doses decline sharply with increasing generation number, due in large part to the tremendous increase in surface area.

Corresponding to Fig. 2, the relative contributions of mucus, conducting airway tissue, and respiratory airway (surfactant lined) tissue to total uptake are depicted in Fig. 3. As the tracheal concentration of O₃ increases, the percent uptake of O₃ by mucus declines sharply and assumes an approximately constant value of 7-9% for inhaled tracheal O₃ concentrations exceeding 750 μg/m³ (0.38 ppm). The uptake of O₃ by respiratory tissue is, on the other hand, almost a mirror image of that of mucus. Respiratory airway uptake increases rapidly as the concentration of inhaled O₃ increases and plateaus at about 46%. The model predicts that the contribution of conducting airway tissue doses to the total uptake of O₃ is slight (less than 8% for all concentrations).

Tissue dose patterns of O₃ in the lungs of rabbits and guinea pigs are presented in Figs. 4 and 5, respectively. As for man, the respiratory bronchioles (model zone 6) are predicted to receive the maximum dose in both animal species. Although several human airway generations may correspond to a morphometric zone in rabbits and guinea pigs, a
general similarity is evident between the three species in the shape of the predicted dose curves. The predicted doses for alveolar ducts and sacs exhibit a greater difference in rabbits, as compared to guinea pigs. Also, Figs. 4 and 5 show that with exposure to a tracheal $O_3$ level of 1000 $\mu g/m^3$, penetration of $O_3$ to the tissue occurs in the trachea of guinea pigs, but not until the second order bronchi are reached in rabbits.

The relationship between respiratory bronchiole dose and the inhaled tracheal $O_3$ concentration is given in Fig. 6. For tracheal concentrations exceeding 100 $\mu g O_3/m^3$ (0.05 ppm $O_3$), this relationship is linear on a logarithmic scale for all three species. From regression analysis applied to the data in Fig. 6 for tracheal $O_3$ concentrations between 100 - 4000 $\mu g/m^3$, the respiratory bronchiole dose of $O_3$ over this range is proportional to the tracheal concentration raised to the 1.0 power for guinea pigs and rabbits and to the 1.07 power for man. For any given tracheal $O_3$ concentration greater than 100 $\mu g/m^3$, the predicted respiratory bronchiole dose for rabbits is twice that for guinea pigs and is 80% of that for man.

With pollutant exposures corresponding to less than 100 $\mu g O_3/m^3$ at the trachea, the predicted respiratory bronchiole dose curve in man is markedly different than the curve for rabbits and for guinea pigs (Fig. 6). As the tracheal $O_3$ concentration decreases from 100 $\mu g/m^3$, there is a more gradual decline in the dose curve for rabbits and guinea pigs than there is in the dose curve for man.
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Model Sensitivity Analyses

Basic to the model structure for radial decay in the conducting airways is the treatment of the production of the components of mucus which will react with O₃. Obtaining estimates of these production rates (Appendix B) involved $\bar{K}_o$, the average rate of production per unit area of reaction components. The question arises as to how sensitive are the model estimated doses to the value of $\bar{K}_o$.

Model analyses were conducted in which $\bar{K}_o$ was varied between 100x smaller and 100x larger than the value of $\bar{K}_o$ (standard) used to obtain the figures presented previously. The predicted respiratory bronchial dose in rabbits as a function of $\bar{K}_o$ is shown in Fig. 7. The tracheal O₃ concentration studied, 325 μg/m³, corresponds to an inhaled ambient concentration of 490 μg/m³ (0.25 ppm), after accounting for nasopharyngeal removal of O₃ (Miller, 1977). Alveolar region effects of O₃ have been shown in rabbits exposed to this level (Hurst et al., 1970) and provide a means whereby the biological implications of different predicted doses can be evaluated.

If $\bar{K}_o$ (standard) represents up to a 100-fold overestimation of the correct value, there is no difference in the predicted respiratory bronchiole dose (Fig. 7). Also, a 10-fold underestimation of the correct value of $\bar{K}_o$ yields no appreciable change in respiratory bronchiole dose. Only if the correct value has been underestimated at least 25-fold, does the model predict significantly different O₃ doses for the respiratory bronchioles.

Although not presented, even with a 25 to 100-fold underestima-
regions is still the same. Only the relative location on the dose-axis and the shape of the conducting airway portion of the curve are changed. In the conducting airways, decreasing $K_0$ allows penetration of $O_3$ to the tissue higher in the respiratory tract, but the doses obtained still do not approach in magnitude those predicted for the respiratory bronchioles. Increasing $K_0$ results in less penetration of $O_3$ to conducting airway tissue.

The dose of $O_3$ delivered to conducting airway tissue can also be decreased by increasing the thickness of the mucous layer (Fig. 8). A comparison of Fig. 8 and Fig. 2 reveals that a 25% increase in the thickness of the mucous layer is not sufficient to alter the predicted dose of $O_3$ to the respiratory regions in man. However, in the conducting airways the dose dropped only slightly for higher tracheal $O_3$ concentrations, but dropped significantly at the lower concentrations studied. There may also be a shift in the prediction of the earliest airway generation in which $O_3$ penetrates to the tissue (i.e. generation 14 with increased mucous thickness as compared to generation 12 for a tracheal concentration of 500 $\mu$g/m$^3$).

**Relationship of Inspiratory Duration and Tidal Volume to Deposition**

As an example of the respiratory parameters which can be studied using the model, the roles of inspiratory duration and tidal volume in the determination of $O_3$ uptake in man were examined. For a tidal volume of 500 cc, as the duration of inspiration increases from 1.0 sec to 4.0 sec, the conducting airway dose increases, due to the increased transit time (Fig. 9). However, the respiratory region $O_3$ dose remains essentially the same.
The % uptake of O₃ in the human lung by mucus and airway walls, as a function of tidal volume, is shown in Fig. 10. An inspiratory time of 2.0 sec was used for tidal volumes of 1250 cc or less, while increased respiratory rates associated with a tidal volume of 1500 cc and 1750 cc were accounted for by using inspiratory times of 1.64 and 1.48 sec, respectively (Vander et al., 1970). Figure 10 shows that for a tracheal concentration of 750 μg O₃/m³, as tidal volume increases over the range from 500-1750 cc, the percent uptake of O₃ by respiratory airway tissue doubles from 46% to 92%. There is a gradual decline in the percent uptake of O₃ by mucus and conducting airway tissue as tidal volume increases. Over the range of tidal volumes studied with this tracheal concentration (750 μg O₃/m³), the percent uptake of O₃ by mucus and by conducting airway tissue did not exceed 11% and 5%, respectively.

Table 2 gives additional data concerning the effects of tidal volume on respiratory airway uptake of O₃. There is a plateau in the total O₃ removed in the first generation of respiratory bronchioles as tidal volume increases. However, when considering the uptake of all respiratory areas, the plateau is not present, indicating that alveolar region O₃ doses continue to increase as tidal volume increases. The model predicts a 7-fold increase in the quantity of O₃ removed in the respiratory regions of the lung for a 3.5-fold increase in tidal volume (Table 2).
Discussion

The $O_3$ dose curves obtained in this study by model analysis of the transport and removal of $O_3$ in the lungs of guinea pigs, rabbits, and man indicate that the respiratory bronchioles receive the maximum dose. The model results are in good agreement with experimental findings in various animal species. Stephens et al. (1973) showed that in rats the Type 1 epithelial cells lining the alveoli immediately beyond the terminal bronchioles are particularly sensitive to $O_3$ exposure. These cells were severely damaged or removed from large areas with as little as 2 hrs of exposure to 980 $\mu g$ $O_3/m^3$ (0.5 ppm). After 6-10 hrs of exposure, necrotic ciliated cells were observed free in the lumen of the terminal bronchiole.

In subsequent studies designed to analyze ultrastructural changes and the sequence of events leading to destruction of the Type 1 cell, Stephens et al. (1974) reported that, as the distance from the point of maximal effect increased, the observed damage rapidly decreased, until only mild mitochondrial and cytoplasmic swelling were observed. These investigators concluded that the threshold exposure level in rats is below 980 $\mu g$ $O_3/m^3$ for 2 hrs.

In primates exposed to $O_3$ 8 hrs/day x 7 days, Dungworth et al. (1975) reported that the most obvious and consistent pulmonary lesions were found in respiratory bronchioles. With exposure to 392 $\mu g$ $O_3/m^3$ (0.2 ppm), the lesion was primarily observed in the proximal generation of respiratory bronchioles. The damage extended to include some proximal portions of alveolar ducts when the $O_3$ exposure level was
1568 μg/m³ (0.8 ppm). Emphysematous lesions, characterized by the apparent loss of alveolar walls and the clubbing of their ruptured extremities, and disruption of the epithelial lining in some bronchioles were found in rabbits exposed to 784 μg O₃/m³ (0.4 ppm) over a 10 month period (P'An et al., 1972). Also, a significant mural thickening of small pulmonary arteries was observed.

There is also evidence from human clinical studies that the respiratory bronchioles are the primary target for O₃. Bates et al. (1972) detected significant changes in the following pulmonary function parameters, as a result of 2 hr exposure to 1470 μg O₃/m³ (0.75 ppm): 1) a reduction of the maximum static elastic recoil pressure of the lung, 2) an increase in pulmonary resistance, and 3) a fall in flow rate at 50% of the actual vital capacity. Even more pronounced changes were observed on various pulmonary function parameters when subjects alternated 15 min periods of exercise and rest.

The level of exercise employed was sufficient to increase minute ventilation from 8-10 l/min to 18-20 l/min. If nasopharyngeal removal of O₃ in man should prove to be similar to that for rabbits and guinea pigs, the exposure level used by Bates et al. (1972) would correspond to a tracheal concentration of O₃ of approximately 750 μg/m³ (Miller, 1977). With this concentration and a tidal volume of 1250 cc (sufficient to increase minute ventilation to 18-20 l/min), the model doses given in Table 2 predict that the first generation of respiratory bronchioles receive a 2.39-fold increase in dose, compared to normal respiration. Also, the total O₃ removed by all respiratory regions is more than 4-fold greater.
One should be cognizant that the pulmonary doses presented in this paper were not experimentally determined, but rather were obtained using a mathematical model which incorporates morphometric and chemico-physical data in an analysis of the convective-diffusion equation governing transport and removal of \( \text{O}_3 \) in the lung. Species differences in nasopharyngeal removal of \( \text{O}_3 \) must be taken into account before making comparisons on the effective dose of \( \text{O}_3 \) to various regions of the lung. The best available biological data has been used in this study. Additional information in such areas as, thickness of the mucous layer in man, production rates of reaction components in mucus, and effective axial diffusivities in guinea pigs and rabbits are needed before a more precise prediction can be made of absolute differences in dose between species. However, based upon the model sensitivity analyses that were performed, considerable differences in the data base are needed before the model predicted doses would be affected. Even then, only the relative location on the dose-axis and the shape of the conducting airways portion of the dose curves would be changed.

Previously, Kliment (1973) showed a high degree of similarity of aerosol particle deposition in the lung between guinea pigs, rabbits, rats, and man, suggesting that deposition data may be compared between these species. Of particular importance in the current study is the similarity between guinea pigs, rabbits, and man of the shape of the predicted dose curves associated with exposure to \( \text{O}_3 \). With exposures yielding tracheal \( \text{O}_3 \) concentrations greater than 100 \( \mu \text{g/m}^3 \) (0.05 ppm), the predicted respiratory bronchiole dose for rabbits
was found to be twice that for guinea pigs and 80% of that for man. The consistency and similarity of the dose curves for the three species lend strong support to the validity of extrapolating to man the results obtained on animals exposed to this pollutant.
References


Table 1
Mole Equivalent Concentrations of O₃ Reactants Present in Human Bronchial Mucus

<table>
<thead>
<tr>
<th>Sourceᵃ</th>
<th>Fatty acid</th>
<th>Weight %</th>
<th>moles cm⁻³ x 10⁷</th>
<th>mole equivalents cm⁻³ x 10⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free fatty acids (18.1%)</td>
<td>16:1</td>
<td>4.0</td>
<td>0.450</td>
<td>0.450</td>
</tr>
<tr>
<td></td>
<td>18:1</td>
<td>30.7</td>
<td>3.100</td>
<td>3.100</td>
</tr>
<tr>
<td></td>
<td>18:2</td>
<td>8.0</td>
<td>0.810</td>
<td>1.620</td>
</tr>
<tr>
<td>Triglycerides (39.0%)</td>
<td>16:1</td>
<td>0.6</td>
<td>0.138</td>
<td>0.138</td>
</tr>
<tr>
<td></td>
<td>18:1</td>
<td>8.0</td>
<td>1.660</td>
<td>1.660</td>
</tr>
<tr>
<td></td>
<td>18:2</td>
<td>1.1</td>
<td>0.230</td>
<td>0.460</td>
</tr>
<tr>
<td></td>
<td>20:2</td>
<td>1.8</td>
<td>0.344</td>
<td>0.688</td>
</tr>
<tr>
<td>Cholesterol esters (2.8%)</td>
<td>16:1</td>
<td>8.0</td>
<td>0.056</td>
<td>0.056</td>
</tr>
<tr>
<td></td>
<td>18:1</td>
<td>26.4</td>
<td>0.178</td>
<td>0.178</td>
</tr>
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<td></td>
<td>18:2</td>
<td>37.7</td>
<td>0.255</td>
<td>0.510</td>
</tr>
<tr>
<td></td>
<td>18:3</td>
<td>0.9</td>
<td>0.006</td>
<td>0.018</td>
</tr>
<tr>
<td>Phosphatidylcholine (11.0%)</td>
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<td>1.2</td>
<td>0.053</td>
<td>0.053</td>
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<td></td>
<td>18:1</td>
<td>22.2</td>
<td>0.972</td>
<td>0.972</td>
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<td></td>
<td>18:2</td>
<td>9.2</td>
<td>0.403</td>
<td>0.806</td>
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<tr>
<td>Phosphatidylethanolamine c,d (5.0%)</td>
<td>16:1</td>
<td>1.2</td>
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<td>0.025</td>
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<td></td>
<td>18:1</td>
<td>22.2</td>
<td>0.468</td>
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<td></td>
<td>18:2</td>
<td>9.2</td>
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<td>0.388</td>
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<tr>
<td>Lysophosphatidyl cholines and sphingomyelin d</td>
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<td>18:1</td>
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<td>18:2</td>
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<td>0.085</td>
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<tr>
<td>Histidine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>17.776</td>
</tr>
</tbody>
</table>

ᵃAll data derived from Lewis (1971), except for histidine (Levine et al., 1969; Marshal, 1972; Mudd et al., 1969; and Potter et al., 1963).

ᵇ% of total lipid weight

cThe current study assumes both fatty acids on this phospholipid are the same.

dThe current study assumes the weight % of this phospholipid is the same as that of phosphatidylcholine.
Table 2
Respiratory Airway Uptake of O₃ in Man for Various Tidal Volumes ($V_T$)\(^a\)

<table>
<thead>
<tr>
<th>$V_T$ (cc)</th>
<th>Total $O_3$ Inhaled (µg)</th>
<th>Respiratory Bronchiole(^b) Uptake (µg)</th>
<th>Uptake ($V_T$=500)</th>
<th>All Respiratory Regions Uptake (µg)</th>
<th>Uptake ($V_T$=500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>0.375</td>
<td>0.033</td>
<td>1.00</td>
<td>0.173</td>
<td>1.00</td>
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<td>750</td>
<td>0.5625</td>
<td>0.052</td>
<td>1.58</td>
<td>0.336</td>
<td>1.94</td>
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<tr>
<td>1000</td>
<td>0.75</td>
<td>0.067</td>
<td>2.03</td>
<td>0.522</td>
<td>3.02</td>
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<tr>
<td>1250</td>
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<td>0.079</td>
<td>2.39</td>
<td>0.728</td>
<td>4.21</td>
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<tr>
<td>1500</td>
<td>1.125</td>
<td>0.080</td>
<td>2.42</td>
<td>0.970</td>
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<tr>
<td>1750</td>
<td>1.3125</td>
<td>0.081</td>
<td>2.45</td>
<td>1.210</td>
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</tr>
</tbody>
</table>

\(^a\)750µg $O_3/m^3$ tracheal concentration

\(^b\)First generation of respiratory bronchioles
Figure 1. O₃-mucus reaction cases.
Figure 2. Predicted tissue deposition of ozone for various regions of the human lung.
Figure 3. Uptake of ozone by mucus and airway walls as a function of tracheal concentration of O₃ in the human lung.
Figure 4. Predicted tissue deposition of ozone for various regions of the rabbit lung.
Figure 5. Predicted tissue deposition of ozone for various regions of the guinea pig lung.
Figure 6. Relationship between respiratory bronchiole dose and concentration of ozone in the trachea of guinea pigs, rabbits, and man.
Figure 7. Sensitivity of respiratory bronchiole ozone dose to the average current of mucous reaction components (325 μg O₃/m³ tracheal concentration in rabbits).
Figure 8. Predicted tissue deposition of ozone in the human lung associated with a 25% increase in thickness of the mucous layer.
Figure 9. Effects of duration of inhalation on predicted tissue doses of ozone in the human lung."
Figure 10. Uptake of ozone by mucus and airway walls as a function of tidal volume (750 μg/m$^3$ tracheal concentration in man).
### Appendix A

Morphometric Parameter Values Used in the Model Analyses

**Table A.1**

Values of Model Parameters for Man

<table>
<thead>
<tr>
<th>Model Segment</th>
<th>Length (cm)</th>
<th>Radius (cm)</th>
<th>Cross-sectional area (cm²)</th>
<th>Surface area (cm²)</th>
<th>Volume (cm³)</th>
<th>Protective layer thickness (μ)</th>
<th>Mucous Production Zone</th>
<th>Weibel generation</th>
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</thead>
<tbody>
<tr>
<td>2-13</td>
<td>1.0</td>
<td>0.90</td>
<td>2.50</td>
<td>5.655</td>
<td>2.5</td>
<td>10.0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>14-17</td>
<td>0.927</td>
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<td>2.374</td>
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<td>1</td>
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<td>1.053</td>
<td>0.61</td>
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<td>8.072</td>
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<td>1</td>
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<tr>
<td>19-20</td>
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<td>24</td>
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<td>0.175</td>
<td>3.084</td>
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<td>5</td>
</tr>
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<tr>
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<td>0.14</td>
<td>3.889</td>
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<td>10.0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
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<td>0.115</td>
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<td>Model Segment</td>
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<td>Radius (cm)</td>
<td>Cross-sectional area (cm²)</td>
<td>Surface area (cm²)</td>
<td>Volume (cm³)</td>
<td>Protective layer thickness (μ)</td>
<td>Mucous Production Zone</td>
<td>Weibel generation</td>
</tr>
<tr>
<td>---------------</td>
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<td>-------------</td>
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<td>-------------------</td>
<td>--------------</td>
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Appendix A

Morphometric Parameter Values Used in the Model Analyses

Table A.2
Values of Model Parameters for Rabbits

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<th>Protective layer thickness (µ)</th>
<th>Mucous Production Zone</th>
<th>Morphometric Zone</th>
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<tr>
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<td>0.211</td>
<td>0.614</td>
<td>0.08</td>
<td>10.0</td>
<td>0</td>
<td>Trachea</td>
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</tr>
<tr>
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<td>0.0076</td>
<td>3.264</td>
<td>61.543</td>
<td>0.235</td>
<td>1.0</td>
<td>-</td>
<td>Bronchioles 2</td>
</tr>
<tr>
<td>37-38</td>
<td>0.0465</td>
<td>0.0109</td>
<td>66.344</td>
<td>781.1</td>
<td>3.085</td>
<td>.125</td>
<td>-</td>
<td>Alveolar Ducts</td>
</tr>
<tr>
<td>39-40</td>
<td>0.0465</td>
<td>0.0109</td>
<td>423.226</td>
<td>5086.2</td>
<td>19.68</td>
<td>.125</td>
<td>-</td>
<td>Alveolar Sacs</td>
</tr>
</tbody>
</table>

*a Based on the data of Luchtel (1976)
Appendix A
Morphometric Parameter Values Used in the Model Analyses

Table A.3
Values of Model Parameters for Guinea Pigs

<table>
<thead>
<tr>
<th>Model Segment</th>
<th>Length (cm)</th>
<th>Radius (cm)</th>
<th>Cross-sectional area (cm²)</th>
<th>Surface area (cm²)</th>
<th>Volume (cm³)</th>
<th>Protective layer thickness (µ)</th>
<th>Mucous Production Zone</th>
<th>Morphometric Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-14</td>
<td>0.261</td>
<td>0.105</td>
<td>0.0345</td>
<td>0.172</td>
<td>0.009</td>
<td>10.0</td>
<td>0</td>
<td>Trachea</td>
</tr>
<tr>
<td>15</td>
<td>0.116</td>
<td>0.105</td>
<td>0.0345</td>
<td>0.077</td>
<td>0.004</td>
<td>10.0</td>
<td>0</td>
<td>Trachea</td>
</tr>
<tr>
<td>16-19</td>
<td>0.25</td>
<td>0.068</td>
<td>0.028</td>
<td>0.214</td>
<td>0.007</td>
<td>10.0</td>
<td>1</td>
<td>Bronchi 1</td>
</tr>
<tr>
<td>20-22</td>
<td>0.2733</td>
<td>0.04</td>
<td>0.0256</td>
<td>0.343</td>
<td>0.007</td>
<td>9.0</td>
<td>2</td>
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<tr>
<td>23</td>
<td>0.2053</td>
<td>0.018</td>
<td>0.0390</td>
<td>0.929</td>
<td>0.008</td>
<td>7.5</td>
<td>3</td>
<td>Bronchi 3</td>
</tr>
<tr>
<td>24</td>
<td>0.1797</td>
<td>0.018</td>
<td>0.0390</td>
<td>0.813</td>
<td>0.007</td>
<td>7.5</td>
<td>3</td>
<td>Bronchi 3</td>
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<td>0.1852</td>
<td>1.368</td>
<td>0.009</td>
<td>5.4</td>
<td>4</td>
<td>Bronchi 4</td>
</tr>
<tr>
<td>26-27</td>
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<td>0.014</td>
<td>0.1852</td>
<td>1.216</td>
<td>0.008</td>
<td>5.4</td>
<td>4</td>
<td>Bronchi 4</td>
</tr>
<tr>
<td>28</td>
<td>0.0426</td>
<td>0.0064</td>
<td>0.2346</td>
<td>3.083</td>
<td>0.010</td>
<td>5.1</td>
<td>5</td>
<td>Bronchioles 1</td>
</tr>
<tr>
<td>29</td>
<td>0.0384</td>
<td>0.0064</td>
<td>0.2346</td>
<td>2.779</td>
<td>0.009</td>
<td>5.1</td>
<td>5</td>
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<tr>
<td>30-31</td>
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<td>0.0054</td>
<td>0.4630</td>
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<td>0.0125</td>
<td>1.0</td>
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<tr>
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<td>0.0081</td>
<td>19.7632</td>
<td>21.4</td>
<td>0.3755</td>
<td>.125</td>
<td>-</td>
<td>Alveolar Ducts</td>
</tr>
<tr>
<td>34-35</td>
<td>0.019</td>
<td>0.0081</td>
<td>152.8</td>
<td>179.3</td>
<td>2.9025</td>
<td>.125</td>
<td>-</td>
<td>Alveolar Sacs</td>
</tr>
</tbody>
</table>
Model for Pulmonary Deposition of O₃ - Miller

Appendix B

Production Rate of O₃ Reaction Components in Mucus

To implement the mathematical model, estimates must be obtained for K, the effective production rate at the airway wall of the components of mucus with which O₃ will react. In view of the type of data in the literature, K was assumed to decrease linearly between the trachea and the terminal bronchioles. The following notation will be useful in examining how estimates of K were obtained:

\[ K_j = \text{for the } j\text{ th mucous zone, the effective production (current) at the airway wall of the components of mucus which will react with O}_3 \text{ (moles/cm}^2\text{-sec)} \]

\[ S_j = \text{total airway surface area (cm}^2\text{) of the } j\text{ th zone} \]

\[ a_0 = \text{total airway surface area (cm}^2\text{) from the terminal bronchioles (zone 5) to the trachea (zone 0)} \]

\[ Q_0 = \text{total flux of mucous reaction components out of the trachea (moles/sec)} \]

\[ \overline{K}_0 = \text{average rate of production per unit area of reaction components (moles/cm}^2\text{-sec)} \]

With the above definition of terms, it is immediately apparent that

\[ (B-1) \quad a_0 = \sum_{j=0}^{5} S_j \]

and

\[ (B-2) \quad \overline{K}_0 = \frac{Q_0}{a_0} = \frac{1}{a_0} \sum_{j=0}^{5} K_j S_j \]

The assumption that the relationship between morphometric zone and production of mucous reaction components will be considered linear yields
Model for Pulmonary Deposition of O₃ - Miller

Appendix B (continued)

(B-3) \( K_j = \alpha + \beta j \quad j=0,1,\ldots,6 \)

Since there is no production of mucus in the respiratory bronchioles,

(B-4) \( K_6 = 0 \)

Using eqs. (B-3) and (B-4) to substitute for \( K_j \) in eq. (B-2) yields

\[
\bar{K}_0 = \frac{1}{a_0} \sum_{j=0}^{5} (\alpha + \beta j)S_j
\]

\[
= \frac{\alpha}{a_0} \sum_{j=0}^{5} S_j + \frac{\beta}{a_0} \sum_{j=0}^{5} jS_j
\]

(B-5) \( \bar{K}_0 = \alpha + \frac{\beta}{a_0} \sum_{j=0}^{5} jS_j \)

Toremalm (1960) measured total tracheal production of mucus in laryngectomized patients as 10 ml/24 hr (i.e. 6.944 x 10⁻³ cm³/min). Since velocity x area equals volume/unit time, a production rate of 6.944 x 10⁻³ cm³/min corresponds to a velocity, \( V \), of 0.0205 cm/sec. Using this velocity and 17.78 x 10⁻⁷ moles/cm³ as the concentration of O₃ reactants in mucus (Table 1), the \( Q_0/a_0 \) representation of \( \bar{K}_0 \) can be used to obtain \( \bar{K}_0 = 3.3 \times 10⁻¹⁴ \) moles/cm²-sec. With this estimate of \( \bar{K}_0 \) and the restriction that there is no production of mucus in the respiratory bronchioles (zone 6), eqs. (B-3) - (B-5) can be used to solve for \( \alpha \) and \( \beta \).

Mucus flow in rats has been studied by Dalhamn (1956) and by Irvani and van As (1972). The tracheal velocity of mucus averaged 0.0225 cm/sec in Dalhamn's studies, while Irvani and van As observed rates which varied from 0.0192 cm/sec in the upper portion of the
lobar bronchus to approximately 0.0067 cm/sec in preterminal bronchioles. Irvani and van As (1972) state that similar results have been obtained with golden hamsters and rabbits. Thus, it would appear that, at least as far as the trachea is concerned, there is evidence to indicate comparable mucous velocities in these animals and man. At present, there is no data available for these animal species on the concentration of mucous components which will react with O₃.

In view of the above facts, the assumption was made that the average rate of production per unit area of mucous reaction components is the same for the three species considered in this study. Additional experimental data is needed to judge the validity of this assumption.

Using $K_0 = 3.3 \times 10^{-14}$ moles/cm²·sec, and eqs. (B-3) - (B-5) estimates of $\alpha$ and $\beta$ were determined as:

<table>
<thead>
<tr>
<th>Species</th>
<th>$\alpha \times 10^{14}$</th>
<th>$\beta \times 10^{14}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbits</td>
<td>10.22</td>
<td>-1.70</td>
</tr>
<tr>
<td>Guinea pigs</td>
<td>7.51</td>
<td>-1.25</td>
</tr>
<tr>
<td>Man</td>
<td>9.69</td>
<td>-1.61</td>
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</table>