Total respiratory tract deposition of fine micrometer-sized particles in healthy adults: empirical equations for sex and breathing pattern

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Kim, Chong S., and Shu-Chieh Hu. Total respiratory tract deposition of fine micrometer-sized particles in healthy adults: empirical equations for sex and breathing pattern. J Appl Physiol 101: 401–412, 2006; doi:10.1152/japplphysiol.00026.2006.—Accurate dose estimation under various inhalation conditions is important for assessing both the potential health effects of pollutant particles and the therapeutic efficacy of medicinal aerosols. We measured total deposition fraction (TDF) of monodisperse micrometer-sized particles [particle diameter (Dp) = 1, 3, and 5 μm in diameter] in healthy adults (8 men and 7 women) in a wide range of breathing patterns; tidal volumes (VT) of 350–1500 ml and respiratory flow rates (Q) of 175–1,000 ml/s. The subject inhaled test aerosols for 10–20 breaths with each of the prescribed breathing patterns, and TDF was obtained by monitoring inhaled and exhaled aerosols breath by breath by a laser aerosol photometer. Results show that TDF varied from 0.12–0.25, 0.26–0.68, and 0.45–0.83 for Dp = 1, 3, and 5 μm, respectively, depending on the breathing pattern used. TDF was comparable between men and women for all conditions used except for very small particles (<0.05 μm). TDF increased with an increase in VT regardless of Dp and Q used. At a fixed VT TDF decreased with an increase in Q for Dp = 1 and 3 μm but did not show any significant changes for Dp = 5 μm. The varying TDF values, however, could be consolidated by a single composite parameter (ω) consisting of Dp, VT, and Q. The results indicate that unifying empirical formulas provide a convenient means of assessing deposition dose of particles under varying inhalation conditions.

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PARTICULATE MATTER (PM) is ubiquitous in the air, and its characteristics, both in size and composition, vary widely depending on the source and the history of particles in time and space. Potential health effects of these particles have been investigated extensively in the field and laboratory (9, 28, 30), and it is generally understood that the toxic potency may vary with particle sizes, particularly among the ultrafine [particle diameter (Dp) ≤ 0.1 μm], fine (0.1 μm < Dp < 2.5 μm), and coarse fractions (2.5 μm < Dp < 10 μm) of ambient aerosols. The ultrafine and fine particles are formed primarily by combustion processes as in automobiles, and these particles are found to be a major factor for observed adverse health effects in urban populations (25, 30, 31), and thus the coarse particles formed mainly by mechanical breakdown of bulk materials, such as wind-blown road dust, have been considered to be less toxic than fine particles. Recent studies, however, have shown that the coarse but not fine particles are associated with adverse health effects in elderly populations (6, 10) and asthmatic children (26, 33). The coarse particle fractions were also found to be more potent in causing inflammatory responses in macrophage cell cultures than the corresponding fine particle fractions of urban ambient PM samples (1, 11, 12). These studies suggest that although particle size is an important factor for delineating potential health effects, all PM, regardless of particle size, may pose harm to human health in their respective ways. Specific mechanisms by which these particles exert observed or potential health effects are not fully understood yet, and it remains unclear what specific attributes of PM are responsible for adverse health effects.

From the dosimetry point of view, the dose at a target organ or at a specific site of the organ is a crucial factor for assessing potential health effects of PM. Estimating the dose at a target organ, however, is a difficult task because of the heterogeneity in the physical (size, shape, and structure) and chemical properties of constituent particles. In addition, individual factors such as lung morphology and breathing pattern have a profound effect on deposition of particles in the respiratory airways (4, 13, 14, 23). Natural breathing patterns vary considerably among individuals, and this may be amplified in those with poor health or respiratory illness (32). People also breathe differently depending on the level of activities, i.e., rest vs. exercise. Thus deposition dose for specific particle sizes and breathing patterns is important for differentiating potential health risks among various subject groups under different exposure conditions. Previously, many studies reported total lung deposition of micrometer-sized particles in normal adult subjects (3, 13–15, 21). Most of the studies, however, used either a small number of subjects (less than five) or a limited number of breathing patterns (one or two) that are not sufficient to cover a range of exposure conditions. Effects of sex have been studied only in a limited scope in both particle size and breathing pattern (3, 20, 24), and the results are not sufficient for use in determining differential doses between men and women under varying inhalation conditions. In our previous studies (17, 22), total lung deposition of ultrafine particles in the size range of Dp = 0.04–0.1 μm was measured in men and women with six different breathing patterns, and deposition was found to be generally comparable between men and women for all conditions used except for very small particles with which deposition was slightly greater in women than men. In the present study we measured total lung deposition of micrometer-sized particles (Dp = 1, 3, and 5 μm) in men and women with 14 different breathing patterns encompassing a range of breathing variability expected in daily life.
The purpose of this study was to obtain specific total lung deposition data in men and women with respect to particle size ($D_p \geq 1 \mu m$) and breathing pattern and to analyze the data to determine 1) the sensitivity of parameters affecting lung deposition and 2) effects of sex. Most of all, the results were further analyzed to identify a composite parameter that may consolidate all deposition data as a single empirical function. Such an empirical function will be very useful for estimating total lung deposition in men and women under varying inhalation conditions expected in the real life.

**EXPERIMENTAL METHODS**

**Subjects.** Fifteen healthy adults (8 men and 7 women), 25–53 yr old, participated in the study. The subjects either had no history of smoking or did not smoke in the past 5 years. All subjects underwent a screening procedure that included a complete medical history and physical examination. Those who passed the initial screening had their basic lung function measured by both spirometry and body plethysmography. Subject characteristics and lung function test results are shown in Table 1. The study protocol was approved by the Institutional Review Board at the University of North Carolina Medical School in Chapel Hill, and informed consent was obtained from all subjects before their participation in the study.

**Generation of test aerosols.** Monodisperse di-2-ethylhexyl sebacate (DES) oil aerosols were generated by an evaporation-condensation-type aerosol generator (MAGE, Lavoro E Ambiente, Bologna, Italy). The performance characteristics of the MAGE generator have been described elsewhere (16). In the present study the original MAGE generator was modified to improve the quality of aerosols, particularly for large-sized particles. Briefly, aqueous solutions of NaCl (5–10 mg/l) were nebulized by a Collision-type atomizer operated with compressed nitrogen gas (20 psi). Solution droplets initially generated were passed through a drying column filled with silica gel and the resulting dry nuclei aerosol was passed at a rate of 1–3 l/min through a “boiler” in which DES oil was heated and vaporized at temperatures of 170–250°C. The mixture of nuclei and DES oil vapor from the boiler was passed through a “reheater” maintained at 280–320°C and subsequently through a vertical condensation column designed to induce condensation of the oil vapor on the surface of nuclei particles. Monodisperse DES aerosols emerging from the condensation column were diluted with clean air (20–100 l/min) using a two-stage diluter. By changing the concentration of nuclei or the temperatures of the boiler and the reheater, we generated monodisperse aerosols with $D_p = 1, 3,$ and $5 \mu m$ in diameter (geometric SD < 1.1) particles. The size of particles was measured by an aerodynamic particle sizer (APS 3310, TSI, St. Paul, MN) equipped with an aerosol diluter (1:100 ratio) (model 3302, TSI).

**Inhalation system.** The inhalation system consists of a monodisperse aerosol generator, an aerodynamic particle sizer, a laser aerosol photometer, a flow-through inhalation bag, a three-way sliding valve, a Fleisch pneumotachograph, and an online data-acquisition system (see Fig. 1). Test aerosols from the aerosol generator are introduced into a large, collapsible, and flow-through bag (15 liters) such that fresh aerosols are always available from the bag for inhalation. A mouthpiece is directly attached to the aerosol detection cell of the laser photometer that in turn is connected to an inhalation bag via a pneumotachograph (Fleisch no. 1, Linton Instrumentation, Norfolk, UK) and a pneumatically controlled three-way sliding valve (Series 8500, Hans Rudolf, Kansas City, MO) in line. The laser aerosol photometer has been used widely for online monitoring of aerosols during inhalation, and the details of the photometer have been described elsewhere (8, 21). Briefly, in the laser aerosol photometer a laser beam (15 mW He-Ne, Melles Griot, Carlsbad, CA) is expanded into a thin sheet via a cylindrical lens and shined through an aerosol detection cell where the laser beam is scattered by aerosol particles.

**Table 1. Pulmonary function measurements of volunteer adult subjects**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>n</th>
<th>Age yr</th>
<th>FRC, liters</th>
<th>FEV1, %Pr.</th>
<th>FVC, %Pr.</th>
<th>FEV1/FVC</th>
<th>sGaw, (cmH2O0s)−1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>8</td>
<td>31 (7)</td>
<td>3.73 (0.3)</td>
<td>108 (12)</td>
<td>107 (15)</td>
<td>0.85 (0.05)</td>
<td>0.57 (0.3)</td>
</tr>
<tr>
<td>Women</td>
<td>7</td>
<td>31 (6)</td>
<td>3.05 (0.5)</td>
<td>113 (9)</td>
<td>117 (10)</td>
<td>0.81 (0.04)</td>
<td>0.33 (0.1)</td>
</tr>
</tbody>
</table>

Values are means and (SD). $n$, Number of subjects; FRC, functional residual capacity; FEV1, forced expired volume at 1 s; FVC, forced vital capacity, sGaw, specific airway conductance; %Pr., % of predicted normal value.
The scattered light is collected on a photomultiplier tube (model 9798B, EMI Gencom, Plainview, NY), and the signals from the photomultiplier tube are amplified to the level of 0–10 V by a current amplifier (model 427, Keithly Instruments, Cleveland, OH) and subsequently transmitted to the data-acquisition system. The aerosol detection cell is heated to 40°C by an electric resistor imbedded in the metallic block of the cell to prevent moisture condensation on the lens during exhalation. Flow rates through the laser photometer are measured by a pneumotachograph (Fleisch no. 1) connected directly to the detector cell. The pressure drop across the pneumotachograph is monitored by a differential pressure transducer (model 239, ±1.27 cmH2O range, Setra Systems, Acton, MA), and the pressure signals are transmitted to the data-acquisition system. The data-acquisition system consists of a signal modulator and a personal computer equipped with a high-speed data-acquisition board capable of sampling signals at a rate of up to 27 kHz (DT2801A, Data Translation, Marlboro, MA). In the present system, the raw data signals were acquired at a rate of 200 Hz, and all experimental data were recorded and analyzed by a single acquisition program written in ASYST language (ASYST Software Technologies, Rochester, NY).

Breathing patterns. Twelve breathing patterns were chosen to cover a range of breathing patterns expected during normal breathing at rest and in mild activity in adult men and women. Specifically, four tidal volumes were chosen first: VT = 350, 500, 750, and 1,000 ml, and then for each VT two or three flow rates were chosen within the range of Q = 175–500 ml/s such that breathing frequencies (f) remained within 7.5–20 breaths/min. The minute ventilation was within 5.25–15 l/min. For mild activities, additional tests were performed at VT = 1,500 ml and f = 30 breaths/min. Selection of the breathing patterns was based on previous studies (2, 3, 32) in which average breathing pattern typically VT and Q˙ was considered to be significant at \( P < 0.05 \). After practice, the subject activates the data-acquisition system by pressing a hand-held electronic switch and starts to inhale a test aerosol from a large collapsible inhalation bag. Fresh aerosols are continuously passed through the bag, and the concentration (C) of the aerosol is maintained constant at a level of ~5 V during inhalation. The subject inhales the aerosol for 10–20 breaths with each of the variously prescribed breathing patterns. All inhalations are initiated from the functional residual capacity (i.e., normal resting lung volume), and the Q is kept constant both for the inspiratory and the expiratory flows. During inhalation, aerosol concentrations and respiratory flow rates are monitored continuously by a laser aerosol photometer and a pneumotachograph, respectively, as described above. Both the aerosol concentration and the airflow signals are supplied to an online data-acquisition system installed in a personal computer, and the total numbers of particles inhaled (\( N_i \)) and exhaled (\( N_e \)) are calculated for each breath by integrating C × Q over the inspiratory and expiratory time, respectively. Total deposition fraction (TDF) in the respiratory tract is then determined by (\( N_i - N_e \))/\( N_i \). Typical signals recorded in the computer (aerosol concentration, flow rate, and expired air volume) and the calculation procedures to obtain TDF are shown in Fig. 2.

Data analysis. For each breath, both VT and Q were examined and those with more than 10% deviation in VT or 15% deviation in Q from the prescribed values were discarded. Mean values (10–20 breaths) in each subject, however, were within 5% deviation from the prescribed values for all breathing patterns used. TDF was examined breath by breath to see whether there were any wash-in effects. Although TDF tended to be higher for the first breath compared with subsequent breaths, there was no consistency. Thus TDFs of all qualified breaths (based on VT and Q) were used for further analyses.

In analyzing the data the mean and standard deviation (SD) of TDF was obtained for each inhalation condition with a specific particle size and breathing pattern. The role of deposition parameters was first examined graphically, and a composite parameter, \( \alpha \), consisting of \( D_{50} \), VT, and Q was identified as a single universal parameter that can consolidate all TDF data onto a single curve. Here, \( D_{50} \) is the aerodynamic diameter of particles that can be determined from the relationship, \( D_{50} = D_{r'}(\rho/\rho_a)^{1/2} \) where \( \rho_a \) is the density of particles and \( \rho_a = \text{1 g/cm}^3 \). TDF values were plotted against \( \alpha \) and the best-fit curves in the form of a logistic function were obtained by the least-squares fit method. TDF values were compared for men vs. women by using the Student’s t-test (SigmaStat, Systat Software, CA), and the difference was considered to be significant at \( P < 0.05 \).
RESULTS

TDF values are presented with respect to particles sizes (Dp = 1, 3, and 5 μm) and breathing patterns with specific tidal volumes and flow rates in healthy adult subjects for both men and women. Effects of each of deposition factors are shown first from TDF data of men, and the results are compared for men vs. women. Empirical equations unifying all TDF data into a single curve are then presented. A complete numerical data set is given in Table 2, and some of the data are presented in Fig. 3 for a quick overview.

Effects of particle size. In Fig. 3, TDF is shown with respect to particle size for eight different breathing patterns. The figure clearly shows that TDF increases with increasing particle size for a given breathing pattern for all breathing patterns tested (see Table 2 for additional breathing patterns). The increase is more prominent from Dp = 1 μm to 3 μm than from Dp = 3 μm to 5 μm as shown by the slope in Fig. 4. The mean ratio of TDF(3 μm)/TDF(1 μm) and TDF(5 μm)/TDF(3 μm) is 2.7 (range = 2.1–3.7) and 1.4 (range = 1.2–1.9), respectively, for men. The corresponding mean ratios for women are 3.2 (range = 2.4–5.1) and 1.3 (range = 1.2–1.7), respectively.

Figure 4 also shows that for a given tidal volume TDF of Dp = 1 and 3 μm particles increases with decreasing flow rate (slow breathing), whereas TDF of Dp = 5 μm shows no or minimal changes with flow rate, particularly for large tidal volumes. For a given flow rate, however, TDF increases with tidal volume for all sizes (compare between panels in Fig. 4). Thus TDF is affected by both tidal volume and flow rate for Dp = 1 and 3 μm, but for Dp = 5 μm TDF is insensitive to flow rate and depends almost entirely on tidal volume.

Table 2. Summary of total respiratory tract deposition of micrometer-sized particles at various breathing patterns for men and women

<table>
<thead>
<tr>
<th>VT, ml</th>
<th>Q, ml/s</th>
<th>f, breaths/min</th>
<th>Dp = 1 μm</th>
<th>3 μm</th>
<th>5 μm</th>
<th>1 μm</th>
<th>3 μm</th>
<th>5 μm</th>
<th>W/M ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>350</td>
<td>175</td>
<td>15</td>
<td>0.15 (0.03)</td>
<td>0.31 (0.02)</td>
<td>0.47 (0.05)</td>
<td>0.15 (0.03)</td>
<td>0.38 (0.06)</td>
<td>0.55 (0.07)</td>
<td>1.00</td>
</tr>
<tr>
<td>500</td>
<td>250</td>
<td>9</td>
<td>0.12 (0.03)</td>
<td>0.27 (0.04)</td>
<td>0.45 (0.05)</td>
<td>0.12 (0.03)</td>
<td>0.33 (0.05)</td>
<td>0.55 (0.08)</td>
<td>0.93</td>
</tr>
<tr>
<td>500</td>
<td>500</td>
<td>20</td>
<td>0.20 (0.03)</td>
<td>0.40 (0.04)</td>
<td>0.63 (0.04)</td>
<td>0.12 (0.03)</td>
<td>0.34 (0.05)</td>
<td>0.69 (0.04)</td>
<td>1.03</td>
</tr>
<tr>
<td>500</td>
<td>1,000</td>
<td>15</td>
<td>0.16 (0.04)</td>
<td>0.40 (0.04)</td>
<td>0.67 (0.04)</td>
<td>0.12 (0.02)</td>
<td>0.44 (0.05)</td>
<td>0.69 (0.06)</td>
<td>1.02</td>
</tr>
<tr>
<td>750</td>
<td>250</td>
<td>10</td>
<td>0.18 (0.03)</td>
<td>0.45 (0.04)</td>
<td>0.71 (0.04)</td>
<td>0.12 (0.03)</td>
<td>0.45 (0.06)</td>
<td>0.77 (0.04)</td>
<td>1.23</td>
</tr>
<tr>
<td>750</td>
<td>500</td>
<td>20</td>
<td>0.17 (0.04)</td>
<td>0.48 (0.03)</td>
<td>0.67 (0.05)</td>
<td>0.19 (0.03)</td>
<td>0.61 (0.05)</td>
<td>0.79 (0.04)</td>
<td>1.08</td>
</tr>
<tr>
<td>1,000</td>
<td>250</td>
<td>7.5</td>
<td>0.27 (0.05)</td>
<td>0.65 (0.03)</td>
<td>0.78 (0.03)</td>
<td>0.16 (0.03)</td>
<td>0.67 (0.06)</td>
<td>0.83 (0.03)</td>
<td>1.05</td>
</tr>
<tr>
<td>1,000</td>
<td>500</td>
<td>20</td>
<td>0.26 (0.04)</td>
<td>0.50 (0.04)</td>
<td>0.72 (0.04)</td>
<td>0.20 (0.03)</td>
<td>0.67 (0.06)</td>
<td>0.83 (0.03)</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Values are means and (SD) of each of 8 men and 7 women; VT, tidal volume; Q, respiratory flow rate; f, breathing frequency; Dp, particle diameter; W/M, women-to-men ratio.

Fig. 3. Total lung deposition fraction vs. particle diameter for 8 different breathing patterns in men. Error bars indicate standard deviation. VT, tidal volume (ml); Q, flow rate (ml/s); T, respiratory period (s); f, breathing frequency (breaths per min).
Effects of breathing pattern. Effects of breathing pattern on TDF are shown in Figs. 5–7 for each of three breathing parameters: tidal volume, flow rate, and respiratory period. In Figure 5, TDF is presented as a function of tidal volume and flow rate at a fixed value of respiratory time $T = 4$ s (or $f = 15$ breaths/min). Because $T$ is fixed, $Q$ increases proportionally with increasing tidal volume. The figure shows that TDF of $D_p = 1 \mu m$ remains more or less the same over a wide range of flow rates and tidal volumes, indicating that deposition of $1 \mu m$ particles depends primarily on the residence time of particles in the lung. For both $D_p = 3$ and $5 \mu m$, however, TDF increases with tidal volume. Here, note that although both VT and Q appear to affect TDF, the increase in TDF is entirely due to tidal volume because Q has negative effects on TDF, particularly for $D_p = 1 \mu m$ as shown in Fig. 4. In other words, the effect of VT is much greater than the opposite effect of Q for these particles.

In Fig. 6, TDF is shown against tidal volume and T at a fixed value of $Q = 250$ ml/s. Here, TDF increases with VT and T for all three $D_p$s. The increase is virtually linear for $1 \mu m$ particles. Although both VT and T appear to affect deposition positively, TDF of $D_p = 1 \mu m$ shown here is influenced mainly by T because the role of VT is relatively small, as shown in Fig. 5. Figure 6 also shows that TDF of $3 \mu m$ particles increases rather quickly compared with those shown in Fig. 5 (note the steep slope of the TDF vs. VT curve). Here, both VT and T work hand in hand and TDF increases above the values expected by VT alone. However, for $D_p = 5 \mu m$, TDF is comparable to that shown in Fig. 5, indicating that the effect of $T$ is negligible for $5 \mu m$ particles. In Fig. 7, the effect of $T$ is explicitly shown for all three particle sizes. It is clearly seen in the figure that $T$ is the dominant factor for $D_p = 1 \mu m$, whereas the role of $T$ is negligible for $D_p = 5 \mu m$. For $D_p = 3 \mu m$, both $T$ and $VT$ have an active role on TDF although $T$ is somewhat less influential than $VT$.

Effects of sex. Figure 8 compares TDF for men vs. women for eight different breathing patterns. The figure shows that there is no difference in TDF between men and women for $D_p = 1 \mu m$ regardless of breathing patterns ($P = NS$). For $D_p = 3$ and $5 \mu m$, TDF is greater in women than men for all breathing patterns used ($P < 0.05$). The difference is in the
range of 9–46% for $D_p = 3 \, \mu m$ and 4–24% for $D_p = 5 \, \mu m$, and the difference is greater for breathing patterns with high flow rates (e.g., $Q = 500$ and 1,000 ml/s), particularly for $D_p = 3 \, \mu m$ (see Table 2). For normal resting breathing ($VT = 350–750$ ml and $f = 9–15$ breaths/min), TDF is greater in average by 15–19% in women than men for $D_p = 3–5 \, \mu m$.

Empirical curve fit. All TDF data were plotted against a composite parameter, $\omega = D_a^n Vr^m Q^p$, and fitted to a logistic function in the form of

$$TDF = 1 - a/(1 + b\omega)$$

Here, $D_a$ is in micrometers, $Vr$ is in milliliters, and $Q$ is in milliliters per second. The constants, $a$ and $b$, in the function and the power indexes of the composite parameter, $m$, $n$, and $p$, were determined by the least-squares fit method. The best-fit curves were obtained for men and women separately and also for the combined data of all subjects. Figure 9 shows that TDF data of men fall tightly along a single curve vs.

$$\omega_m = D_a^{1.845} Vr^{1.541} Q^{-0.481}$$

with $a = 0.91$ and $b = 6,874 \times 10^{-5}$ ($r^2 = 0.98$). The power indexes of $\omega_m$ indicate that the most influential factor for TDF is $D_a$ followed by $Vr$ and $Q$. Between $Vr$ and $Q$, $Vr$ is nearly three times more influential than $Q$. TDF of women is also well represented by a single curve ($r^2 = 0.98$) against

$$\omega_f = D_a^{2.023} Vr^{1.566} Q^{-0.343}$$

with $a = 0.92$ and $b = 4.766 \times 10^{-5}$ (see Fig. 10). Note that the constants and power indexes in the fitted equations are somewhat different between men and women because the two data sets are distinctive, as shown in Fig. 8. Thus, when both men’s and women’s data are plotted together against the common $\omega$, the two data sets are clearly separate over most of the range and the best-fit curve runs between the data sets with

$$\omega_{mf} = D_a^{1.894} Vr^{1.498} Q^{-0.466}$$

and $a = 0.92$ and $b = 7.098 \times 10^{-5}$ ($r^2 = 0.96$) as shown in Fig. 11. Note that the data merge in the lower end of $\omega_{mf}$.
because TDFs are comparable for men and women with Dp = 1 μm. The fitted curve for the combined data lies within ±10% deviation from the best-fit curves of men and women only. The summary of these fitted equations are shown in Table 3.

Although the equations above are expressed by the composite parameter consisting of VT and Q, other breathing parameters, T or f (=1/T), can be readily incorporated into the equations by substituting Q with 2VT/T or 2VTf. Then, the fitted equation for men can be expressed by

\[ \omega_{m2} = D_{a}^{1.845} VT^{1.541} f^{0.481} \]  (5)

or

\[ \omega_{m3} = D_{a}^{1.845} VT^{1.060} f^{0.481} \]  (6)

with \(a = 0.91\) and \(b = 4.899 \times 10^{-5}\) \(r^{2} = 0.98\). Here, T is the respiratory period (in s) and f is the breathing frequency (in s\(^{-1}\)). A plot of TDF vs. \(\omega_{m2}\) is shown in Fig. 12 that looks virtually the same as Fig. 9 plotted against \(\omega_{m1}\), indicating that a similar functional relationship of TDF with \(\omega\) is maintained regardless of choice of breathing parameters. Noted in \(\omega_{m2}\) and \(\omega_{m3}\) is that the tidal volume is nearly twice times more influential to TDF than T or f.

Comparison with other studies. Figure 13 shows the present data of men compared with those previously reported by Heyder et al. (15). Those data were chosen for comparison because the data were obtained from men by use of an experimental method similar to ours. Among the range of data reported, TDFs with Dp = 0.4–7-μm particles at VT = 500–1,500 ml and Q = 250–750 ml/s were used here. The figure shows a good agreement between two studies over the entire range of \(\omega_{m}\) plotted. It is particularly noted that the present fit curve can be extended to particles as small as Dp = 0.4 μm shown in the range of \(\omega_{m} < 1,000\).

Effects of lung function. Figures 14 and 15 show TDF values of individual subjects with respect to the functional residual capacity (FRC) and specific airway conductance (sGaw), respectively, for Dp = 1, 3, and 5 μm particles at a

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Parameters of Fitted Equations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
</tr>
<tr>
<td>Men</td>
<td>0.91</td>
</tr>
<tr>
<td>Women</td>
<td>0.92</td>
</tr>
<tr>
<td>Combined</td>
<td>0.92</td>
</tr>
<tr>
<td>Men-2†</td>
<td>0.90</td>
</tr>
<tr>
<td>Women-2†</td>
<td>0.94</td>
</tr>
</tbody>
</table>

The fitted equation is in the form of total deposition fraction (TDF) = \(1 - a/(1 + b\omega)\) where the single composite parameter (\(\omega\)) = \(D_{a}^{\omega} VT^{\omega} Q^{\omega}\). D\(_{a}\) aerodynamic diameter of particles (μm); VT, tidal volume (ml); Q, mean respiratory flow rate (ml/s); \(r^{2}\), correlation coefficient. *Men and women combined. †Plotted with the best-fit \(\omega\) obtained with the combined data.
typical normal breathing pattern, $V_T = 500$ ml and $Q = 250$ ml/s. In Figure 14, TDF remains virtually flat over a range of FRC for $D_p = 3$ and 5 μm in men and $D_p = 1$ μm in women ($r^2 = 0$). Also, TDF tends to decrease with increasing FRC for $D_p = 1$ μm in men and for $D_p = 3$ and 5 μm in women ($r^2 < 0.2$). The inconsistency between men and women and very low $r^2$ values indicates that FRC is not an important factor for TDF in healthy adult subjects. Effects of $sGaw$ are also variable, as seen in Figure 15. TDF remains virtually unchanged with $sGaw$ for $D_p = 3$ μm for women and 5 μm in both men and women ($r^2 < 0.1$). TDF shows a tendency to decrease with increasing $sGaw$ for $D_p = 1$ μm in both men and women and $D_p = 3$ μm in men ($r^2 = 0.19–0.45$). The inconsistency again indicates that $sGaw$ is not a reliable indicator of TDF in normal adults.

**DISCUSSION**

Micrometer-sized particles deposit in the respiratory tract mainly by inertial impaction and gravitational sedimentation, both of which are fundamentally governed by the mass of the particles. Thus deposition increases with particle size as the primary factor. Breathing patterns then play a modulating role by transporting the particles into the lung and providing dynamic conditions under which particles come into contact with the surface of the lung airways. For a given particle size inertial impaction is governed by flow velocity, whereas sedimentation is time dependent. Thus inertial impaction and sedimentation have an opposite effect on deposition, and their relative contribution to TDF varies depending on breathing pattern and particle size. For example, with a given particle size the...
relative contribution by inertial impaction would increase with fast breathing.

Effects of breathing pattern. The present results show that TDF of 1-μm particles remains virtually constant as long as the respiratory time is fixed, even if Q varies widely (see Fig. 4). However, TDF increases almost linearly with increasing time as shown in Fig. 7. In other words, the respiratory time is the most influential factor for Dp = 1 μm, and the absolute values of Vr and Q are less important as long as the ratio Vr/Q is maintained. This also indicates that sedimentation is the dominant mechanism for deposition of these particles during normal breathing. Although sedimentation is expected to be more effective in the deep lung regions where airway dimensions are small, it is interesting to note that TDF of 1-μm particles increases only marginally with increasing tidal volume. This may be attributed to the fact that the airway dimensions increase as the lung expands with larger tidal volumes, partially neutralizing the effects of deeper penetration, particularly for particles having very low sedimentation velocity. For Dp = 3 and 5 μm particles, both inertial impaction and sedimentation play an active role and their relative contribution to TDF is affected by multiple factors. Both Vr and Q or T appear to be important factors for these particles, as shown in Figs. 5 and 6. However, the cross-examination of Figs. 4–7 shows that TDF of Dp = 5 μm particles is minimally affected by either Q or T (see Figs. 4 and 7) but depends almost entirely on Vr, particularly for large Vr = 1,000 ml. This means that as Q and T reciprocally change at a fixed Vr, an increase in inertial impaction is cancelled out by a decrease in sedimentation and vice versa, indicating that inertial impaction and sedimentation have a kind of seesaw relationship in influencing Dp = 5 μm particles. For smaller Vr values (e.g., 500 ml), however, TDF increases with T, apparently because Q is not high enough to counteract sedimentation. Unlike Dp = 1 and 5 μm particles, there is no single dominant breathing parameter for determining TDF of Dp = 3 μm. TDF increases with an increase in T and Vr or with a decrease in Q. However, the results showing a consistent increase of TDF with T at a fixed Vr (see Fig. 7) indicate that sedimentation is more effective than inertial impaction with Dp = 3 μm in a range of breathing patterns expected during normal breathing.

Empirical curve fit. The present results show that TDF of particles with Dp = 1–5 μm can be represented by a function of a single composite parameter consisting of D, Vr, and Q within the range expected during normal breathing. Although Vr and Q were initially chosen to represent breathing patterns, Q can be readily substituted with T or f so that the composite parameter may be explicitly expressed by any breathing parameters of interest as discussed above. From Figs. 9–12 it is clearly seen that TDF increases with an increase in Vr and T while decreasing with an increase in Q or f. Thus TDF increases with slow and deep breathing. This indicates that TDF of micrometer-sized particles, at least in the size range of Dp = 1–5 μm, is dictated primarily by deposition by sedimentation during normal breathing via the mouth. The empirical fit curve also shows an excellent agreement with the TDF data of Dp = 0.4 and 7 μm as shown in Fig. 13, indicating that the present results can be applicable to a broad range of particle sizes that may be extended down to Dp = 0.4 μm. Unlike micrometer-sized particles, deposition of small submicrometer particles, typically Dp < 0.3 μm, is governed primarily by diffusion, and TDF increases with decreasing particle size. Thus the present empirical fit curves showing a decrease in TDF with decreasing particle size are not suitable for use for Dp < 0.4 μm. In our previous study (22), TDF of such small-sized particles was found instead to be represented by a different composite parameter consisting of D, T, and Vr, where D is the diffusion coefficient of particles. Because TDFs are represented by a unique function of a composite parameter, the empirical fit equations are very useful for estimating TDF of particles under various inhalation conditions so long as particle size and breathing patterns are known. The equation is also useful to estimate a range of variations in TDF under different inhalation conditions when inhalation conditions cannot be accurately described. One should note, however, that the present empirical equations were obtained in normal adult subjects breathing normally via the mouth at rest and may not be applicable to the situations involving extreme breathing patterns or subjects with abnormal lungs.

Effects of sex. Our present results show that TDF is comparable for Dp = 1 μm in men and women but is greater in women than men for Dp = 3 and 5 μm at the same controlled breathing patterns via the mouth. Previous studies reported that TDF values were comparable between men and women for 1-μm particles (24) but slightly greater in women than in men for 2-μm particles at a fixed breathing pattern (3). The present results are consistent with these earlier studies and further demonstrate that a sex effect exists in a range of particle sizes, Dp > 1 μm at all breathing patterns expected during normal breathing. In our earlier studies using nano-sized particles, we found that TDF was greater in women than in men with Dp = 0.04 μm but not with Dp = 0.08 and 0.10 μm particles (17, 22). The difference was inconsistent with Dp = 0.06 μm, varying with breathing patterns. Thus, from both the present and earlier studies, sex effects may be considered only for particles smaller than Dp = 0.06 μm and larger than Dp = 1 μm. For particles between Dp = 0.06 and 1 μm no sex effects are found on TDF.

Reasons for the particle size dependent sex effects are not immediately obvious, but two possibilities may be considered. First, the average lung volume (i.e., FRC) of female subjects was smaller than that of male subjects. With a fixed tidal volume, this would allow inhaled aerosols to reach deeper into the lung in female subjects, which is equivalent to a slight increase in tidal volume. Because an increase in Vr would result in an increase in TDF for Dp = 3 and 5 μm but not for Dp = 1 μm as shown in Fig. 5, this appears to be a fitting explanation for the observed sex difference in TDF. However, in Fig. 14, TDF clearly shows no or minimal changes over a wide range of FRC. Furthermore, TDF tends to be greater in women than men at the same level of FRC, suggesting that the smaller lung volume per se may not entirely explain the enhanced TDF observed in women. Second, the dimensions of the conducting airways including the larynx and tracheobronchial tree are considerably smaller in women than in men even with the same lung or body size (5, 7, 27). Deposition in the conducting airways driven by inertial impaction would therefore be increased in women, particularly for Dp = 3 and 5 μm and at high flow rates, and this would result in elevated TDF regardless of FRC. Previous studies, indeed, have shown a greater deposition of micrometer-sized particles in the tracheobronchial region in women than men (20, 29). More specifi-
cally, in our previous studies measuring regional deposition using a serial bolus techniques (20), we found enhanced deposition of \( D_p = 3 \) and 5 \( \mu \)m but not 1 \( \mu \)m in the upper and tracheobronchial airway regions in women compared with men, and also greater TDF of \( D_p = 3 \) and 5 \( \mu \)m in women than men. The present results are consistent with these previous studies and suggest an important role of the airway anatomy in altering particle deposition in women compared with men.

**Deposition mechanisms.** Although deposition of micrometer-sized particles in the lung is governed mainly by mechanisms of inertial impaction and gravitational sedimentation, the relative role of these two mechanisms in determining TDF is not immediately clear from experimental data, particularly when breathing patterns vary widely. This is largely because TDF varies not only with \( Q \) (inertial factor) or \( T \) (sedimentation factor) but also with \( V_t \). Because effects of \( V_t \) are two to three times greater than those of \( Q \) or \( T \) as shown in the composite parameter \( \omega \) (see Eqs. 2–6), the exact role of \( Q \) or \( T \) is difficult to assess unless \( V_t \) is fixed. Nonetheless, Figs. 9–12 show that TDF increases with an increase in \( T \) but decreases with increasing \( Q \) at any given \( V_t \), which indicates that sedimentation is the dominant mechanism for TDF for these particles. The relative role, however, may be better explained if the results are analyzed using characteristic deposition parameters, i.e., Stokes number (\( Stk = 2 \mu \rho D_p^2 Q/9\pi \mu d^3 \)) for inertial impaction and normalized settling distance \( (V_t T_m/d) \) for sedimentation. Here, \( V_s = (\mu D_p^2 g/18\mu d) \) is the settling velocity by gravity, \( \mu \) is the absolute viscosity of air, \( g \) is the gravitational acceleration, \( T_m \) (=0.5T) is the mean respiratory time, and \( d \) is the characteristic distance, namely the tracheal diameter. The ratio \( Stk/(V_t T_m/d) \) may then represent the relative importance of inertial vs. sedimentation deposition. In Fig. 16 TDF values normalized by \( V_t \) as TDF/(\( V_t / FRC \))\(^{0.45} \) are plotted against \( Q/T_m \) for all of the present data obtained in a wide range of breathing pattern. Note that the ratio \( Stk/(V_t T_m/d) \) is reduced to \( C \cdot (Q/T_m) \) where \( C = 4/(\mu d^2 g) \) is the constant. Therefore, \( Q/T_m \) correctly represents the relative strength of the two competing mechanisms. The index of the normalizing \( V_t \) was obtained by trial and error for the best grouping of TDF values for each \( D_p \). Figure 16 clearly shows that TDF consistently decreases with an increase in \( Q/T_m \) for all conditions used, indicating that sedimentation indeed is the dominating mechanism for TDF for these micrometer size particles. The decrease in TDF with \( Q \), however, is rather flat for \( D_p = 5 \) \( \mu \)m. This indicates that the role of inertial impaction grows with increasing particle size and becomes comparable to that of sedimentation at \( D_p = 5 \) \( \mu \)m. Thus the present results suggest that an effective delivery and deposition of micrometer-sized particles for at least up to \( D_p = 5 \) \( \mu \)m can be achieved by a slow and deep breathing maneuver. Inertial impaction, however, may become a dominant factor for TDF at \( D_p \gg 5 \) \( \mu \)m.

**Applications to risk assessment and drug aerosol delivery.** In assessing the risk of exposure to toxic particles, the fundamental strategy is to obtain the dose-response relationship of particular substance of interest. The same principle applies to drug aerosol delivery to find an optimum dose for therapeutic treatment. Our present study provides TDF values per breath as a fraction of the amount inhaled. Therefore, total deposition dose (TDD) over a period of time, \( t \), may be obtained by

\[
TDD(t) = C \cdot V_E \cdot t \cdot TDF
\]

where \( C \) is the concentration of aerosol particles, \( V_E \) is the minute ventilation, and \( t \) is exposure duration (in min). Here, TDF is defined by a particular breathing pattern. When exposure conditions vary during daily activities, TDD may be obtained by

\[
TDD(t) = \sum_i (C \cdot V_E \cdot t \cdot TDF_i)
\]

Here, \( i \) indicates a segmental time period during which a particular inhalation condition is maintained. In estimating a realistic lung dose, one must recognize that natural breathing patterns vary widely among individuals (2, 3) and thus inter-subject variability would be considerable in TDD, even at the same values of \( C \) and \( t \). Between men and women, TDF of women is greater than or comparable to that of men with the same breathing patterns, as shown in the present results. During spontaneous breathing, however, the tidal volume and TDF are usually smaller in women. The minute ventilation is also smaller, and all of these differences work toward lower TDDs in women than men under natural exposure conditions.

Although our present study provides only TDF values, regional deposition patterns also vary with particle size and breathing patterns. Normally, deposition increases in the proximal airway regions (i.e., extrathoracic or tracheobronchial airways) with increasing particle size or flow rate. Conversely, a slow and deep inhalation helps increase deposition in the pulmonary region. In our earlier studies we reported detailed regional deposition patterns of \( D_p = 1, 3, \) and 5 \( \mu \)m particles in young adults and found that deposition takes place unevenly along the respiratory tract, with peak deposition occurring in the transition airway region but shifting more proximally with increasing particle size (20). Because an increase or decrease in TDF parallels with regional deposition, the present results of TDF when combined with regional deposition data reported earlier would provide dose information that may be directly related to potential toxic effects of pollutant particles.

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**Fig. 16.** Total deposition fraction normalized by dimensionless tidal volume, TDF/(\( V_t / FRC \))\(^{0.45} \) vs. the ratio of inertial to sedimentation parameter represented by \( Q/T_m \) for \( D_p = 1 \) \( \mu \)m (□), 3 \( \mu \)m (●), and 5 \( \mu \)m (○) particles for a wide range of breathing patterns; \( Q = 150–1,000 \) ml/s and \( T_m = 1–6 \) s. FRC, functional residual capacity; \( T_m \), mean respiratory time. FRC = 3,000 ml was used here.
It should be noted that the present results are applied only to normal adults. TDF is usually greater in patients with obstructed airway disease such as asthma and chronic bronchitis (4, 23), and the effects of particle size and breathing pattern are likely to be more pronounced in the patients than normal subjects. Although TDF varies widely among patients mainly because of the variable nature of airways obstruction (18, 19), a good correlation has been observed between TDF and measures of pulmonary functions (4, 23, 24). Figure 14, however, shows only marginal effects of sGaw on TDF in normal subjects. Reasons for the discrepancy are not obvious. But TDF may be more affected by irregular airway obstruction occurring in patients than by slight differences in airway dimensions among normal subjects.

In conclusion, we measured total lung deposition fraction of micrometer-sized particles in healthy men and women over a wide range of breathing patterns representing breathing conditions of sleep, resting, and mild exercise. It was found that effects of breathing patterns were not consistent on TDF of different size particles. Respiratory period (T) was a dominant factor for Dp = 1 μm whereas tidal volume (VT) was a dominant parameter for Dp = 5 μm. Both VT and T were equally influential to TDF of Dp = 3 μm. Compared with men, TDF was slightly greater in women for Dp = 3 and 5 μm at the same breathing patterns. TDF values at different breathing patterns were unified by a single function of a composite parameter consisting of Dp, VT, and Q or T. The best-fit curves showed that TDF increases with VT and T but decreases with Q, indicating that sedimentation is the dominant mechanism for determining TDF for these micrometer-sized particles. Overall, VT was found to be the most influential breathing parameter for TDF, followed by T. The empirical equation provides a convenient means of estimating TDF in men and women at various inhalation conditions. The relationships between TDF and breathing parameters are also very useful for determining an optimum inhalation mode for maximizing the delivery of medicinal aerosols.

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REFERENCES


