Longitudinal distribution of chlorine absorption in human airways: a comparison to ozone absorption
Vladislav Nodelman and James S. Ultman

You might find this additional info useful...

This article cites 13 articles, 8 of which can be accessed free at:
/content/87/6/2073.full.html#ref-list-1

This article has been cited by 4 other HighWire hosted articles

Particle capture into the lung made simple?
Talita Felipe de Vasconcelos, Bernard Sapoval, José S. Andrade, Jr., James B. Grotberg, Yingying Hu and Marcel Filoche
[Abstract] [Full Text] [PDF]

Elucidating mechanisms of chlorine toxicity: reaction kinetics, thermodynamics, and physiological implications
Giuseppe L. Squadrito, Edward M. Postlethwait and Sadis Matalon
[Abstract] [Full Text] [PDF]

Inhibition of Lung Fluid Clearance and Epithelial Na⁺ Channels by Chlorine, Hypochlorous Acid, and Chloramines
Weifeng Song, Shipeng Wei, Yongjian Zhou, Ahmed Lazrak, Gang Liu, James D. Londino, Giuseppe L. Squadrito and Sadis Matalon
[Abstract] [Full Text] [PDF]

Ozone absorption in the human nose during unidirectional airflow
Lizzie Y. Santiago, Matthew C. Hann, Abdellaziz Ben-Jebria and James S. Ultman
[Abstract] [Full Text] [PDF]

Updated information and services including high resolution figures, can be found at:
/content/87/6/2073.full.html

Additional material and information about Journal of Applied Physiology can be found at:
http://www.the-aps.org/publications/jappl

This information is current as of August 19, 2014.
Longitudinal distribution of chlorine absorption in human airways: a comparison to ozone absorption

VLADISLAV NODELMAN AND JAMES S. ULTMAN
Biomolecular Transport Dynamics Laboratory, Department of Chemical Engineering, Pennsylvania State University, University Park, Pennsylvania 16802

Nodelman, Vladislav, and James S. Ultman. Longitudinal distribution of chlorine absorption in human airways: a comparison to ozone absorption. J. Appl. Physiol. 87(6): 2073–2080, 1999.—The bolus inhalation method was used to measure the fraction of inhaled chlorine (Cl2) and ozone (O3) absorbed during a single breath as a function of longitudinal position in the respiratory system of 10 healthy nonsmokers during oral and nasal breathing at respired flows of 150, 250, and 1,000 ml/s. At all experimental conditions, <5% of inspired Cl2 penetrated beyond the upper airways and none reached the respiratory air spaces. On the other hand, larger penetrations of O3 beyond the upper airways occurred as flow increased and during nasal than during oral breathing. In the extreme case of oral breathing at 1,000 ml/s, 35% of inhaled O3 penetrated beyond the upper airways and ~10% reached the respiratory air spaces. Mass transfer theory indicated that the diffusion resistance of the tissue phase was negligible for Cl2 but important for O3. The gas phase resistances were the same for Cl2 and O3 and were directly correlated with the volume of the nose and mouth during nasal and oral breathing, respectively.

Air pollution; inhalation toxicology; lung dosimetry; mass transfer coefficient; regional uptake

CHLORINE (Cl2) and ozone (O3) are gaseous pollutants that can irritate the human respiratory tract. The time-weighted exposure limit of Cl2 and O3 exposure for an 8-h work shift are 0.5 and 0.1 parts per million (ppm) by volume, respectively (1). Short-term exposure of volunteers to Cl2 concentrations as low as 1.0 ppm and O3 concentrations as low as 0.12 ppm can cause decrements in forced vital capacity and forced expiratory volume in 1 s (11, 14). Although the health effects of long-term Cl2 and O3 exposure in humans have not been determined, nonneoplastic lesions have been observed in animals chronically exposed to O3 or Cl2. In rats and monkeys, airway lesions resulting from Cl2 exposure were focused primarily in the nasal cavities (10, 16), whereas lesions resulting from O3 exposure were observed in alveolated air spaces (2, 4). It is possible that these differences in lesion distribution were due to corresponding differences between the uptake patterns of Cl2 and O3.

The uptake of O3 has been determined by direct sampling of respired gas within the human respiratory tract (5, 6). These experiments made use of indwelling tubes that limited measurements to only a few large airway sites and undoubtedly disturbed local flow and concentration profiles. To circumvent these problems, the distribution of O3 uptake in the human respiratory tract can be noninvasively measured by bolus inhalation, an indirect method that utilizes gas sampling at the airway opening alone (7). Bolus inhalation measurements indicated that the portion of inhaled O3 absorbed in the upper airways of healthy adult nonsmokers is 80% during quiet nasal breathing compared with 50% during quiet oral breathing. In neither case did O3 reach the respiratory air spaces (9). When oral flow was increased to a light exercise condition of 1,000 ml/s, however, 25% of inhaled O3 reached the respiratory air spaces (8). Recently, the bolus inhalation method was adapted to Cl2. During nasal and oral quiet breathing, >90% of inhaled Cl2 was absorbed in the upper airways of healthy nonsmokers (12).

In the present work the longitudinal distributions of Cl2 and O3 were directly compared in the same group of healthy nonsmokers during nasal and oral breathing at respiratory flows of 150, 250, and 1,000 ml/s. Because O3 is a poorly soluble gas whereas Cl2 rapidly and reversibly hydrolyzes in aqueous solution, it is hypothesized that increasing the respiratory flow will increase the amount of O3 but not Cl2 that reaches the respiratory air spaces during either mode of breathing. The availability of uptake data from these two gases of widely different solubilities also provides an opportunity to study the relative role of their gas phase and mucus phase diffusion resistances. Although a bolus inhalation study of O3 uptake during oral breathing at 150–1,000 ml/s has been carried out (8), it is important to repeat these experiments on the same group of subjects and with the identical breathing apparatus used to obtain the Cl2 bolus inhalation data.

MATHEMATICAL MODELING

As previously described by Nodelman and Ultman (12), the human airways were modeled as a series of nasal/oral (N/O), pharyngeal (PH), lower airway (LA), and respiratory air space (RA) compartments. On the basis of a simplified solution of the one-dimensional unsteady diffusion equation, Hu and associates (8) derived the relationship between the absorbed fraction (\(\Lambda\)) and the penetration volume (\(V_P\)) of a reactive gas bolus inhaled into such a compartmental model. For ease in applying a linear regression analysis, this relationship can be expressed as follows

\[
\ln(1 - \Lambda) = - 2(V_P) (Ka)_{N/O} (V_{PO} - V_P) + I_1 [(Ka)_{PH} - (Ka)_{N/O}] (V_{PI} - V_P) + I_2 [(Ka)_{LA} - (Ka)_{PH}] (V_{P2} - V_P)
\]

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

http://www.jap.org 8750-7587/99 $5.00 Copyright © 1999 the American Physiological Society
where \( \dot{V} \) is the respiratory flow rate and \((K_a)_{i}\) is the product of an overall mass transfer coefficient \((K)\) and the surface-to-volume ratio \((a)\) in compartment \(i\) (i.e., N/O, PH, or LA). \(V_{P0}, V_{P1},\) and \(V_{P2}\) are the penetration volumes that correspond to the entrance of the N/O, PH, and LA compartments, respectively. \(I_1\) and \(I_2\) are indicator variables defined as follows: \(I_1 = 1\) if \(V_p > V_{P1}\), and \(I_1 = 0\) otherwise; \(I_2 = 1\) if \(V_p > V_{P2}\), and \(I_2 = 0\) otherwise. The RA compartment has been omitted from Eq. 1, because the reactive gas reaching this compartment was never sufficient to allow a reliable estimation of \((K_a)_{RA}\).

The local absorption of \(Cl_2\) and \(O_3\) can be better understood by considering the individual factors that contribute to \(K_a\). As \(Cl_2\) or \(O_3\) absorbs into an airway (or air space), it encounters a diffusion resistance created by a respiratory gas boundary layer and a second resistance imposed by the surrounding mucus (or surfactant) film. The overall resistance to mass transfer within a compartment is equal to the sum of these diffusion resistances (15)

\[
1/Ka = 1/k_g a + \lambda/k_{ti} a
\]

where \(k_g\) and \(k_i\) are the individual mass transfer coefficients in the gas boundary layer and the mucus layer, respectively, and \(\lambda\) is the equilibrium partition coefficient of \(Cl_2\) or \(O_3\) concentration between gas and mucus. Of particular importance is the fact that \(k_g\) depends on the geometry and gas flow in the airway lumen.

The value of \(k_g\) in a specific geometry is often predicted from equations of the following form (15)

\[
Sh = m' Re^n Sc^p
\]

where \(m', n,\) and \(p\) are constants. As applied to radial absorption of \(Cl_2\) or \(O_3\) in an airway, the Sherwood (Sh), Reynolds (Re), and Schmidt (Sc) numbers are dimensionless groups defined by

\[
Sh = k_g d/D_g, \quad Re = \dot{V}d/A, \quad Sc = \nu/D_g
\]

where \(d\) is the airway diameter, \(A\) is the cross section available for flow, \(D_g\) is the binary diffusivity of \(Cl_2\) or \(O_3\) in air, and \(\nu\) is the kinematic gas viscosity. Combining Eqs. 3 and 4 results in

\[
k_g = m\dot{V}^n d^{-1}/A^n
\]

where

\[
m = m'D_g^{1-p} \nu^{p-n}
\]

The value of \(\nu\) can be approximated by the viscosity of pure air, \((D_g)/(D_g)_{air}\), is estimated to be 0.8 (15), and \(p = 0.8-1.3\) in human airways (13). It follows from Eq. 6 that \(m\) has similar values for \(Cl_2\) and \(O_3\) and from Eq. 5 that \(k_g\) is essentially the same for the two gases. In addition, the average value of \(n\) for inspiration and expiration is close to unity (13), so Eq. 5 may be approximated as

\[
(k_g a/V) = (ma/A)
\]

where \(m\) can be considered to be a constant, whereas \(a\) and \(A\) depend on compartment geometry.

Because \(k_a a/V\) is essentially the same for both test gases, Eq. 2 can be simultaneously applied to \(Cl_2\) and \(O_3\)

\[
1/Ka = (\dot{V}/k_g a)(1/V) + (K_a/\lambda a)_{Cl21} + (K_a/\lambda a)_{O3}(1 - l)
\]

where \(l = 1\) when \(K_a\) corresponds to \(Cl_2\) absorption and \(l = 0\) when \(K_a\) refers to \(O_3\) absorption. Within a particular airway compartment of a particular subject, Eq. 7 implies that \(k_a a/V\) is constant, and Eq. 8 further implies that plots of \(1/Ka\) vs. \(1/V\) for \(Cl_2\) and for \(O_3\) should be parallel lines with a common slope of \(V_k a\) but different intercepts of \((K_a a)_{Cl21}\) and \((K_a a)_{O31}\), respectively.

**METHODS**

Subject population. Five healthy men and five healthy nonpregnant women, all nonsmokers with no history of cardiovascular, pulmonary, and upper airway disease or allergy, were accepted in the investigation. For each subject, nasal volume (\(V_{NS}\)) and cross-sectional area \((A_{NS})\), oral volume \((V_{OR})\) and cross-sectional area \((A_{OR})\), and pharyngeal volume \((V_{PH})\) and cross-sectional area \((A_{PH})\) were measured by acoustic reflection. Conducting airway volume \((V_D)\) was determined by single-breath nitrogen washout during oral breathing. Lower conducting airway volume \((V_{LA})\) was defined as \(V_D - (V_{OR} + V_{PH})\). The subjects in this study were the same as those in a study of \(Cl_2\) uptake during quiet breathing, for which more detailed descriptions of the screening procedures and the respiratory system volume measurements were previously reported (12). All procedures employed in the present experiments, including the informed consent of each subject, were approved by the Institutional Review Board of the Pennsylvania State University.

Bolus measurements. The bolus inhalation apparatus consisted of a custom-designed Teflon breathing assembly that monitored respiratory flow and \(Cl_2\) and \(O_3\) concentration and injected boluses containing a peak pollutant concentration of 3.0 ppm \(Cl_2\) or 1.0 ppm \(O_3\). A mouthpiece or a nasal cannula fixture could be attached to the proximal end of the breathing assembly for oral or nasal breathing maneuvers, respectively. The volume of both fixtures was 20 ml. The detailed design and performance of the bolus inhalation system were described previously (12). The only modification of the apparatus made in this study was the use of a larger heated pneumotachometer (model 4719, Hans Rudolph) to monitor respired flow in the 1,000 ml/s experiments than was used in the previous quiet breathing experiments.

During a research session, the subject was seated comfortably on a stool, wore noseclips during oral breathing, and maintained a closed mouth during nasal breathing. To carry out a bolus test breath, the subject donned the mouthpiece or nasal cannula, activated the inhalation apparatus by depressing a hand-held switch, and inhaled beginning at functional residual capacity while viewing a computer monitor on which the integrated pneumotachometer signal (i.e., the respired volume) was displayed in real time. Throughout the breath, the subject corrected his or her respiratory flow rate so that respired volume coincided, as closely as possible, with a predrawn isosceles triangle corresponding to equal inspiratory and expiratory flows of 150, 250, or 1,000 ml/s and an inhaled tidal volume of 500 ml. At a predetermined time during inhalation, a \(Cl_2\)-air or \(O_3\)-air bolus was automatically injected into the inspiratory flow. Because the subject always

---

This text is a detailed explanation of the respiratory absorption of chlorine and ozone in human airways, focusing on the methodology and mathematical models used to predict the absorption rates. It includes descriptions of the experimental setup, subject selection, and the specific calculations used to determine absorption rates under various conditions. The text is rich with scientific notation and equations, typical of academic research in the field of respiratory physiology.
began a test breath at functional residual capacity, the penetration of the bolus into the respiratory system could be systematically varied from breath to breath by changing the injection time. A complete experiment consisted of 50–70 bolus test breaths recorded at penetrations of 0–200 ml. All 10 subjects participated in six sessions lasting 2–4 h, in which Cl$_2$ or O$_3$ bolus measurements were made during nasal and oral breathing at a fixed respired flow of 150, 250, or 1,000 ml/s. For each subject, a Cl$_2$ session at 250 ml/s was carried out first. This was followed by Cl$_2$ sessions at 150 and 1,000 ml/s that were performed in an order that was randomized among subjects. The same sessions were then repeated using O$_3$ as a test gas. Within each session, the order of nasal and oral experiments was randomized, and bolus test breaths were carried out at increasing penetrations in some experiments and at decreasing penetrations in other experiments. To minimize carryover of exposure effects, each session was separated by ≥1 wk.

Data analysis. As previously described in detail (12), the Cl$_2$ and O$_3$ concentration curves of each bolus test breath were numerically integrated with respect to respired volume. The fraction of inhaled Cl$_2$ or O$_3$ that was absorbed within each of the five compartments ($\Delta \Lambda$), the $\Lambda$ values of Cl$_2$ or O$_3$ at the proximal boundaries of the PH, LA, and RA compartments were first calculated from Eq. 1. $\Lambda$ values within a compartment was then calculated as the difference between the $\Lambda$ values of Cl$_2$ or O$_3$ at the distal and proximal boundaries of the compartment.

A two-tailed Student’s t-test was used to compare parameter values between different experimental conditions. Comparisons were made only if at least eight values were available at each condition. Paired comparisons were made when values for all 10 subjects were available in both compared conditions. Otherwise, an unpaired comparison was made. The risk of making a type I error in the comparisons was controlled at $\alpha = 0.05$.

RESULTS

Characteristics of subjects. The anthropometric characteristics of the 10 healthy, young, adult nonsmokers who participated in the study are given elsewhere (12), and their compartmental volumes and average cross-sectional areas are given in Table 1. Whereas $V_{\text{NS}}$ was somewhat smaller than $V_{\text{OR}}$ ($P = 0.18$) for the subject population as a whole, there was no correlation between $V_{\text{NS}}$ and $V_{\text{OR}}$ (coefficient of determination adjusted for number of subjects $r^2 = 0.00$). The values of $V_{\text{OR}}$ and $A_{\text{OR}}$ for different subjects were highly correlated ($r^2 = 0.85$), the values of $V_{\text{PH}}$ and $A_{\text{PH}}$ were reasonably correlated ($r^2 = 0.50$), but the values of $V_{\text{NS}}$ and $A_{\text{NS}}$ were not correlated ($r^2 = 0.00$).

Absorbed fraction. In Fig. 2 the $\Lambda$-$V_p$ distributions are pooled for all participants at each experimental condition. On average, Cl$_2$ was absorbed more efficiently than O$_3$ during nasal and oral breathing. Furthermore, the difference between the absorption efficiency of Cl$_2$ and O$_3$ increased with increasing respiratory flow rate during nasal and oral breathing. For example, during nasal breathing at a respiratory flow rate of 150 ml/s, values of $\Lambda$ at the proximal end of the pharynx in an average subject (i.e., $V_p = 64$ ml)

---

Table 1. Compartmental dimensions of the study population

<table>
<thead>
<tr>
<th>$V_{\text{OR}}$, ml</th>
<th>$V_{\text{NS}}$, ml</th>
<th>$V_{\text{PH}}$, ml</th>
<th>$V_{\text{LA}}$, ml</th>
<th>$A_{\text{OR}}$, cm$^2$</th>
<th>$A_{\text{NS}}$, cm$^2$</th>
<th>$A_{\text{PH}}$, cm$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>54 ± 20</td>
<td>44 ± 4</td>
<td>22 ± 10</td>
<td>78 ± 26</td>
<td>5.3 ± 1.7</td>
<td>2.4 ± 0.4</td>
</tr>
<tr>
<td>Range</td>
<td>22–80</td>
<td>37–51</td>
<td>8–37</td>
<td>41–114</td>
<td>2.7–8.2</td>
<td>1.9–3.2</td>
</tr>
</tbody>
</table>

$V_{\text{OR}}$, combined volume of oral cavity and oropharynx (OR); $V_{\text{NS}}$, combined volume of nasal cavities and nasopharynx (NS); $V_{\text{PH}}$, volume of hypopharynx (PH); $V_{\text{LA}}$, volume of lower conducting Airways ($V_{\text{D}} - V_{\text{OR}} - V_{\text{PH}}$; LA); $A_{\text{OR}}$, average cross-sectional area (i.e., ratio of volume to length) of OR compartment; $A_{\text{NS}}$, average cross-sectional area of NS compartment; $A_{\text{PH}}$, average cross-sectional area of PH compartment.
were −0.95 for Cl₂ and 0.90 for O₃. When the respiratory flow was increased to 1,000 ml/s, Λ decreased to 0.90 for Cl₂ and 0.45 for O₃. Similarly, during oral breathing at 150 ml/s, the values of Λ at the proximal end of the pharynx in an average subject (i.e., V_P = 74 ml) were 0.95 for Cl₂ and 0.80 for O₃, but Λ decreased to 0.85 for Cl₂ and 0.25 for O₃ when the respiratory flow increased to 1,000 ml/s.

Figure 2 also indicates that Cl₂ absorption was similar during nasal and oral breathing but O₃ absorption was more efficient during nasal breathing, particularly at the higher respiratory flows. For example, Λ for Cl₂ at the proximal boundary of the pharynx was 0.95 during nasal and oral breathing at 150 ml/s and 0.90 during nasal breathing and 0.85 during oral breathing at 1,000 ml/s. In contrast, the corresponding values of Λ for O₃ were 0.90 during nasal breathing and 0.80 during oral breathing at 150 ml/s and 0.45 during nasal breathing and 0.25 during oral breathing at 1,000 ml/s. As a result, a higher dose of inspired Cl₂ was absorbed in the NS and OR compartments, respectively, and <1% of the inspired Cl₂ was absorbed in the RA. The dose distribution of O₃, however, changed substantially: only 45 and 25% of the inspired O₃ was absorbed in the NS and OR compartments, respectively, and 5–10% of the inspired O₃ was absorbed in the RA.

Mass transfer coefficients. Table 2 summarizes the Ka values that were calculated from the individual regression of each subject’s Λ−V_p distribution. At all three respiratory flow rates, the values of Ka for Cl₂ were significantly higher for Cl₂ than for O₃ in the NS and OR compartments (P < 0.04), but not in the PH and LA compartments (P > 0.1). Furthermore, the values of Ka for O₃ were always significantly higher in the NS compartment than in the OR compartment (P < 0.02) but were similar in the PH compartment during both modes of breathing (P > 0.2). In contrast, the Ka values for Cl₂ were larger in the NS compartment than in the OR compartment at the higher respiratory flow rates (P < 0.04), but not at the lowest respiratory flow (P = 0.5). Because of extensive absorption of Cl₂ and O₃ in
the proximal compartments, there was a paucity of $\Lambda-V_P$ data in the PH and LA compartments, resulting in large uncertainties in the $K_a$ values. In some subjects, there were insufficient data to even compute $K_a$ in the PH and LA compartments.

Table 3 summarizes the values of the gas phase absorption parameter ($k_{ga}/V$) and the mucus phase absorption parameter ($k_{ta}/l$) that were estimated by regression of each subject’s $K_a$ values in the NS, OR, and PH compartments according to Eq. 8. Because of extensive absorption in the NS and OR compartments, however, the $K_a$ data were only sufficient to compute absorption parameters for the PH compartment in one subject during nasal breathing and two subjects during oral breathing. Theoretically, $k_{ga}/V$ is essentially the same for Cl$_2$ and O$_3$, but $k_{ta}/l$ can have separate values for the two gases. In fact, the value of $(\lambda/k_{ta})$ was so small that the tissue phase did not limit the rate of Cl$_2$ absorption. On the other hand, $k_{ta}/l$ did have a significant effect on O$_3$ absorption. As suggested by the standard deviations in Table 3, there was no significant difference between $k_{ga}/V$ values in the NS and OR compartments ($P = 0.9$), but the value of $k_{ta}/l$ was larger in the NS compartment than in the OR compartment ($P = 0.09$).

**DISCUSSION**

The primary objective of this research was to determine how the physical-chemical properties of Cl$_2$ and O$_3$ affect their uptake distributions in the intact respiratory tract. To be absorbed into the epithelial lining fluid (ELF), both gases must overcome the in-series diffusion resistances of the respired gas and adjacent liquid film (Eq. 2). Because both gases have similar diffusion coefficients in respired air, their gas phase diffusion resistances should be similar, an expectation that is illustrated by the parallelism of the lines in the $(1/Ka)-(1/V)$ correlation (Fig. 1). It follows that differences between the absorption rates of these two gases are due to their interactions with the ELF.

The physical solubilities of Cl$_2$ and O$_3$ in ELF are low, but Cl$_2$ reacts with water to form hypochlorous and hydrochloride acids, whereas O$_3$ irreversibly oxidizes biochemical substrates such as albumin, fatty acids, urate, and ascorbate. Because of the abundance of...
Because the liquid phase diffusion resistance of Cl₂ is so small, the absorption rate of Cl₂ is generally limited by gas phase diffusion, which is proportional to respiratory flow rate. This is exactly counterbalanced by the inverse dependence of bolus residence time on respiratory flow rate, explaining why the \( \Delta V_f \) distribution for Cl₂ is relatively insensitive to respiratory flow (Fig. 2). On the other hand, the O₃ absorption rate is sensitive to diffusion through ELF, which is independent of respiratory flow rate. Therefore, a progressive reduction of absorption occurs in the proximal airways as increases in respiratory flow shorten the residence time of a bolus. This is the basis of the progressive distal shift of the O₃ distribution that occurs as respiratory flow rate increases.

At the lowest nasal respiratory flow of 150 ml/min, the gas phase diffusion resistances of Cl₂ and O₃ dominate their liquid phase resistances, so that the \( \Delta V_f \) distributions for the two gases are similar (Fig. 2). During an oral flow of 150 ml/min, however, a significant resistance of O₃ diffusion through ELF causes a distal shift of the O₃ distribution relative to the corresponding Cl₂ distribution. Because the saliva in the mouth probably lacks much of the antioxidant capacity of nasal mucus, it is not surprising that the diffusion resistance of O₃ is more important in the mouth than in the nose. The hydrolysis of Cl₂, on the other hand, should suppress the diffusion resistance of the liquid film in the nose and the mouth.

The specific values of the liquid phase resistance (\( \lambda/k_a\)) for O₃ were 0.042 s in the nasal compartment and 0.18 s in the oral compartment, whereas \( \lambda/k_a \) values estimated for Cl₂ were not significantly different from zero. Because of this, the gas phase resistance of Cl₂ accounted for 100% of the overall diffusion resistance in the nasal and oral compartments at all respiratory flow rates. On the other hand, the gas phase resistance of O₃ at respiratory flow rates of 150, 250, and 1,000 ml/s made contributions to the overall nasal diffusion resistance of 86, 79, and 49%, respectively, and contributions to the overall oral diffusion resistance of 64, 51, and 21%, respectively.

### Table 2. Compartmental values of the overall absorption parameters

<table>
<thead>
<tr>
<th>Flow, ml/s</th>
<th>((K_a)_{Cl_2}), s⁻¹</th>
<th>((K_a)_{O_3}), s⁻¹</th>
<th>((K_a)_{LA}), s⁻¹</th>
<th>(V_{P0}), ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>3.4 ± 0.4</td>
<td>1.2 ± 1.2</td>
<td>0.6 ± 0.1</td>
<td>2.5 ± 5.2</td>
</tr>
<tr>
<td>250</td>
<td>6.2 ± 0.8</td>
<td>1.0 ± 1.0</td>
<td>0.7 ± 0.6</td>
<td>7.7 ± 2.6</td>
</tr>
<tr>
<td>1,000</td>
<td>25.3 ± 5.5</td>
<td>6.8 ± 7.7</td>
<td>15.6 ± 5.4</td>
<td></td>
</tr>
</tbody>
</table>

Because the liquid phase diffusion resistance of Cl₂ is so small, the absorption rate of Cl₂ is generally limited by gas phase diffusion, which is proportional to respiratory flow rate. This is exactly counterbalanced by the inverse dependence of bolus residence time on respiratory flow rate, explaining why the \( \Delta V_f \) distribution for Cl₂ is relatively insensitive to respiratory flow (Fig. 2). On the other hand, the O₃ absorption rate is sensitive to diffusion through ELF, which is independent of respiratory flow rate. Therefore, a progressive reduction of absorption occurs in the proximal airways as increases in respiratory flow shorten the residence time of a bolus. This is the basis of the progressive distal shift of the O₃ distribution that occurs as respiratory flow rate increases.

At the lowest nasal respiratory flow of 150 ml/min, the gas phase diffusion resistances of Cl₂ and O₃ dominate their liquid phase resistances, so that the \( \Delta V_f \) distributions for the two gases are similar (Fig. 2). During an oral flow of 150 ml/min, however, a significant resistance of O₃ diffusion through ELF causes a distal shift of the O₃ distribution relative to the corresponding Cl₂ distribution. Because the saliva in the mouth probably lacks much of the antioxidant capacity of nasal mucus, it is not surprising that the diffusion resistance of O₃ is more important in the mouth than in the nose. The hydrolysis of Cl₂, on the other hand, should suppress the diffusion resistance of the liquid film in the nose and the mouth.

The specific values of the liquid phase resistance (\( \lambda/k_a\)) for O₃ were 0.042 s in the nasal compartment and 0.18 s in the oral compartment, whereas \( \lambda/k_a \) values estimated for Cl₂ were not significantly different from zero. Because of this, the gas phase resistance of Cl₂ accounted for 100% of the overall diffusion resistance in the nasal and oral compartments at all respiratory flow rates. On the other hand, the gas phase resistance of O₃ at respiratory flow rates of 150, 250, and 1,000 ml/s made contributions to the overall nasal diffusion resistance of 86, 79, and 49%, respectively, and contributions to the overall oral diffusion resistance of 64, 51, and 21%, respectively.

### Table 3. Compartmental values of the individual absorption parameters

<table>
<thead>
<tr>
<th>Gender</th>
<th>((k_a/V)_{Cl_2}), liters⁻¹</th>
<th>((k_a/V)_{O_3}), liters⁻¹</th>
<th>((k_a/\lambda)_{Cl_2}), s⁻¹</th>
<th>((k_a/\lambda)_{O_3}), s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>male (m)</td>
<td>22 ± 1</td>
<td>27 ± 3</td>
<td>13 ± 3</td>
<td>35 ± 38</td>
</tr>
<tr>
<td>m</td>
<td>25 ± 4</td>
<td>31 ± 9</td>
<td>16 ± 10</td>
<td>8 ± 7</td>
</tr>
<tr>
<td>m</td>
<td>27 ± 3</td>
<td>28 ± 2</td>
<td>10 ± 3</td>
<td>11 ± 30</td>
</tr>
<tr>
<td>m</td>
<td>34 ± 9</td>
<td>16 ± 1</td>
<td>10 ± 2</td>
<td>11 ± 30</td>
</tr>
<tr>
<td>m</td>
<td>26 ± 5</td>
<td>13 ± 1</td>
<td>16 ± 11</td>
<td>4 ± 5</td>
</tr>
<tr>
<td>m</td>
<td>24 ± 3</td>
<td>15 ± 1</td>
<td>11 ± 7</td>
<td>4 ± 5</td>
</tr>
<tr>
<td>f</td>
<td>24 ± 3</td>
<td>15 ± 1</td>
<td>11 ± 7</td>
<td>4 ± 5</td>
</tr>
<tr>
<td>female (f)</td>
<td>23 ± 1</td>
<td>19 ± 4</td>
<td>10 ± 2</td>
<td>11 ± 30</td>
</tr>
<tr>
<td>f</td>
<td>24 ± 3</td>
<td>16 ± 1</td>
<td>16 ± 11</td>
<td>4 ± 5</td>
</tr>
<tr>
<td>f</td>
<td>26 ± 4</td>
<td>23 ± 4</td>
<td>11 ± 7</td>
<td>4 ± 5</td>
</tr>
<tr>
<td>f</td>
<td>22 ± 4</td>
<td>22 ± 1</td>
<td>11 ± 7</td>
<td>4 ± 5</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>25 ± 2</td>
<td>21 ± 7</td>
<td>11 ± 4</td>
<td>35 ± 9, 5 ± 25</td>
</tr>
</tbody>
</table>

Values are means ± SD of absorption parameters computed by averaging individual values from all subjects. \((k_a/V)_{Cl_2}\), gas phase absorption parameter for Cl₂ and O₃ in nasal cavity and nasopharynx during nasal breathing or in oral cavity and oropharynx during oral breathing; \((k_a/V)_{O_3}\), gas phase absorption parameter for Cl₂ and O₃ in PH; \((k_a/\lambda)_{Cl_2}\) and \((k_a/\lambda)_{O_3}\), corresponding tissue absorption parameters that apply to O₃ only.
Although \( K_a \) values in the nose and mouth were generally larger for \( \text{Cl}_2 \) than for \( \text{O}_3 \), most paired comparisons of \( K_a \) values in the PH and LA compartments showed a lack of significant differences between \( \text{Cl}_2 \) and \( \text{O}_3 \). A post hoc power analysis indicated, however, that the probability of a type II error (i.e., falsely concluding that the values of \( K_a \) for \( \text{Cl}_2 \) and \( \text{O}_3 \) were similar) was \( \sim 0.75 \). Reduction of this probability to an acceptable level of 0.2 would require testing approximately twice as many subjects or improving the precision of the test breath concentration data, possibly by increasing the peak inhaled bolus concentration.

A substantial dose of \( \text{O}_3 \) was absorbed in the LA compartment under all experimental conditions and in the RA compartment during oral breathing at the highest respiratory flow rate of 1,000 ml/s (Fig. 3). This suggests that an increase in respiratory flow coupled with a switch from nasal to oral breathing, as normally occurs during exercise, is likely to cause a distal shift in the \( \text{O}_3 \) dose distribution, which increases the likelihood of damage to alveolar and bronchiolar tissues. In contrast, inspired \( \text{Cl}_2 \) was primarily absorbed in the NS and OR compartments. Even during oral breathing at a respiratory flow of 1,000 ml/s, >85% of the inspired \( \text{Cl}_2 \) was still absorbed in the OR compartment compared with only 25% of the inspired \( \text{O}_3 \) (Fig. 3). Because this result was consistent for all 10 subjects, it is likely that \( \text{Cl}_2 \)-induced tissue damage is localized in the upper airways of the human respiratory tract, irrespective of the mode of breathing or respiratory flow rate.

The measurements of \( \text{O}_3 \) bolus inhalation in this study are consistent with the results of previous studies that used healthy nonsmokers. Hu et al. (8) showed that \( \Lambda \) was \( \sim 0.50 \) at \( V_P \) of 50 ml and 0.90 at \( V_P \) of 170 ml during oral breathing at 150 ml/s. When the oral flow was increased to 1,000 ml/s, \( \Lambda \) decreased to \( \sim 0.10 \) at \( V_P \) of 50 ml and to 0.75 at \( V_P \) of 170 ml. In the present study the corresponding values of \( \Lambda \) were \( \sim 0.60 \) and 0.95 during oral breathing at 150 ml/s and 0.10 and 0.90 during oral breathing at 1,000 ml/s (Fig. 2). Therefore, the \( \Lambda \) values obtained during oral breathing of \( \text{O}_3 \) in this study were slightly higher than those reported previously. This previous study did not include female subjects, who are known to exhibit higher \( \Lambda \) values than men during oral breathing (3). During nasal breathing at a resired flow rate of 250 ml/s, Kabel et al. (9) reported \( \Lambda \) of \( \sim 0.70 \) at \( V_P \) of 50 ml and 0.90 at \( V_P \) of 170 ml. In this study, corresponding values of \( \Lambda \) were \( \sim 0.65 \) and 0.95. Thus the \( \Lambda \) values obtained during nasal quiet breathing were quite similar in the present and the previous study.

Previous studies have shown that \( \text{Cl}_2 \) and \( \text{O}_3 \) uptake rates during quiet breathing are related to airway geometry because of its effect on the gas phase diffusion resistance (3, 12). To further explore this phenomenon in the present study, Eq. 7 was applied to the N/O compartment. By writing \( \Lambda \) in an explicit manner, Eq. 7 becomes

\[
\frac{k_aV}{a} = (m/V)(S/A) \quad (9)
\]

where \( V, S, \) and \( A \) are the airway volume, surface area, and average cross-sectional area, respectively. If the geometric shape of an airway was the same in everyone, then the \( S/A \) ratio would be a constant from subject to subject and \( k_aV \) would be inversely proportional to the airway volume. To test this possibility, a weighted log-log regression of the individual subject's values of \( k_aV \) to the corresponding values of \( V \) was performed in the NS as well as in the OR compartment. Weights were computed as the squared reciprocal of the standard error of each value of \( k_aV \).

The results of the two regressions were as follows (Fig. 4)

\[
\frac{k_aV}{a}_{\text{OR}} = 0.44(V_{\text{OR}})^{-0.79\pm0.09} \quad (10)
\]

and

\[
\frac{k_aV}{a}_{\text{NS}} = 0.22(V_{\text{NS}})^{-0.58\pm0.16} \quad (11)
\]

where the standard error is shown for the regressed value of the exponent. For the OR compartment described by Eq. 10, variations in \( k_aV/\text{OR} \) were almost completely predicted by variations in \( V_{\text{OR}} \) \( (r^2 = 0.89) \), and the exponent on airway volume was not much different from the expected value of \( -1.0 \) \( (P = 0.043) \). This indicates that everyone's mouth had a similar shape, as was also suggested by the strong correlation between \( V_{\text{OR}} \) and \( A_{\text{OR}} \) \( (r^2 = 0.85) \). For the NS compart-
ment described by Eq. 11, variations in \((k_{a}/\sqrt{V})_{c_{N}}\) were not as well predicted by variations in \(V_{c_{N}}\) \((r^2 = 0.61)\), and the exponent on \(V_{c_{N}}\) deviated from \(-1.0 \ (P = 0.033)\) by a greater amount. These results suggest that the shape of the nasal compartment was not constant among the 10 subjects. This conclusion is also consistent with the fact that \(V_{c_{N}}\) was not correlated with \(A_{c_{N}}\) \((r^2 = 0.00)\).

At the highest respiratory flow employed in this study, the spatial resolution of the bolus inhalation method was limited. During each test breath, a pulse of Cl\(_2\)-air (or O\(_3\)-air) was injected into the inhaled airstream by using a miniature solenoid valve that was opened for 0.1 s. At the lowest airflow of 150 ml/s, the Cl\(_2\) pulse formed an inhaled bolus by mixing with the 15 ml of air that passed the injection point during 0.1 s. At the highest airflow of 1,000 ml/s, the Cl\(_2\) pulse mixed with 100 ml of air to form the inhaled bolus. In other words, the volume of the inhaled Cl\(_2\)-air (or O\(_3\)-air) bolus ranged from 15 ml at 150 ml/s, which was smaller than the smallest compartmental volume, to 100 ml at 1,000 ml/s, which was somewhat larger than the largest compartmental volume (Table 1). In addition to dispersive mixing of the inhaled bolus, dispersion occurred as the bolus was convected within the respiratory system (12). This further compromised the spatial resolution of the absorption data.

Summary. The longitudinal distribution of Cl\(_2\) and O\(_3\) absorption was measured by the bolus inhalation method in 10 subjects during nasal and oral breathing at flow rates of 150, 250, and 1,000 ml/s. Irrespective of the mode of breathing and respiratory flow rate, \(>95\%\) of the inspired Cl\(_2\) was absorbed in the upper airways, whereas the dose delivered to the lower airways was \(<5\%\). In contrast, the dose distribution of O\(_3\) was relatively sensitive to the mode of breathing as well as to respiratory flow rate. As respiratory flow increased, the O\(_3\) dose delivered to the upper airways ranged from 95 to 50\%, whereas the dose delivered to the LA ranged from 0 to 35\%. These differences between Cl\(_2\) and O\(_3\) dosimetry were attributed to the greater tissue phase resistance of O\(_3\) than of Cl\(_2\). During quiet oral breathing, tissue phase diffusion resistance accounted for \(~50\%\) of the overall absorption resistance of O\(_3\) but for virtually none of the overall absorption resistance of Cl\(_2\). The lack of a tissue phase resistance for Cl\(_2\) probably resulted from its rapid hydrolysis in the airway mucosa. The gas phase resistances of Cl\(_2\) and O\(_3\) were similar and were related in an inverse manner to the volumes of the oral and nasal cavities.

The authors are grateful to S. Arnold, R. Bascom, and A. Ben-Jebria for insightful suggestions.

This work was supported in part by the Chlorine Institute through a subcontract with the Chemical Industry Institute of Toxicology and by National Institute of Environmental Health Sciences Research Grant ES-06075. Clinical support was provided by the General Clinical Research Center through funding by National Institutes of Health Grant M01 RR-10732.

Address for reprint requests and other correspondence: J. S. Ultman, Dept. of Chemical Engineering, Penn State University, 106 Fenske Lab, University Park, PA 16802 (E-mail: JU@SU.EDU).

Received 23 November 1998; accepted in final form 26 July 1999.

REFERENCES


