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A Probabilistic Model for Intersubject Deposition Variability of Inhaled Particles

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Experimental data on total and regional deposition of inhaled particles in the human respiratory tract show a significant amount of intersubject variability even under well-controlled breathing conditions. To explain this variability, a probabilistic lung model is proposed in which two random scaling factors are introduced to account for intersubject differences in airway dimensions, one for the tracheobronchial region and the other for the alveolar region. The calculated deposition based upon this model shows excellent agreement with experimental data, thus further supporting the view that the major cause of intersubject deposition variability in various regions is difference in airway size.

INTRODUCTION

It has been well established that the amount of inhaled particles deposited in the respiratory tract depends on the particle characteristics and the airflow condition, as well as on the structure and dimensions of the respiratory tract. Experimental measurements of total and regional depositions using monodisperse aerosols under controlled steady breathing conditions have shown considerable variability among subjects (Altshuler et al., 1957; Love et al., 1971; Giacomelli-Maltoni et al., 1972; Davies et al., 1977; Palmes and Lippmann, 1977; Foord et al., 1978; Heyder et al., 1978, 1980; Tarroni et al., 1980; Chan and Lippmann, 1980; Stahlhofen et al., 1981). The major cause of this variability was proposed by theory (Yu et al., 1979) and confirmed by experiment (Heyder et al. 1980) to be differences in tract morphology.

The earlier theoretical-model study of Yu et al. (1979) on intersubject variability had not included deposition in the extrathoracic or head region. This deposition is important for particles with aerodynamic diameter larger than 2 μm (Stahlhofen et al., 1981). Because aerosol particles enter the lung after escaping capture in the head region, deposition variability in the tracheobronchial and alveolar regions will be affected if head deposition is included. There has been some speculation that the observed deposition variability in the tracheobronchial and alveolar regions is caused by that in the head. To answer this question and to obtain an accurate estimate of deposition variability in various regions, a probabilistic analysis of particle deposition in a complete respiratory system is presented in this paper.

HEAD DEPOSITION EFFICIENCIES

Inhaled particles are deposited along the air passages in the head before entering the lung. The dynamics of particle motion in this region is very complex owing to the complexity of the passage geometry. The residence time of the particles in this passage, however, is relatively short ($\sim$0.2 sec). Thus, for micron-sized particles, sedimentation is insignificant and the major mechanism of deposition is impaction.

There were two previous theoretical studies (Landahl, 1950; Scott et al., 1978) on nasal deposition at inspiration. These studies had not

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provided a useful formula for predicting deposition. At the present time, useful deposition formulas are derived only empirically. Yu et al. (1981) have reported the following expressions for deposition efficiency in the head, based on a comprehensive analysis of all existing experimental data: At inspiration,

$$\left.\begin{aligned}\bar{\eta}_{NI} &= -0.014 + 0.023 \log I \\ \sigma_{NI} &= 0.034\end{aligned}\right\}, \quad I < 337, \tag{1a}$$

$$\left.\begin{aligned}\bar{\eta}_{NI} &= -0.959 + 0.397 \log I \\ \sigma_{NI} &= 0.145\end{aligned}\right\}, \quad I > 337, \tag{1b}$$

$$\bar{\eta}_{MI} = \sigma_{MI} = 0, \qquad I < 3000, \tag{2a}$$

$$\left.\begin{aligned}\bar{\eta}_{MI} &= -1.117 + 0.324 \log I \\ \sigma_{MI} &= 0.144\end{aligned}\right\}, \quad I > 3000; \tag{2b}$$

and at expiration,

$$\left.\begin{aligned}\bar{\eta}_{NE} &= 0.033 + 0.003 \log I \\ \sigma_{NE} &= 0.046\end{aligned}\right\}, \quad I < 215, \tag{3a}$$

$$\left.\begin{aligned}\bar{\eta}_{NE} &= -0.851 + 0.399 \log I \\ \sigma_{NE} &= 0.140\end{aligned}\right\}, \quad I > 215, \tag{3b}$$

$$\bar{\eta}_{ME} = \sigma_{ME} = 0, \qquad \text{all } I. \tag{4}$$

where $\bar{\eta}$ is the mean deposition efficiency, σ is the standard deviation, the subscripts M and N refer, respectively, to mouth and nose breathing and $I = \rho d_p^2 Q$, in which ρ is particle mass density in grams per cubic centimeter, d_p is the particle diameter in microns, and Q is the flow rate in cubic centimeters per second. It has also been shown in their analysis that deposition variability for all cases closely follows a normal distribution. This variability is believed to have been caused by differences in the geometry of the air passages and in the density of nasal hairs among subjects.

PROBABILISTIC LUNG MODEL

The effect of lung airway morphology on the deposition of inhaled particles has recently been studied by Yu and Diu (1982). Employing various lung models in the calculation of particle deposition pattern, they demonstrated that, while total deposition does not vary markedly from model to model, considerable variation does not exist in regional deposition. Because different lung models were developed based on the morphological measurements of different lungs, the differences in the calculated deposition from different lung models will represent the observed intersubject deposition variability under specified breathing conditions.

At the present time, morphological measurements of the airways are not adequate to provide detailed statistical information on intersubject variability. Data are only available for the dimension of trachea, main bronchus and very small airways (<0.2 mm; see Jesseph and Merendino, 1957; Matsuba and Thurlbeck, 1971). It is not possible to construct from these limited data a complete statistical lung model including both structural and dimensional considerations for a normal population of subjects. However, our previous deposition calculations using different lung models (Yu and Diu, 1982) have shown that Weibel's model gives an average deposition among all models for both total and regional deposition. We therefore select this model to be the population mean. The individual variations from the Weibel model are accounted for by the use of two random scaling constants, one for the tracheobronchial region and the other for the alveolar region. Let the total lung volume at rest or function residual capacity (FRC) be V_l. Then for each human subject we may express

$$V_l = V_b + V_a = \alpha V_{bw} + \beta V_{aw}, \tag{5}$$

where V_b and V_a are the volume of airspace in the tracheobronchial and alveolar regions, respectively, the subscript w refers to the Weibel model, and α and β are two independent constants, which differ from subject to subject. The implication of Eq. (5) is that all subjects have the same airway structure as that of Weibel, but their airway dimensions in the tracheobronchial and alveolar regions differ. This is, of course, a very crude lung model in which individual variation is accounted for, but it is consistent with the present level of experimental capability since only regional deposition can be measured. In a human population, the constants α and β

have probabilistic distribution given by $f(\alpha)$ and $g(\beta)$, respectively. For the sake of simplicity we assume these functions to be the same and to have a log normal distribution. The expected value and variance of V_l are then found to be

$$\bar{V}_l = \int_0^\infty \int_0^\infty (\alpha V_{bw} + \beta V_{aw}) f(\alpha) g(\beta)\, d\alpha\, d\beta$$

$$= \bar{\alpha} V_{bw} + \bar{\beta} V_{aw} \tag{6}$$

and

$$\mathrm{Var}\{V_l\} = \overline{V_l^2} - \bar{V}_l^2$$

$$= \mathrm{Var}\{\alpha\} V_{bw}^2 + \mathrm{Var}\{\beta\} V_{aw}^2. \tag{7}$$

Heyder et al. (1980) have measured total deposition for 20 subjects under identical breathing conditions. These subjects, chosen to vary in age, sex, and smoking habit, may be regarded as a representative cross-section of the general public. Table 1 lists some individual characteristics of these subjects. From the data we obtain an average lung volume $\bar{V}$ of 3210.5 cm^3 for the experimental group. Since Weibel's tabulated lung model has a total volume of 4800 cm^3 in which 174.8 cm^3 is for the tracheobronchial region and the remainder for the alveolar region, we first scale this model to the present lung volume of 3210.5 cm^3. The procedure leads to a value of 116.9 cm^3 for V_{bw} and 3093.6 cm^3 for V_{aw}. Consequently, $\bar{\alpha} = \bar{\beta} = 1$. From the data in Table 1 we also obtain a value for $\mathrm{Var}\{V_l\}$ of 595.701 cm^6. Using this result and that for V_{bw} and V_{aw}, we find from Eq. (7)

$$\mathrm{Var}\{\alpha\} = \mathrm{Var}\{\beta\} = \frac{\mathrm{Var}\{V_l\}}{V_{bw}^2 + V_{aw}^2} = 0.062. \tag{8}$$

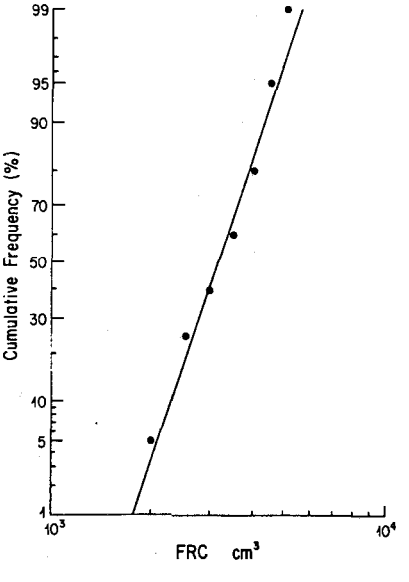
The standard deviations of α and β, denoted σ_α and σ_β, respectively, then each have the value 0.249. Figure 1 shows the culmulative distribution of the lung volumes for the 20 subjects. The straight line in this figure is the assumed log normal distribution with the same mean volume and variance of the data. It is seen that all data points lie closely to the line, indicating that the log normal distribution is a good approximation.

The relationships between the airway dimensions and the lung volume in the human lung

TABLE 1. Characteristics of the Human Subjects in the Experiment of Heyder et al. (1980)

Subject	Age (yr)	Sex	Smoker	FRC (cm^3)
1	45	M	no	2200
2	39	M	no	3000
3	40	M	yes	2800
4	51	M	no	4200
5	25	F	yes	2100
6	30	M	no	3400
7	42	M	no	3900
8	39	F	yes	4200
9	36	F	yes	3400
10	27	M	no	1900
11	40	M	no	3500
12	29	F	no	2700
13	58	M	yes	2700
14	52	M	no	3000
15	24	M	no	4100
16	42	M	yes	3700
17	50	M	yes	4800
18	27	M	yes	2700
19	48	F	no	2400
20	46	M	yes	3500

FIGURE 1. Cumulative distribution of lung volume for the 20 subjects of Heyder et al. (1980). The solid line represents the assumed log normal distribution.



have not been established. From the measurement of dog lungs, Hughes et al. (1972) have found that both airway diameter and length vary with the cube root of the lung volume. We assume that these relationships hold for the human lung and apply them to each region of the lung for deposition calculation.

DEPOSITION CALCULATIONS

Deposition calculations were made by considering the head as a random filter with different filtering characteristics at inspiration and expiration. For deposition with mouth breathing, the calculation is considerably simplified because there is no deposition in the head during expiration. In this case, only one probabilistic parameter is needed to describe the inspiratory deposition in the head. Let us write

$$\eta_{MI}=\gamma\bar{\eta}_{MI} \tag{9}$$

where γ is a constant. Since η_{MI} has a normal distribution with standard deviation σ_{MI} and mean $\bar{\eta}_{MI}$, the distribution function of η_{MI} has the form

$$\begin{aligned}\tilde{h}(\eta_{MI})&=\frac{1}{\sqrt{2\pi}\sigma_{MI}}\exp\left[-\frac{(\eta_{MI}-\bar{\eta}_{MI})^2}{2\sigma_{MI}^2}\right]\\&=\frac{1}{\sqrt{2\pi}\sigma_{MI}}\exp\left[-\frac{(\gamma-1)^2\bar{\eta}_{MI}^2}{2\sigma_{MI}^2}\right]\\&=h(\gamma).\end{aligned} \tag{10}$$

For a sample population, the total and regional mean deposition $\bar{X}$ is determined by the expression

$$\bar{X}=\int_0^\infty\int_0^\infty\int_0^\infty X(\alpha,\beta,\gamma)f(\alpha)g(\beta)h(\gamma)\,d\alpha\,d\beta\,d\gamma, \tag{11}$$

and the corresponding standard deviation is given by

$$\sigma_X=(\overline{X^2}-\bar{X}^2)^{1/2}, \tag{12}$$

in which

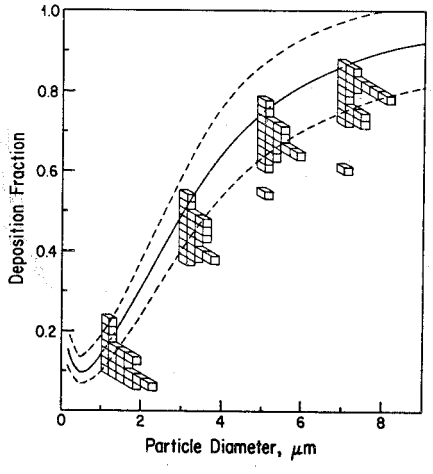
$$\overline{X^2}=\int_0^\infty\int_0^\infty\int_0^\infty X^2(\alpha,\beta,\gamma)f(\alpha)g(\beta)h(\gamma)\,d\alpha\,d\beta\,d\gamma. \tag{13}$$

Using the deposition model we developed earlier (Yu, 1978; Yu and Diu, 1982), $X(\alpha, \beta, \gamma)$ can be determined for a specified set of values α, β, and γ. This value of X is then substituted into Eqs. (11)-(13) and integrated with respect to α, β, and γ numerically to obtain $\bar{X}$ and σ_X for a human population.

RESULTS AND DISCUSSION

Figure 2 shows a comparison of the calculated total deposition and the experimental data on 20 subjects obtained by Heyder et al. (1980). The experiment was conducted using monodisperse di-2-ethylhexyl sebacate particles (density 0.91 g/cm^3) at a controlled breathing condition of 800 cm^3 tidal volume, 4-sec breathing period, with equal time for inspiration and expiration without pause. The solid line in the figure represents the calculated total mean deposition $\bar{T}$, while the dotted lines represent $\bar{T}\pm\sigma_T$, where σ_T is the standard deviation. It is seen that although in this case the calculated mean deposition is slightly higher than the experimental data, remarkable agreement is found for de-

FIGURE 2. Comparison of calculated total deposition at mouth breathing with experimental data of Heyder et al. (1980). The solid line represents the calculated mean deposition, and the dotted lines are the mean ± 1 standard deviation. $\sigma_\alpha = \sigma_\beta = 0.249$.

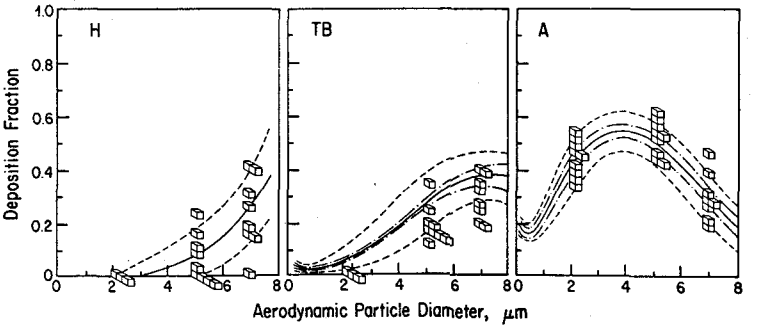


position variability. Also, Figure 2 shows that the amount of variability depends on particle size, increasing as particle size increases for large particles. This indicates that impaction deposition is more sensitive to airway size than the other mechanisms of deposition.

Stahlhofen et al. (1981) have measured regional deposition for nine subjects from the group of subjects used by Heyder. Figure 3 shows their data together with the calculated deposition. The experimental conditions in this case are different from Heyder's. Iron oxide particles (density 3.2 g/cm^3) tagged with ^{198}Au were used for inhalation study. The breathing rate was fixed at 4 sec for inspiration and 4 sec expiration, and tidal volume was 1000 cm^3. The first panel from the left in Figure 3 is the measured head deposition data for mouth breathing. The solid and dotted lines are the mean head deposition $\bar{H}$ and $\bar{H} \pm \sigma_H$, obtained by Stahlhofen et al. (1981) from their data. Using these head deposition results, we calculated deposition in the tracheobronchial and alveolar regions; the results are shown in the second and third panels in Figure 3. The solid lines in these panels are again the calculated mean depositions, while the dotted lines represent the mean deposition ± 1 standard deviation. For the case in which there is no variation in the airway dimensions, $\sigma_\alpha = \sigma_\beta = 0$, deposition variability in the tracheobronchial and alveolar regions can only be caused by that in the head deposition alone. We see that in this case the calculations give a very small deposition variability in the tracheobronchial and alveolar regions, which is inconsistent with the experimental data. However, as σ_α and σ_β increase from zero to a value of 0.249, the amount of variability in regional deposition increases rapidly and excellent agreement between calculation and experiment is finally obtained, as shown in Figure 3. Thus, deposition variability in the head region is incapable of producing the amount of deposition variability observed in the tracheobronchial and alveolar regions. The variability in these regions is caused principally by the differences in the airway dimensions in the lung.

Figures 4–6 show several additional comparisons between the calculated deposition and the experimental data from other investigators. These experiments were conducted with mouth breathing under spontaneous breathing conditions; thus, they included variations in flow rate during breathing. The head depositions efficiencies used in these figures are Eqs. (2a), (2b), and (4). It is seen that the calculated deposition variability is generally smaller than the experimental value for all particle sizes. This is because of the absence of flow rate variations in the calculation and possibly because the values of σ_α and σ_β used in the calculation are not sufficiently high to represent all experimental subjects. Indeed, increasing σ_α and σ_β will increase the standard deviation of total and regional de-

FIGURE 3. Comparison of calculated tracheobronchial deposition TB and alveolar deposition A at mouth breathing with experimental data of Stahlhofen et al. (1981). The solid lines represent the calculated mean deposition. The broken lines are the mean deposition ± 1 standard deviation. $\sigma_\alpha = \sigma_\beta = 0$ (–·–) and $\sigma_\alpha = \sigma_\beta = 0.249$ (– – –).



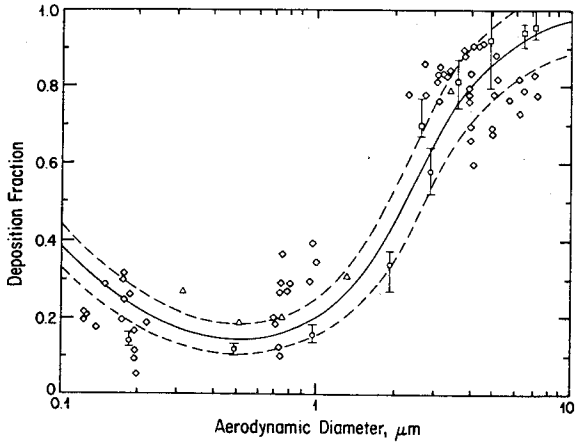


FIGURE 4. Comparison of calculated total deposition by mouth breathing with experimental data by several investigators [diamonds, Chan and Lippman (1980)—14 breaths/min; triangles, Martins and Jacobi (1974)—14 breaths/min; squares, Foord et al. (1976)—15 breaths/min; circles, Heydes et al. (1978)—15 breaths/min] for spontaneous breathing (tidal volume, 1000 cm^3). The solid line represents the calculated mean deposition, and the dotted lines are the mean ± 1 standard deviation. $\sigma_\alpha = \alpha_\beta = 0.249$.

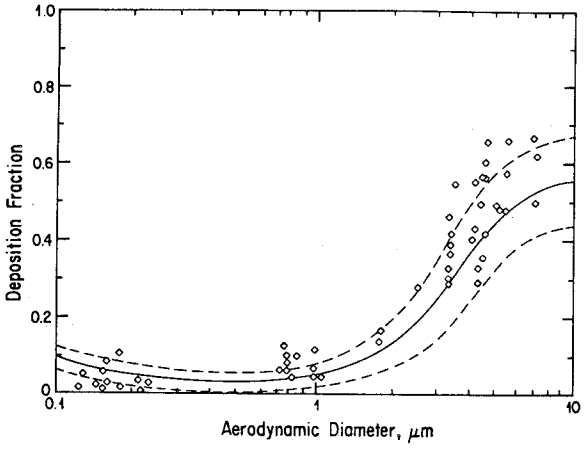


FIGURE 5. Comparison of calculated tracheobronchial deposition at mouth breathing with experimental data of Chan and Lippmann (1980) for spontaneous breathing. (Tidal volume, 1000 cm^3; 14 breaths/min.) The solid line represents the calculated mean deposition, and the dotted lines are the mean ± 1 standard deviation. $\sigma_\alpha = \sigma_\beta = 0.249$.

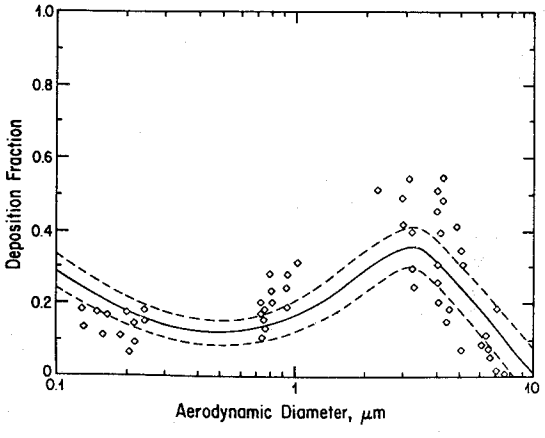


FIGURE 6. Comparison of calculated alveolar deposition at mouth breathing with experimental data by Chan and Lippmann (1980) for spontaneous breathing. (Tidal volume, 1000 cm^3; 14 breaths/min.) The solid line represents the calculated mean deposition, and the dotted lines are the mean ± 1 standard deviation. $\sigma_\alpha = \sigma_\beta = 0.249$.

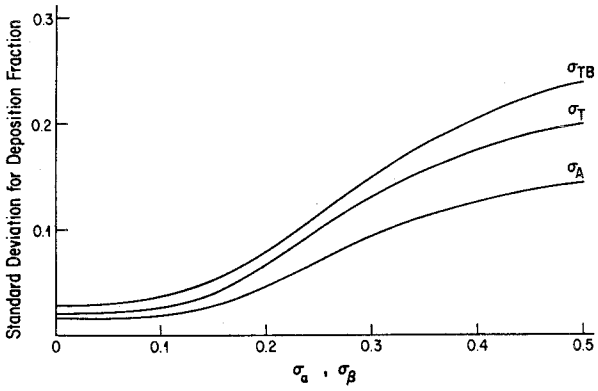


FIGURE 7. Variations of σ_{TB}, σ_A, and σ_T with σ_α and σ_β for 3.2 μm aerodynamic diameter particles in mouth breathing. The breathing conditions are described in the text.

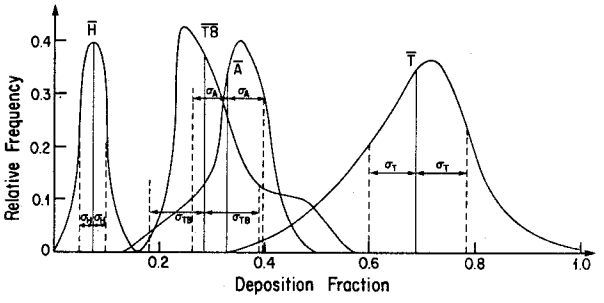


FIGURE 8. Frequency distribution of total and regional deposition for 3.2 μm aerodynamic diameter particles in mouth breathing. The breathing conditions are described in the text.

positions markedly, as shown in Figure 7, which is obtained for a 3.2 μm aerodynamic diameter particle and breathing at constant flow rate and no pause with 1000 cm^3 tidal volume and 14 breaths/min. It is also observed that σ_{TB} is almost twice as large as σ_A, even though the mean tracheobronchial (TB) deposition in this case is slightly lower than the alveolar (A) deposition.

To gain further insight on deposition variability, we calculated the frequency distribution of total and regional deposition for the same particle size and breathing condition used in Figure 7 at $\sigma_\alpha = \sigma_\beta = 0.249$ (Figure 8). Again, we see that the standard deviation of the tracheobronchial deposition is the largest, and the distribution of this deposition is considerably skewed. This appears to be in general agreement with experimental observations.

It is shown in this analysis that airway size is the single most important factor in the consideration of intersubject variability of total and regional deposition under normal steady breathing conditions. The importance of the airway dimensions in deposition has been recognized earlier (Palmes and Lippman, 1977). Our results further support this view.

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