

MEASUREMENT OF TOTAL LUNG DEPOSITION OF INHALED ULTRAFINE PARTICLES IN HEALTHY MEN AND WOMEN

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Ultrafine particles (< 0.10 μm in diameter) are present in great number in polluted urban air, thus posing a potential health risk. In this study, the total deposition fraction (TDF) of ultrafine aerosols with a narrow size distribution (number median diameter NMD = 0.04–0.1 μm and geometric standard deviation $\sigma_g = \sim 1.3$) was measured in a group of young healthy adults (11 men and 11 women). TDF was obtained with 6 different breathing patterns: tidal volume (V_t) of 500 ml at respiratory flow rates (Q) of 150 and 250 ml/s; $V_t = 750$ ml at Q of 250 and 375 ml/s; and $V_t = 1$ L at Q of 250 and 500 ml/s. Aerosols were monitored continuously by a modified condensation nuclei counter while subjects were inhaling them with prescribed breathing patterns. For a given breathing pattern, TDF increased as particle size decreased, regardless of the breathing pattern used. For example, with $V_t = 500$ ml and Q = 250 ml/s, TDF (mean \pm SD) was $0.26 \pm .04$, $0.30 \pm .05$, $0.35 \pm .05$, and $0.44 \pm .07$ for NMD = 0.10, 0.08, 0.06, and 0.04 μm , respectively. For a given NMD, TDF increased with an increase in V_t and a decrease in Q. TDF was greater for women than men at NMD = 0.04 μm within all breathing patterns used ($p < .05$), but the difference was smaller or negligible for larger sized particles. The results suggest that the TDF of ultrafine particles increases with a decrease of particle size and with breathing patterns of longer respiratory time, a pattern that is consistent with diffusion deposition of ultrafine particles. The results also suggest that there is a differential lung dose of ultrafine particles and thus there may be a differential health risk for men versus women.

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The ultrafine fraction ($<0.10 \mu\text{m}$ in diameter) of ambient particulate matter has less mass than the coarse particle fraction, but ultrafine particles are much greater in number in ambient air and have a relatively large surface area to mass ratio, making them potential carriers of harmful gaseous compounds. Animal studies have shown that exposure to high doses of ultrafine particles can cause lung injuries and even death (Oberdörster et al., 1992, 1995). Recent epidemiological studies have indicated that ultrafine particles may have greater adverse respiratory effects than fine or coarse particles in urban air (Peters et al., 1997). However, it is not known how ultrafine particles cause such effects. Furthermore, opinions vary among scientists whether ultrafine ambient particles are capable of causing harmful health effects.

Exposure-dose relationships are required to better interpret the health effects of particulate matter. However, there is a scarcity of human data on the respiratory deposition of ultrafine particles. Few studies have reported total lung deposition fraction of ultrafine particles for normal adults (Blanchard & Willeke, 1984; Tu & Knutson, 1984; Wilson et al., 1985; Schiller et al., 1986) or for patients with obstructive lung disease (Anderson et al., 1990). The number of subjects studied in these studies was small (from one to five subjects) and all subjects were male. There was considerable variation in the quality of the aerosol used; both size distribution ($\sigma_g = 1.1-1.90$) and the type of aerosol material (oils, soots, salts, and metals) varied widely. Methods of measuring lung deposition also were different among these studies. Because of the small sample size and the lack of aerosol uniformity, these results cannot not be generalized to the general population. Unlike ultrafine aerosols, the lung deposition of fine and coarse particles ($>1 \mu\text{m}$ in diameter) has been studied extensively (Stahlhofen et al., 1989). Studies have reported considerable variation in lung deposition among healthy individuals (Heyder et al., 1982; Kim et al., 1999) and a consistent difference in total and regional deposition between men and women (Pritchard et al., 1986; Bennett et al., 1996; Kim & Hu, 1998). However, because of different deposition mechanisms, these results may not apply to ultrafine particles. The existing deposition data for ultrafine particles lacks the scope and depth to address either of these important risk assessment issues.

The purposes of the present study therefore were (1) to measure total lung deposition of ultrafine particles using large samples of both male and female subjects; (2) to investigate intersubject variability and a potential gender effect in lung deposition of ultrafine particles under carefully controlled inhalation conditions; and (3) to improve the database of exposure-dose relations for use in the health risk assessment of particulate matter.

EXPERIMENTAL METHODS

Subjects

Healthy young adults (11 men and 11 women) ranging in age from 20 to 40 yr were recruited locally. The subjects either had no history of

smoking or had not smoked in the past five years. All subjects underwent a screening procedure that included a complete medical history, physical examination, SMA-20 blood chemistry screen, and complete blood count with differential. 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.

Aerosol Generation

Ultrafine aerosols were generated by condensing sebacate oil (di-2-ethylhexyl sebacate) vapor on nonhygroscopic metallic nuclei particles. The aerosol generator consisted of a monodispersed condensation aerosol generator manufactured by TSI (model 3470, TSI, Inc., St. Paul, MN) and a nuclei aerosol generator utilizing a nickel–chromium heating wire. The TSI generator was modified because ultrafine sebacate oil particles generated with sodium chloride nuclei were found to be somewhat hygroscopic. Briefly, a metallic nuclei aerosol is produced by heating a coiled Ni–Cr wire (3–4 Ω) at low electric voltage (1.1–1.6 V AC). The nuclei aerosol (~ 3 L/min) is then passed through a “boiler” in which sebacate oil is heated and vaporized at 70–100°C. The mixture of nuclei and oil vapor from the boiler is first passed through a reheater that is maintained at 190°C, and then through an unheated vertical column designed to induce condensation of oil vapor onto the surface of nuclei particles. The aerosols emerging from the generator are diluted with filtered air (~ 100 L/min) and supplied to the inhalation system. In the present study, ultrafine aerosols of four different particle sizes were generated: 0.04, 0.06, 0.08, and 0.1 μm in number median diameter (NMD) with a geometric standard deviation (σ_g) in the range of 1.27–1.34. The size distribution was measured by a scanning mobility particle sizer (model 3934, TSI, Inc., St. Paul, MN) immediately before and after each inhalation. Aerosols were sampled directly from the breathing bag in which aerosol concentration was maintained at $\sim 50,000$ particles/cm³. Typical size distributions of the aerosols used are shown in Figure 1.

Inhalation Procedure

The subject first inhaled clean air via the mouthpiece and practiced the prescribed breathing patterns displayed on the computer screen. After the practice, the subject activated a pneumatically controlled three-way sliding valve (series 8500, Hans Rudolph, Inc., Kansas City, MO) and started to inhale a test aerosol from a large collapsible bag (20 L). Fresh aerosols were continuously passed through the bag, and the concentration of the aerosol was maintained at a level of $\sim 50,000$ particles/cm³ during inhalation. The subject inhaled the aerosol for 10–20 breaths for each of 6 prescribed breathing patterns: tidal volume (V_t) of 500 ml at respiratory flow rates (Q) of 150 and 250 ml/s; $V_t = 750$ ml at Q of 250 and 375 ml/s; and, $V_t = 1$ L at Q of 250 and 500 ml/s. After completion of one breathing pattern, the subject removed the mouthpiece and breathed room air for ~ 2 min while the collected data were being reviewed and the computer was

TABLE 1. Summary of subject characteristics and lung function test results

Sex	n	Age (yr)	Height (cm)	FVC (ml)	FEV ₁ (ml)	FEV ₁ /FVC (ml)	Raw (cm H ₂ O/L/s)	FRC (ml)	TLC (ml)
Men	11	31 ± 4	173 ± 7	5388 ± 847	4404 ± 708	0.82 ± 0.06	1.00 ± 0.6	3911 ± 892	6598 ± 980
Women	11	31 ± 4	165 ± 6	4278 ± 587	3467 ± 540	0.81 ± 0.06	1.24 ± 0.6	3314 ± 547	5282 ± 599

Note. FVC, forced vital capacity; FEV₁, forced expiratory volume at 1 s; Raw, airway flow resistance; FRC, functional residual capacity; TLC, total lung capacity.

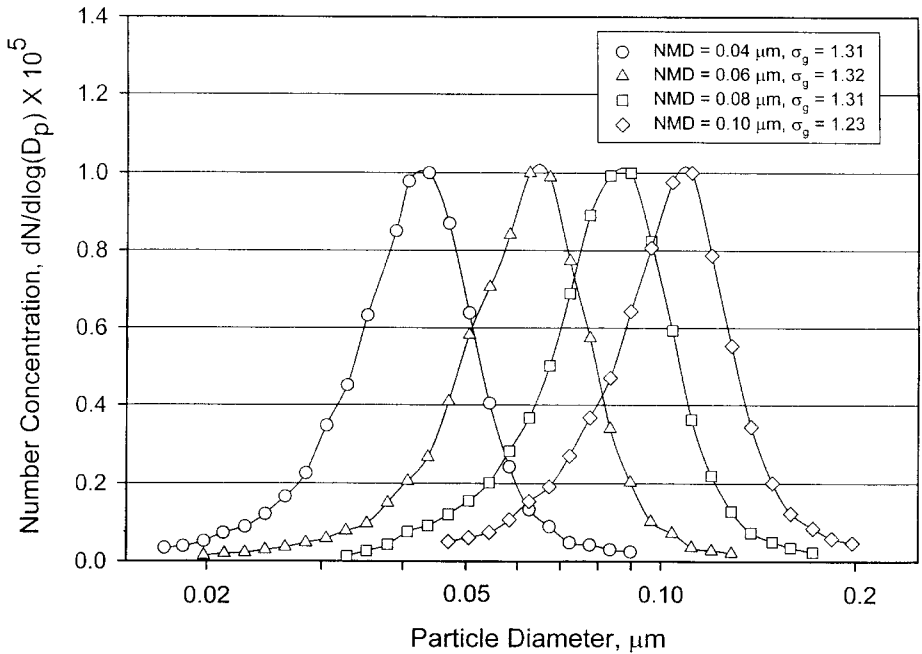


FIGURE 1. Typical size distributions of ultrafine aerosols generated by a condensation aerosol generator. Size distributions were measured by a scanning mobility particle sizer (TSI model 3934). NMD, number median diameter; σ_g , geometric standard deviation.

being set for the next breathing pattern. All inhalations were initiated from functional residual capacity (FRC), and Q was the same for the inspiratory and expiratory flows. During inhalation, the aerosol concentration was monitored continuously by an ultrafine condensation particle counter (model 3025A, TSI, Inc., St. Paul, MN), and flow rates were monitored by a Fleisch pneumotachograph (no. 1) in conjunction with a low pressure transducer (model 239, ± 1.27 cm H_2O range, Setra Systems, Acton, MA). Both aerosol concentration and respiratory flow signals were supplied to an online personal computer, and the total number of particles inhaled (N_i) and exhaled (N_e) was calculated breath by breath. Total lung deposition fraction (TDF) was then determined by $(N_i - N_e)/N_i$. The typical signals recorded in the computer (aerosol concentration, respiratory flow rate, and air volume) and used in calculating TDF are shown in Figure 2.

RESULTS

The entire data set of total deposition fraction (TDF) results is summarized in Table 2. The TDF (mean \pm SD) of four different ultrafine aerosols (NMD = 0.04, 0.06, 0.08, and 0.1 μm) is shown for male (up to $n = 11$) and female (up to $n = 11$) subjects separately, and then combined (up to $n = 22$). For each particle size, TDF is shown for 6 different breathing pat-

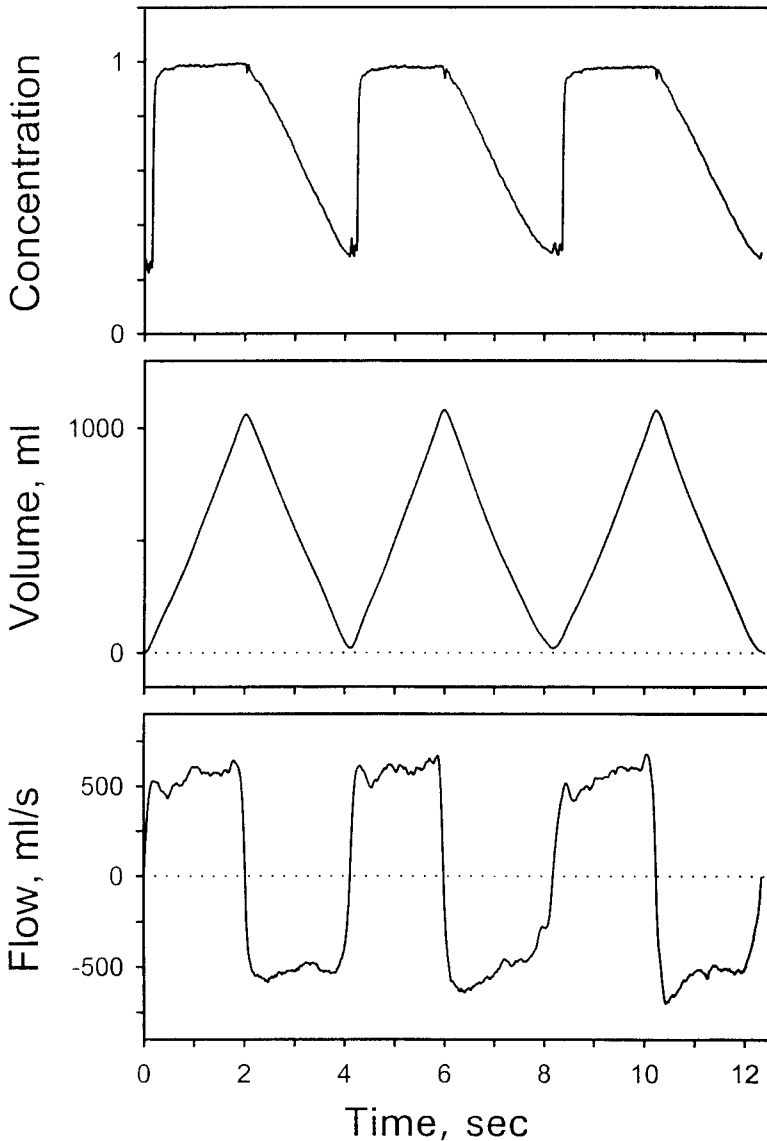


FIGURE 2. Typical online data signals for aerosols (top panel), respiratory volume (middle panel), and flow rate (bottom panel).

terns: tidal volume (V_t) of 500 ml at respiratory flow rate (Q) of 150 and 250 ml/s; and $V_t = 750$ ml at $Q = 250$ and 375 ml/s; and $V_t = 1000$ ml at $Q = 250$ and 500 ml/s. It should be noted that not all subjects completed all six breathing patterns. Therefore, the number of subjects was different for each inhalation condition. For all breathing patterns studied, the TDF increases with a decrease in particle size from $NMD = 0.1$ to $0.04 \mu\text{m}$.

For example, TDF (mean ± SD) of all subjects was 0.53 ± 0.07, 0.44 ± 0.07, 0.40 ± 0.07, and 0.34 ± 0.06 at $V_t = 500$ ml and $Q = 150$ ml/s, and 0.44 ± 0.07, 0.35 ± 0.05, 0.30 ± 0.05, 0.26 ± 0.04 at $V_t = 500$ ml and $Q = 250$ ml/s for particles with NMD = 0.04, 0.06, 0.08, and 0.1 µm, respectively. Additionally, for a given breathing pattern, TDF became significantly greater for each successively smaller particle size ($p < .05$). Thus, relatively small differences in particle size have a significant influence on lung deposition. For any given particle size, TDF increased with an increase in tidal volume and with a decrease in flow rate. An overview of this relationship is shown in Figure 3, in which TDF values with all six breathing patterns are plotted side by side for each particle size.

In Table 2, we also can see that the variability of TDF between subjects is consistent regardless of particle sizes and breathing patterns used.

TABLE 2. Summary of results of total lung deposition of ultrafine particles in healthy men and women

NMD (µm)	V_t (ml)	Q (ml/s)	All subjects			Men			Women		
			n	TDF	CV (%)	n	TDF	CV (%)	n	TDF	CV (%)
0.04	500	150	22	0.53 ± 0.07	13.2	11	0.50 ± 0.07	14.2	11	0.56 ± 0.06 ^a	10.3
		250	22	0.44 ± 0.07	15.9	11	0.41 ± 0.07	15.8	11	0.47 ± 0.06 ^a	12.9
	750	250	10	0.59 ± 0.07	11.7	6	0.56 ± 0.06	11.0	4	0.64 ± 0.06 ^a	8.7
		375	10	0.52 ± 0.07	13.4	6	0.49 ± 0.06	11.4	4	0.56 ± 0.07	13.0
	1000	250	22	0.66 ± 0.05	7.6	11	0.64 ± 0.04	6.7	11	0.68 ± 0.07 ^a	7.2
		500	10	0.54 ± 0.06	11.6	6	0.53 ± 0.04	7.6	4	0.56 ± 0.08	14.8
0.06	500	150	22	0.44 ± 0.07	15.1	11	0.43 ± 0.07	15.9	11	0.46 ± 0.06	13.4
		250	22	0.35 ± 0.05	14.9	11	0.33 ± 0.05	15.0	11	0.37 ± 0.05 ^a	12.3
	750	250	13	0.48 ± 0.06	12.0	7	0.46 ± 0.06	13.6	6	0.50 ± 0.04	7.3
		375	12	0.42 ± 0.06	14.9	7	0.40 ± 0.07	16.5	5	0.45 ± 0.05	10.4
	1000	250	22	0.56 ± 0.05	9.7	11	0.56 ± 0.06	11.1	11	0.56 ± 0.04	7.9
		500	12	0.45 ± 0.06	12.8	7	0.43 ± 0.06	13.4	5	0.46 ± 0.05	11.0
0.08	500	150	15	0.40 ± 0.07	16.6	7	0.39 ± 0.05	13.7	8	0.41 ± 0.08	18.5
		250	15	0.30 ± 0.05	15.7	7	0.31 ± 0.05	15.7	8	0.30 ± 0.05	15.8
	750	250	10	0.40 ± 0.07	16.7	5	0.41 ± 0.07	16.3	5	0.39 ± 0.07	18.6
		375	10	0.32 ± 0.07	20.8	5	0.33 ± 0.08	22.6	5	0.30 ± 0.05	16.4
	1000	250	15	0.47 ± 0.06	13.6	7	0.48 ± 0.07	13.5	8	0.46 ± 0.06	13.4
		500	10	0.33 ± 0.06	17.8	5	0.35 ± 0.05	15.1	5	0.31 ± 0.07	18.4
0.1	500	150	21	0.34 ± 0.06	17.0	10	0.34 ± 0.05	15.3	11	0.35 ± 0.06	18.2
		250	21	0.26 ± 0.04	15.1	10	0.26 ± 0.04	17.0	11	0.25 ± 0.03	12.7
	750	250	10	0.35 ± 0.05	14.7	5	0.36 ± 0.06	17.8	5	0.34 ± 0.04	11.3
		375	10	0.27 ± 0.04	14.5	5	0.28 ± 0.05	18.0	5	0.27 ± 0.03	11.8
	1000	250	18	0.40 ± 0.05	13.5	7	0.42 ± 0.05	12.1	11	0.39 ± 0.05	13.0
		500	10	0.28 ± 0.05	16.6	5	0.29 ± 0.04	12.5	5	0.27 ± 0.05	19.7

Note. NMD, number median diameter; V_t , tidal volume; Q, respiratory flow rate; TDF, total deposition fraction (mean ± SD); CV, coefficient of variation (%); n, number of subjects.

^aSignificant difference ($p < .05$) versus men.

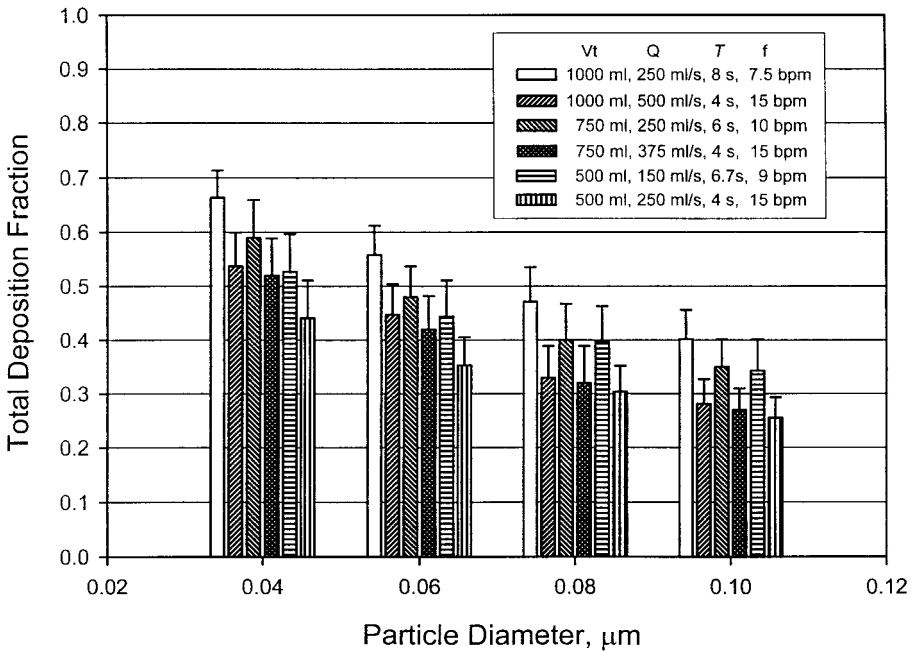


FIGURE 3. Total deposition fraction as a function of particle size. Six different breathing patterns are shown for each particle size. For each breathing pattern, TDF is different ($p < .05$) for two successive particle sizes. V_t , tidal volume (ml); Q , respiratory flow rate (ml/s); T , respiratory time (s); f , breathing frequency in breaths/min (bpm).

The percent coefficient of variation (CV) of TDF was mostly in the range of 12 to 18% for all breathing patterns, and was similar within each set of breathing patterns. The value of CV was as low as 7–10% for some breathing conditions. The intersubject variability of TDF was comparable for male and female subjects; CV = 14.2 versus 13.2% (male vs. female, $p = \text{NS}$) for all inhalation conditions used. Figure 4 presents scatter plots of TDF of individual subjects as a function of particle size. Here, TDF is shown for $V_t = 500$ ml at $Q = 150$ and 250 ml/s and $V_t = 1000$ ml at $Q = 250$ and 500 ml/s. It is clearly seen that the degree of scatter of data points is comparable at different particle sizes for both male and female subjects.

From the results shown in Table 2, it is noted that the relationship between TDF and NMD, or TDF and breathing pattern (V_t and Q), is consistent between male and female subjects. However, the value of TDF was not consistent depending on particle size. TDF was greater in female than male subjects for NMD = 0.04 μm ($p < .05$) for most breathing patterns; the difference ranged between 6 and 15%. These differences were moderate with NMD = 0.06 μm , and no significant differences were observed for NMD = 0.08 and 0.10 μm particles (see also Figure 5).

In Figure 6, the mean TDF for each particle size is compared for two different flow rates at a constant tidal volume of $V_t = 500$ and 1000 ml. In

all cases, TDF is higher at the lower flow rate. For example, for NMD = 0.10, 0.08, 0.06, and 0.04 μm and $V_t = 500$ ml, the mean TDF was 0.26, 0.30, 0.35, and 0.44 at $Q = 250$ ml/s, and increased to 0.34, 0.40, 0.44, and 0.53, respectively, at $Q = 150$ ml/s. At the largest tidal volume evaluated (i.e., $V_t = 1000$ ml) and for the same sequence of particles, TDF was 0.28, 0.33, 0.45, and 0.54 at $Q = 500$ ml/s, and increased to 0.40, 0.47,

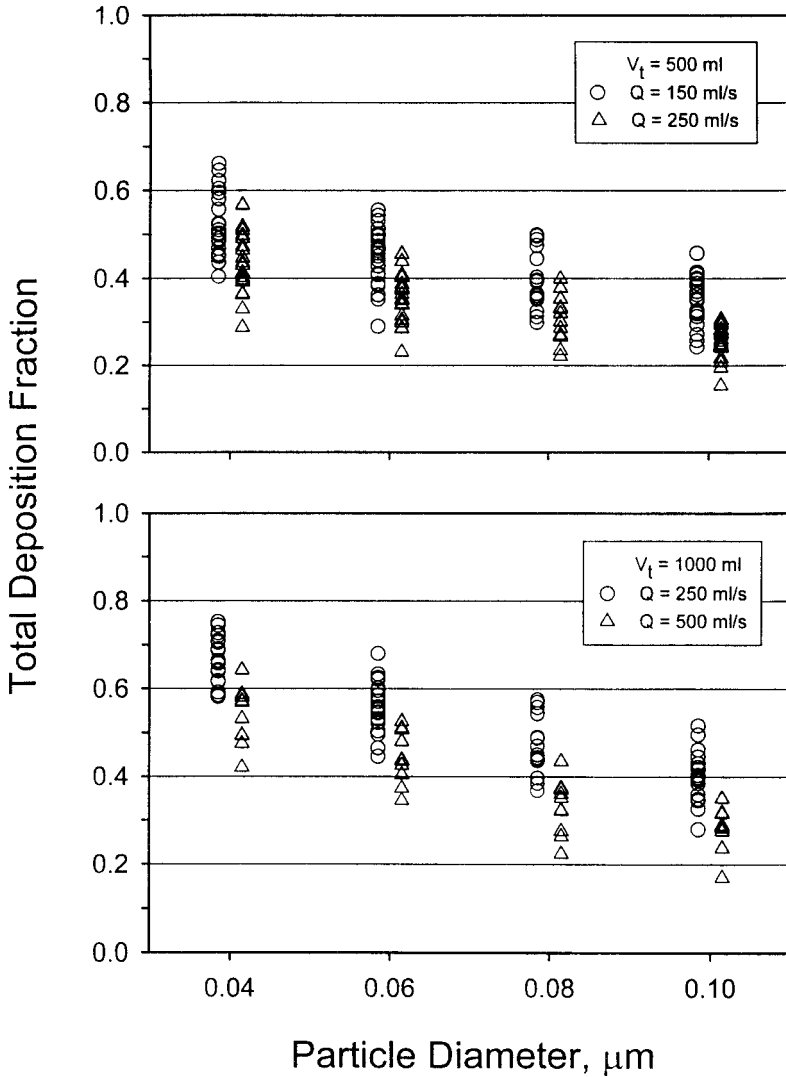


FIGURE 4. Scatter plot of individual data points of total lung deposition fraction showing intersubject variability among 22 healthy men and women under 4 different breathing conditions. Upper panel, tidal volume $V_t = 500$ ml and flow rate $Q = 150$ (\circ) and 250 (Δ) ml/s; lower panel, $V_t = 1000$ ml and $Q = 250$ (\circ) and 500 (Δ) ml/s.

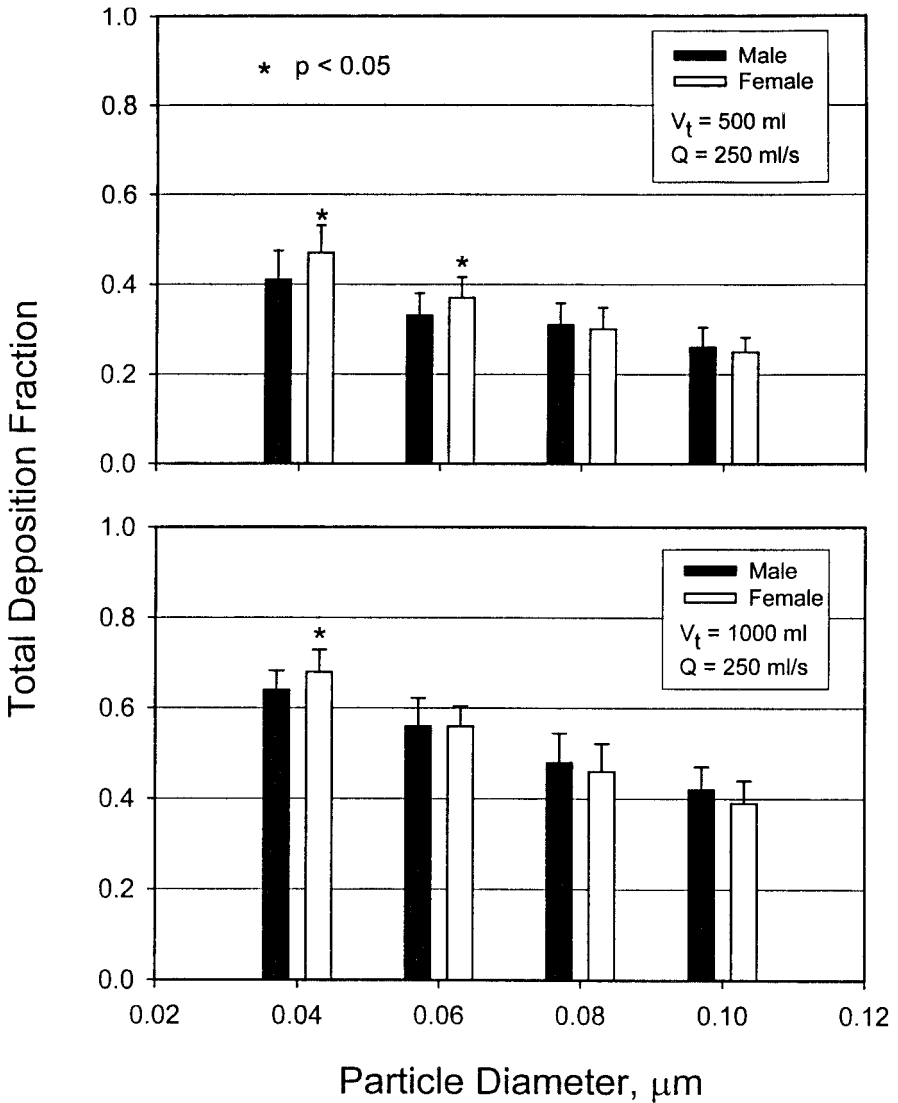


FIGURE 5. Comparisons of total lung deposition values between men (solid bar) and women (open bar) for four different size ultrafine aerosols. Tidal volume (V_t) of 500 ml (upper panel) and 1000 ml (lower panel) at a respiratory flow rate (Q) of 250 ml/s. Error bars represent standard deviations. Asterisk indicates significant difference ($p < .05$) versus men.

0.56, and 0.66 at $Q = 250$ ml/s. The increases in TDF were significant in both cases ($p < .05$). In Figure 7, we compare the effects of tidal volume on TDF at a constant flow rate of 250 ml/s for each particle size. Here, TDF is greater for the larger tidal volume at all particle sizes evaluated. Because Q was fixed, the respiratory time (T) was longer with an increase in tidal volume: $T = 4, 6,$ and 8 s for $V_t = 500, 750,$ and 1000 ml, respec-

tively. These results indicate that the TDF of ultrafine particles increases with breathing patterns of longer respiratory time.

Figure 8 illustrates the relationship between TDF and respiratory time for $NMD = 0.04$ and $0.1 \mu\text{m}$ aerosols. The general trend demonstrates that TDF increases with T for all breathing patterns between 4 and 8 s. However, for a given value of T , TDF also is seen to increase with an increase in tidal volume. The magnitude of the effect of V_t on TDF is greater for $NMD = 0.04 \mu\text{m}$ than $0.10 \mu\text{m}$. For example, for $NMD = 0.10 \mu\text{m}$, TDF (all subjects) ranges from 0.26 at $V_t = 500 \text{ ml}$ and $Q = 250 \text{ ml/s}$,

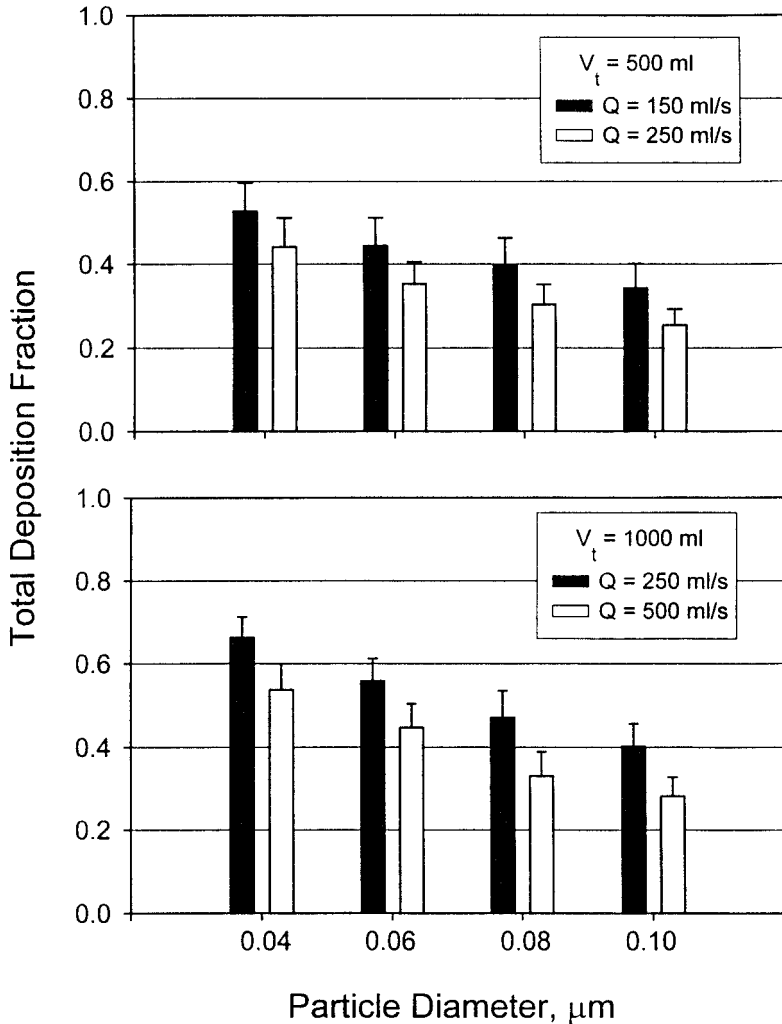


FIGURE 6. Effect of respiratory flow rate (Q) on total lung deposition of ultrafine particles. For a given value of tidal volume, $V_t = 500 \text{ ml}$ (upper panel) and 1000 ml (lower panel), two different flow rates are compared: 150 versus 250 ml/s and 250 versus 500 ml/s . Error bars represent standard deviations.

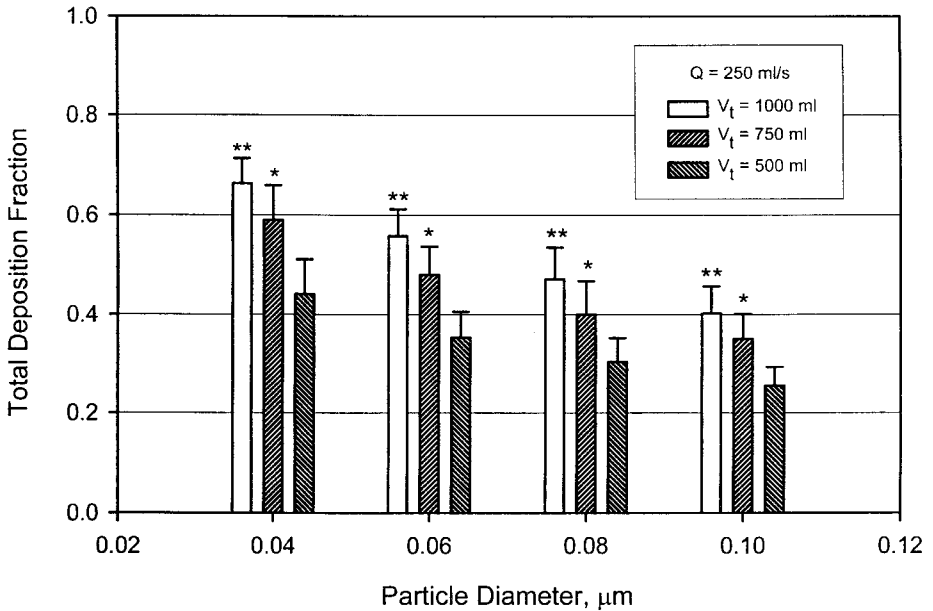


FIGURE 7. Effect of tidal volume (V_t) on total lung deposition fraction of ultrafine particles. At a constant flow rate of 250 ml/s, results with three different tidal volumes (500 ml, left hatched; 750 ml, right hatched; 1000 ml, open bar) are compared for each of four different sized ultrafine aerosols. Double and single asterisks indicate a significant difference ($p < .05$) versus $V_t = 750$ and $V_t = 500$ ml, respectively.

to 0.28 at $V_t = 1000$ ml and $Q = 500$ ml/s. The differences in TDF for NMD = 0.04 µm for these same respective breathing conditions range between 0.44 and 0.54. The increase was 23% for NMD = 0.04 µm, versus 8% for NMD = 0.1 µm. However, the rate of increase in TDF with T does not differ between particle sizes for a given tidal volume, where no observable differences exist between their slopes. These results reflect the fact that V_t , T , and NMD all affect TDF, but they also suggest that flow rate may have an inconspicuous influence on the TDF of smaller ultrafine particles, as discussed next.

DISCUSSION

For all breathing patterns studied (i.e., $V_t = 500$ ml at $Q = 150$ and 250 ml/s; $V_t = 750$ ml at $Q = 250$ and 375 ml/s; and $V_t = 1000$ ml at $Q = 250$ and 500 ml/s), the total deposition fraction (TDF) in healthy adult lungs increases with a decrease in ultrafine particle size. The results in the present study also show that total deposition is greater for breathing patterns with longer respiratory time and larger tidal volume. These results are consistent with theoretical predictions that deposition of ultrafine particles is mainly dictated by diffusive motion of particles, the effec-

tiveness of which is greater with smaller particle size and longer diffusion time. The present study is the first to provide TDF data for ultrafine particles based on a large number of subjects and the first to compare results from male and female subjects.

Effects of Breathing Pattern

Typical activity patterns of individuals vary substantially, resulting in a variety of breathing patterns and exposures to ambient particles. Using noninvasive inductive plethysmograph techniques, the tidal volume and breathing frequency of healthy adults at a resting condition have been reported to be in the range of 400–500 ml and 15–17 breaths/min, respectively (Tobin et al., 1983; Bennett et al., 1996). The respiratory flow rate was in the range of 200–280 ml/s in those studies. During exercise, individuals inhale more deeply and more rapidly: for example, $V_t \approx 1000$ ml and $Q \approx 750$ ml/s during light exercise (ICRP, 1994). Therefore, the breathing patterns used in the present study may represent those expected during resting and light exercise. In theory, for aerosols with particle diameter (d_p) $< \sim 0.16 \mu\text{m}$, the effect of diffusion tends to dominate particle deposition, in comparison to that from settling losses, which are determined by the gravitational force (Hinds, 1982). Because diffusive motion

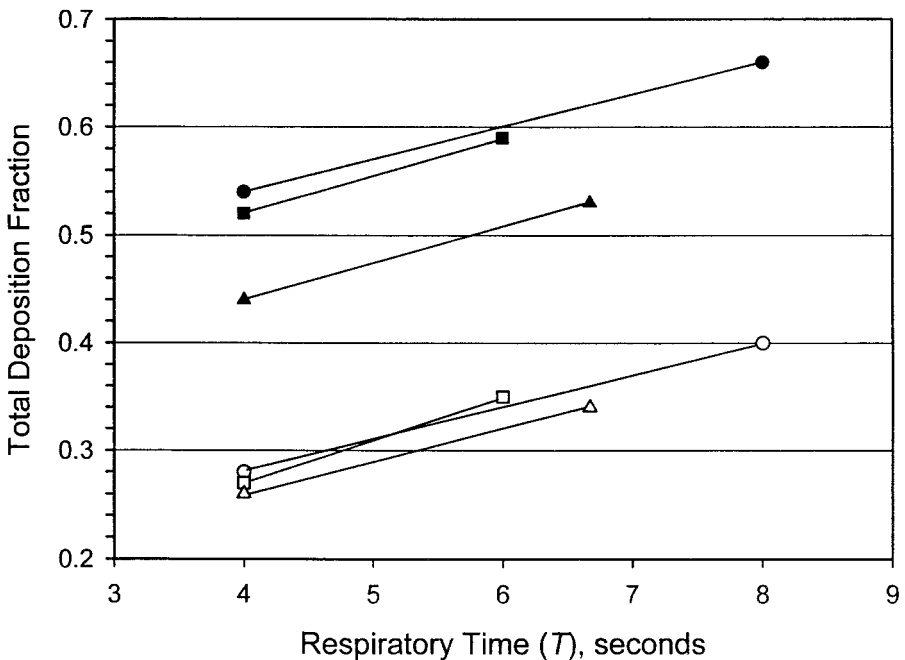


FIGURE 8. Total lung deposition fraction as a function of respiratory time and tidal volume for ultrafine particles with NMD = $0.04 \mu\text{m}$ (solid symbols) and $0.10 \mu\text{m}$ (open symbols). Three different tidal volumes are compared: 500 (triangle), 750 (square), and 1000 (circle) ml. NMD, number median diameter.

is more effective with smaller sized particles and with longer diffusion times, the TDF of ultrafine particles is expected to increase with smaller particles and with breathing patterns having longer respiratory times (i.e., longer particle residence time in the lung). Our results agree with theoretical predictions and show a consistent increase in TDF with decreasing particle size from $NMD = 0.1$ to $0.04 \mu\text{m}$ and with increasing respiratory time from 4 to 8 s. It should be noted that the rate constant of coagulation is much greater for ultrafine particles than for larger particles (Fuchs, 1964). This may cause changes in particle size and subsequently affect TDF if the respiratory time is too long. However, the coagulation rate is primarily dictated by aerosol concentration, and a noticeable change in particle size can occur only if aerosol concentration is very high, that is, $>10^7$ particles/cm³. Under the present experimental conditions, aerosol concentration = $\sim 5 \times 10^5$ particles/cm³ and $T < 10$ s; thus, the coagulation effect is negligible.

Our results shown in Figure 8 indicate that in addition to respiratory time, tidal volume plays an additional role in the lung deposition of ultrafine particles. When the tidal volume is increased with respiratory time held constant, the lung deposition of fine particles ($d_p < \sim 1 \mu\text{m}$) is expected to increase because (1) particles penetrate deeper into the lung, where airway dimensions are small (i.e., short deposition distance), and (2) particles reside for a longer period of time in the deep lung regions (vs. proximal airway regions) (Kim et al., 1983; Yu & Diu, 1983). For example, for a given value of respiratory time of $T = 4$ s, the residence time of particles in the alveolar region will increase from 2.8 to 3.4 s as the tidal volume is increased from 500 to 1000 ml (assuming that the deadspace volume, i.e., ~ 150 ml, remains unchanged). This longer residence time, combined with a short deposition distance, is clearly a formula for the enhancement of lung deposition for ultrafine particles, whose deposition takes place mainly by a time-dependent mechanism, Brownian diffusion. The present results show that the tidal volume effect is pronounced, particularly for $NMD = 0.04 \mu\text{m}$, compared to larger ultrafine particles ($NMD = 0.1 \mu\text{m}$). This may be attributed partly to the fact that deposition efficiency is much greater with $NMD = 0.04 \mu\text{m}$ than $0.1 \mu\text{m}$ (i.e., Brownian diffusion coefficient = 3.553×10^{-5} vs. 6.749×10^{-6} cm²/s). Therefore, TDF is affected to a greater degree with smaller ultrafine particles by small changes in breathing pattern. Nevertheless, the present results show that both the respiratory time and tidal volume are important breathing parameters affecting the deposition of ultrafine particles in the lungs.

Differences Between Men and Women

Previous studies have investigated a potential difference in TDF between male and female subjects, primarily for supramicrometer particles, $d_p = 1\text{--}7.5 \mu\text{m}$ (Pritchard et al., 1986; Kim et al., 1988; Bennett et al., 1996; Kim & Hu, 1998). These studies have shown that TDF is greater by

10–30% for women versus men for coarse particles with $d_p \geq 2 \mu\text{m}$, but there was no gender effect on TDF for fine particles with $d_p = 1 \mu\text{m}$. Based on detailed analyses of the regional deposition patterns of these particles, the observed gender effect was attributed to the local deposition enhancement in the proximal region of the lung in female subjects, which probably occurred because of the smaller dimensions of their upper airways and subsequent enhancement of inertial impaction (Kim & Hu, 1998). These results may not have a direct relevance to ultrafine particles because inertial impaction is not expected to have any significant effect on deposition of such particles. However, the present results reveal a greater TDF in women than men for NMD = $0.04 \mu\text{m}$, but not for larger ultrafine particles (i.e., NMD = $0.1 \mu\text{m}$), consistent with the earlier finding that there is a gender effect only for those particles having an inherently large deposition probability. It should be noted that lung deposition of particles takes place minimally at $d_p \approx 0.5 \mu\text{m}$ and is generally inefficient within the size range of $d_p = 0.1\text{--}1 \mu\text{m}$ (Yu, 1978; Stahlhofen et al., 1989). The present results suggest that the factors causing differential TDF between men and women may be subtle, but can be important under certain inhalation conditions.

The differential TDF for gender may be related to the differences in male and female lung size. Because all subjects inhaled aerosols with the same tidal volumes, aerosols may have penetrated the lung more deeply, and this may have resulted in greater deposition for subjects with smaller lungs. The effect of lung size on TDF is essentially the same as that of tidal volume, as discussed earlier. The average lung size was smaller in female than male subjects in the present study (FRC = 3014 vs. 3911 ml), which could explain the observed differences in TDF. However, when TDF was compared among individuals within each gender group, there was no significant correlation between TDF and lung volume either in men or women, despite the wide variation in lung size (the range of FRC was 2943–5913 ml in males and 2117–3953 ml in females). This finding is consistent with a previous ultrafine particle deposition study (Blanchard et al., 1984) in which TDF did not correlate with measures of lung volume or body size. These results therefore suggest that lung volume itself may not be an important factor for the differential TDF observed between men and women, and that some other factors may play a role, either solely, or in conjunction with a lung volume effect. It has been shown that the dimensions of the upper airways, particularly the larynx, are much smaller in women than men, even if the lung or body size is the same (Martin et al., 1987; Eckel et al., 1994). Therefore, it may be expected that the airflow environment of the upper airways is more turbulent for women than men (note that airflow is usually turbulent in the upper airways). Under such conditions, deposition of ultrafine particles is likely to be dictated by turbulent diffusion, and this can result in a greater TDF in women compared to men (Kim et al., 1998). However, it is unclear if the small difference in dose could lead to the differential health effects between the genders.

Comparison to Earlier Studies

There are only a few studies that have investigated lung deposition of ultrafine particles. In the studies of Tu and Knutson (1984), the TDF of one subject is shown in the range of 0.34–0.60 for $d_p = 0.04\text{--}0.095\ \mu\text{m}$ at a breathing pattern of $V_t = 750\ \text{ml}$ and $Q = 375\ \text{ml/s}$, and 0.26–0.38 for $d_p = 0.083\text{--}0.12\ \mu\text{m}$ at a breathing pattern of $V_t = 1000\ \text{ml}$ and $Q = 500\ \text{ml/s}$. These results appear to be substantially in agreement with the present results. Schiller et al. (1986) have reported that the TDF for their five subjects was in the range of 0.21–0.39 at a breathing pattern of $V_t = 500\ \text{ml}$ and $Q = 250\ \text{ml/s}$, and 0.34–0.60 at a breathing pattern of $V_t = 1000\ \text{ml}$ and $Q = 250\ \text{ml/s}$ for $d_p = 0.038\text{--}0.10\ \mu\text{m}$. These deposition values are somewhat smaller than the present results. However, it should be noted that there were many differences between the previous studies and present study, such as, in aerosol material, size distribution of aerosols, aerosol detection method, control of breathing, and so on. Most of all, the number of subjects studied was very small in the previous studies ($n = 1$ and 5) compared to that in the present study ($n = 22$). Because of these differences, direct comparisons of TDF between the previous and present studies may not be meaningful. Nevertheless, all results are within the $\pm 20\%$ range. The present results are based on a larger number of subjects and therefore are more representative of the general population. They should be useful for estimating lung dose of ultrafine particles in both men and women.

CONCLUSIONS

Total lung deposition fraction (TDF) of ultrafine aerosols has been measured in healthy men and women under controlled breathing conditions. As expected from theory, TDF increased with a decrease in particle size from $\text{NMD} = 0.1$ to $0.04\ \mu\text{m}$ and increased with breathing patterns having longer respiratory time (i.e., longer residence time of particles in the lung). Intersubject variability of TDF was comparable between men and women regardless of particle size and breathing pattern used, but TDF was greater in women than men, particularly for very small ultrafine particles. These results, based on a large number of both male and female subjects, provide reliable data that may be useful for estimating lung dose of ultrafine particles in humans under normal breathing conditions.

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