

The Sensitivity of an Inhaled Aerosol Tracheobronchial Deposition Model to Input Parameters

ROBERT F. PHALEN,¹ G. MICHAEL SCHUM,² and
MICHAEL J. OLDHAM¹

¹*Air Pollution Health Effects Laboratory, Department of Community and Environmental
Medicine, University of California, Irvine, CA 92717*

²*Toxic Substances Control Division, California Department of Health Services,
Sacramento, CA 94234*

ABSTRACT

Mathematical predictions of inhaled particle deposition patterns are widely used for evaluating hazards, modeling respiratory tract physiology and designing aerosol medical procedures. The parameters that are used in aerosol deposition models are physical and biological factors including those associated with the suspended particles, the suspending medium, the gravitational force field, the ventilatory airflow and the respiratory tract airways. It is useful to know how each parameter influences the predicted particle deposition in a calculation; that is, how sensitive the prediction is to a variation in each parameter. With such sensitivity information one a) might better estimate the required accuracy and precision of the input parameters for a calculation, and b) can develop new insights into inhaled particle phenomena in humans.

Our sensitivity analysis covered deposition efficiency in the tracheobronchial region only during inspiration. We used a mathematical deposition model published by Yeh and Schum (1980) and our 16 generation airway model (Phalen et al., 1985). The analysis involved varying one model parameter at a time about a pre-selected nominal value. The following parameters were varied: particle diameter; particle density; viscosity of air; acceleration due to gravity; air flow rate; airway lengths; airway radii; airway branch angles; and airway gravity angles. Each analysis was performed for three particle diameters (0.1, 1.0 and 10 micrometers) and two subject ages (2 and 18 years).

The results indicated that variations in each of the parameters can produce significant changes in particle deposition, but the most sensitive parameters were particle diameter and density, air flow rate, and airway lengths and radii.

Key Words: Aerosol, Deposition, Model, Child, Sensitivity

INTRODUCTION

There are many reasons for performing a parameter-by-parameter sensitivity analysis of an aerosol deposition model. From the model improvement point of view, such an analysis can clearly indicate where the model itself must be scrutinized. Those input or intrinsic parameters that most influence the deposition prediction are the parameters that must be carefully considered and most accurately known. A sensitivity analysis can also provide new insights into the phenomena being modeled. For example, an analysis relating to inhaled particle deposition can provide insights into the areas of aerosol medicine and aerosol risk analysis. By examining the case of altered gravity, aerosol inhalation during space travel can be addressed. Also, the analysis may be used to guide airway morphometrists by indicating the accuracy needed in their various anatomical measurements. The results of a sensitivity analysis, however, only provide predictions. These predictions must be independently tested before they are accepted as valid.

Some theoretical and experimental work has been performed related to the sensitivity of aerosol deposition to various physical and biological factors. However, except for the effect of particle size, existing information is very limited. Agnew et al. (1984) examined the various impaction deposition mechanism equations used in calculating particle deposition (for 5 micrometer diameter particles). They considered the theoretical significance of variations in branching angle, air flow rate and lung volume (airway sizes were varied to generate new lung volumes), and compared their calculations to published experimental data. Their findings were 1) that Landahl's impaction equation was in "reasonable agreement" with experimental data, 2) that as branching angle increased from 15° to 45°, predicted particle deposition in a generation 4 airway increased 3 to 10 fold, and 3) that lung volume and air flow rate influenced impaction via their effect on the Reynolds and Stokes numbers.

The effect of exercise (and thus airflow rate) on aerosol deposition has been studied in humans by Bennett et al. (1985) using 2.6 micrometer diameter particles, and by Morgan et al. (1984) using submicron particles. They both concluded that the tracheobronchial deposition fraction was not greatly affected by exercise. However, the increased volume of air inhaled lead to greater total deposition per unit time during exercise and enhanced deposition in larger airways.

Inhaled particle deposition efficiencies for resting humans are quite variable (Lippmann, 1977; Tarroni et al., 1980; Raabe, 1982). There is currently some controversy over the principal reason for this. Bennett (1988) reviewed the data and concluded that differences in breathing pattern are a greater contributor to this variability than are airway anatomical differences. Heyder et al. (1988) concluded that the variability in particle deposition is "primarily due to morphological differences." A sensitivity analysis might shed light on this issue.

Heyder et al. (1980) measured particle deposition in humans using very controlled breathing patterns in order to assess the effects of particle density, inspiration and expiration time, and flow rate. They found that increased density (and thus aerodynamic diameter) for particles with geometrical diameters larger than 0.5 micrometers was associated with increased deposition efficiency. Increased inspiratory and expiratory times also produced greater deposition, due mainly to increased time for sedimentation. Increased air flow rate did not influence the deposition of 1 micrometer diameter particles, but it strongly increased the deposition of the larger particles. As a result of these studies, a deposition parameter X_m was proposed.

$$X_m = [\log (Q/Q_0) - 1.43] \log [pd^2/p_0d_0^2 (t/t_0)^{24/(Q/Q_0)\%}]$$

Where $p_0 = 1 \text{ g/cm}^3$ (particle density); $d_0 = 1$ micrometer (particle diameter); $t_0 = 1$ sec (inspiration and expiration time); and $Q_0 = 1 \text{ cm}^3/\text{sec}$ (average flow rate).

Stuart and Wash (1973) reviewed the development of theoretical aerosol deposition models, and discussed the effects of particle size, shape and density on deposition, but they did not perform a quantitative sensitivity analysis. The authors discussed the influence of several of the parameters used in models on particle deposition efficiency.

Yu and Xu (1987) performed a sensitivity analysis for several parameters on their age-dependent deposition model for inhaled diesel exhaust particles. They concluded that mean particle size (and geometric standard deviation) had the greatest effect on the deposition predictions. They found little effect due to particle density in the particle sizes of interest (0.1 to 0.3 micrometer diameter). They studied the effect of minute ventilation and frequency of breathing on regional deposition and noted that at a given frequency, increasing minute ventilation was associated with decreasing tracheobronchial deposition. The authors also examined tracheobronchial deposition using various published airway geometry models and scaled Weibel's model to various lung volumes (by varying airway sizes). Similar results were obtained with the various models, and larger airway sizes in the Weibel model did not lead to altered tracheobronchial deposition (although total and alveolar deposition were decreased). This sensitivity analysis appears to have been the most complete published to date.

METHODS

For an analysis of inhaled aerosol deposition, a set of deposition equations, an anatomical model, and a set of "nominal values" for each of the model parameters must be chosen. Because we currently use their approach, the equations published by Yeh and Schum (1980) were selected. These equations, which have evolved from earlier models, consider the mechanisms of diffusion, sedimentation and inertial impaction for each generation of the tracheobronchial region (See Appendix). Other approaches to predicting particle deposition exist, but essentially all models incorporate these three deposition mechanisms (Schum and Yeh, 1980; Agnew et al., 1984; Yu and Xu, 1987; Ferron et al., 1985; Cuddihy et al., 1988).

Various numerical descriptions of the tracheobronchial airways have been used in particle deposition models, and each has been useful (Agnew et al., 1984; Ferron et al., 1985). We have selected our own 16-generation tracheobronchial descriptions because they were based on detailed measurements (of lengths diameters and branch angles) on 20 replica, in-situ human casts, and they provide the necessary data for an age range of newborn to young adult (Phalen et al., 1985). The airway dimensions in these models are scaled according to body height using regression equations based on actual morphometric data. For nominal values, we chose a minute ventilation equivalent to 10 liters in the adult, and scaled it to the body mass of a younger (2 year old) individual (Phalen et al., 1985). We selected unit density (1 g/cm^3) spherical particles, in air (viscosity = 181 micropoise) under a 1 g gravity ($g = 980 \text{ cm/sec}^2$). In the sensitivity analysis several parameters were incremented one at a time by $\pm 5\%$, $\pm 10\%$, $\pm 25\%$, $\pm 50\%$, and in some cases intermediate or larger increments. The parameters that were changed included the physical factors of particle diameter and density, viscosity of the gas, and the acceleration due to gravity, and the biological factors including air flow rate (assuming steady inspiratory flow), radii and lengths of the airways, and airway branch and gravity angles. Each time a parameter was changed, the particle deposition calculation was run for 2 ages (2

years and 18 years) and for 3 particle diameters (0.1, 1.0 and 10 micrometers). These particles include 3 regimes for airway deposition: diffusion-dominated, transitional, and inertia-dominated.

It would have been possible for the sensitivity analysis to have been performed theoretically by differentiating the deposition equations, but considering their complexity, and that 16 airway generations would be involved in each calculation, that approach was considered to be too unwieldy.

RESULTS

Physical Factors

The calculated deposition efficiencies using nominal values are shown in Table 1. The results of the sensitivity analysis are summarized in Tables 2-4. Both diameter (aerodynamic for 1 and 10 micrometer diameter particles, geometrical for 0.1 micrometer diameter) and density of the aerosol particle are very important parameters for the 1 and 10 micrometer diameter particles for both ages studied (Figures 1 and 2). As expected, an increasing particle size or density for the two larger particle sizes was associated with increased tracheobronchial deposition via inertial and sedimentational deposition mechanisms. Our results indicate, for example, that underestimating either the diameter or the density of a 1 micrometer particle by only 25% could lead to an underestimate of the tracheobronchial dose for an adult by about 20% of the "true" value.

Similarly, the value of the viscosity of the gaseous medium significantly influenced the predicted deposition of 1 and 10 micrometer particles. For the child and adult, a viscosity change of 10% produced a change in deposition of 1 micrometer diameter particles of about 6%. (Table 3).

As expected, the acceleration due to gravity influenced the deposition of particles that have significant sedimentation (Table 3, 4). For example, in zero-gravity the model predicts that the tracheobronchial deposition of 10 micrometer diameter particles will be about 60% of the value for full-gravity for the 2 year old.

Biological Factors

The air flow rate during breathing was an important parameter that influenced the deposition of all of the particle sizes examined (Figure 3, Table 2, 3, 4). Increased flow rate produced predicted decreases in deposition, except for 10 micrometer diameter particles in the adult, where a slight increase in deposition efficiency was seen for air flows that were elevated. The insensitivity of large particle deposition to increased airflow is due to the very high deposition efficiency that already exists at the nominal air flows.

Airway length increases produced greater deposition for all of the particle sizes modeled (Table 2, 3, 4) due to enhancement of the time-dependent sedimentation and diffusion mechanisms. Changes in airway radii produced significant effects on calculated particle deposition for the 1 and 10 micrometer diameter particles (Figure 4). Deposition efficiency decreased as radii increased. Here, two mechanisms for particle deposition compete: as airway radii increase, sedimentation times increase but impaction velocities decrease.

Airway branch angle increases produced significant increases in predicted deposition efficiency for 1 and 10 micrometer particles via the inertial impaction mechanism. As expected, the effect of changes in gravity angle were related to the sedimentation mechanism. As airways moved toward being more parallel to the gravity vector, deposition decreased for 1 and 10 micrometer diameter particles. This

effect was strongest in the small airways (where gravity angle is very difficult to measure).

Table 1 Calculated tracheobronchial particle deposition efficiencies, as % of the number of particles entering the trachea, for 20 l/min steady flow, inspiration only, using the nominal physical (particle density of 1 g/cm³, g = 980 cm/sec², air viscosity = 181 micropoise) and biological (airway sizes and ventilation from Phalen et al., 1985) parameter values.

Age (Yr)	Diameter (microns)		
	0.1	1.0	10
2	10	4.9	95
18	5.1	3.2	81

Table 2 For a 0.1 micrometer geometrical diameter particle, the percent change in calculated particle deposition in the tracheobronchial tree produced by a ± 10% change in each input parameter. Cases for which the change in deposition is less than 1% are omitted.

	Adult		Child	
	-10%	+10%	-10%	+10%
<u>Biological Factors</u>				
Air Flow	+6	-5	+6	-5
Tube Length	-6	+4	-5	+6

Table 3 For a 1 micrometer aerodynamic diameter particle, the percent change in calculated particle deposition in the tracheobronchial tree that is produced by a ± 10% change in each input parameter.

	Adult		Child	
	-10%	+10%	-10%	+10%
<u>Physical Factors</u>				
Part. Diam.	-9	+9	-8	+9
Part. Density	-5	+5	-6	+6
Viscosity	+6	-5	+6	-5
Grav. Accel.	-2	+2	-4	+4
<u>Biological Factors</u>				
Air Flow	-1	+1	+4	-3
Tube Length	-3	+3	-8	+2
Tube Radius	+12	-8	+4	-1
Branch Angle	-4	+3	-2	+2
Grav. Angle	+1	-2	+3	-3

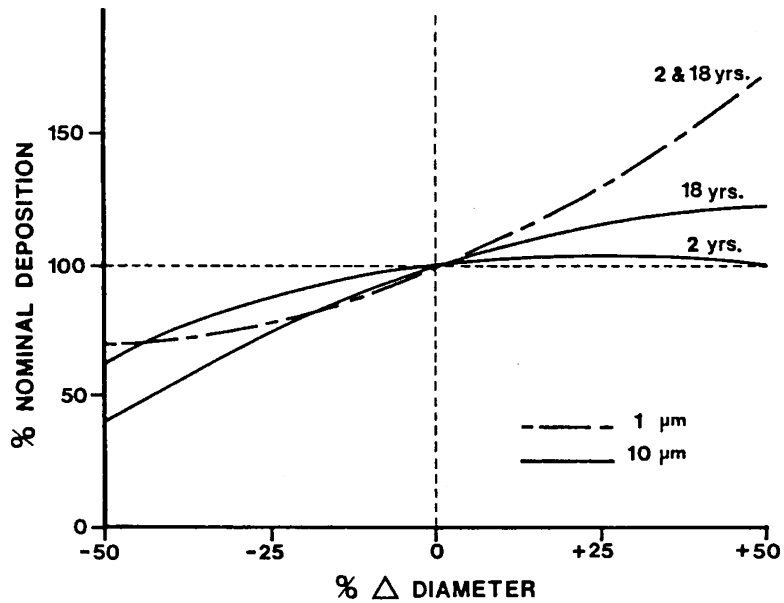


FIGURE 1. Sensitivity of calculated tracheobronchial deposition efficiency to changes in particle diameter. Ages 2 and 18 years are represented. See Table 1 for nominal values.

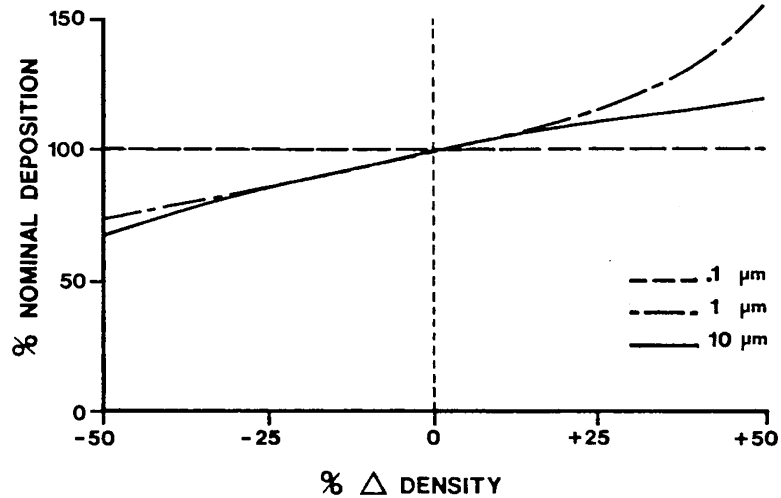


FIGURE 2. Sensitivity of calculated tracheobronchial deposition efficiency to changes in particle density. Age 18 is represented. See Table 1 for nominal values.

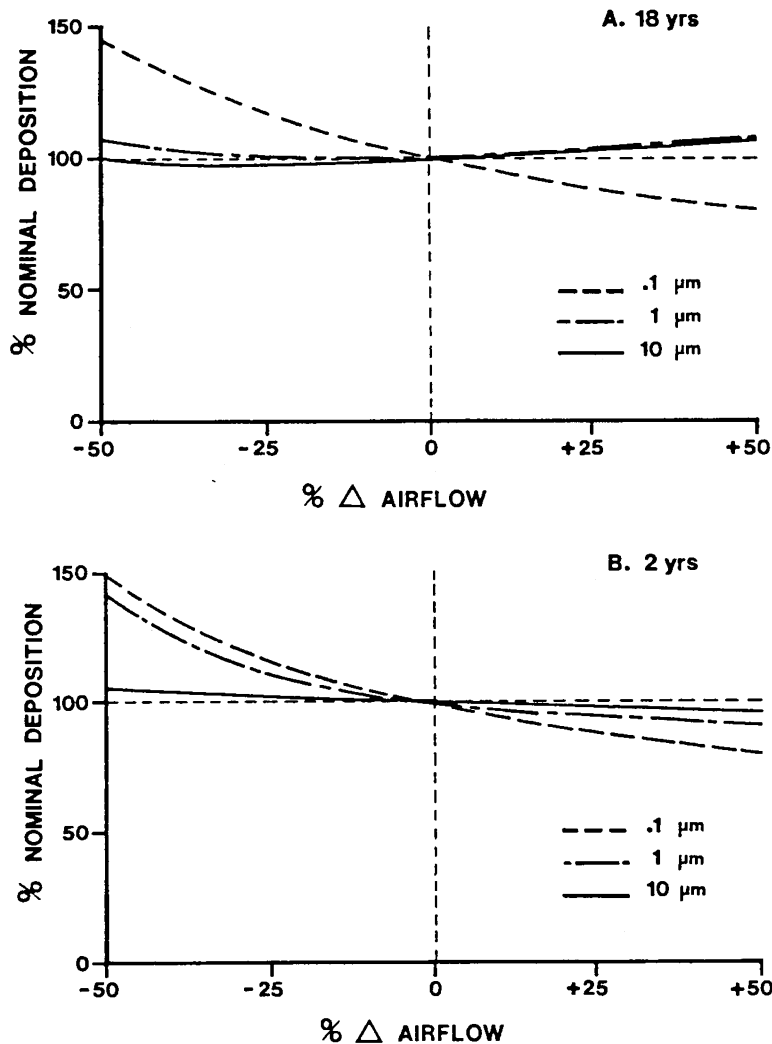


FIGURE 3. Sensitivity of calculated tracheobronchial deposition to changes in inspiratory airflow. A: Age 18 years, B: Age 2 years. See Table 1 for nominal values.

DISCUSSION

Physical Factors

It is clearly indicated that the diameter and density of aerosol particles must be accurately and precisely known in deposition calculations for particles larger than about 1 micrometer in diameter. Thus, in aerosol studies, the accuracy of size estimates that are provided by instrumentation is critical. One should also be aware that aerosol particle densities can differ substantially from the bulk density of the same material, so handbook density values may not be adequate.

The viscosity of the gas can be a significant factor influencing particle deposition, but this fact usually has little practical importance. Because clinical breathing mixtures consist of components with similar viscosities (nitrogen, helium, and oxygen), because

Table 4 For a 10 micrometer aerodynamic diameter particle, the percent change in calculated particle deposition in the tracheobronchial tree that is produced by a $\pm 10\%$ change in each input parameter. Cases for which the change in deposition is less than 1% are recorded as zero.

<u>Physical Factors</u>	<u>Adult</u>		<u>Child</u>	
	-10%	+10%	-10%	+10%
Part. Diam.	-9	+7	-5	+3
Part. Density	-4	+4	-2	+2
Viscosity	+4	-4	+2	-2
Grav. Accel.	-1	+1	-2	+1
<u>Biological Factors</u>				
Air Flow	-1	+2	+1	-1
Tube Length	-1	+1	-1	+2
Tube Radius	+8	-6	0	0
Branch Angle	-3	+3	0	0
Grav. Angle	+1	-1	+1	-1

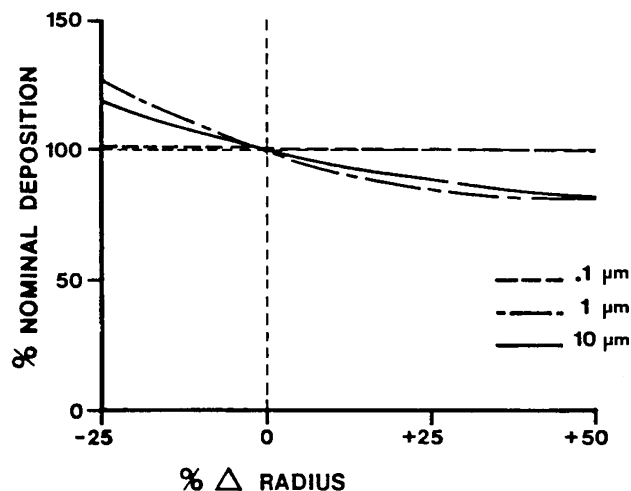


FIGURE 4. Sensitivity of calculated tracheobronchial deposition to changes in airway radius. Age 18 is represented. Changes in airway radius less than -25% produced unrealistic tracheobronchial dead space volumes and were omitted. See Table 1 for nominal values.

variations in water vapor content under livable conditions do not alter viscosity significantly, and because the surrounding pressure does not influence viscosity (except under extreme conditions), the viscosity parameter cannot usually be effectively manipulated. There are two theoretical cases where viscosity could be influential in particle deposition: liquid breathing (extremely high viscosity), and hydrogen gas mixture breathing (very low viscosity).

In the era of space exploration, exposure to low or zero-gravity environments occur. Such environments can greatly reduce the deposition efficiencies for large particles. The implications for space travelers have already been described by Morrow (1967) and by Landahl (1972). Morrow (1967) pointed out that in the absence of gravity the air itself may be more heavily contaminated with aerosol

particles, and that very large (including millimeter-sized objects) that would normally settle can be inhaled and deposit by the interception mechanism. This mechanism is typically neglected in aerosol deposition calculations.

Biological Factors

Inspiratory flow rate can probably be effectively manipulated to increase or decrease particle deposition in the tracheobronchial tree, especially in the young child. A 50% decrease in airflow rate can lead to a predicted increase of about 50% over the normal deposition efficiency for 0.1 micrometer particles. Similarly, a 50% increase in the flow rate over the nominal value can reduce the deposition of these particles by about 20%.

Individual variations in bronchial dimensions can be expected to significantly influence particle deposition. People with unusually long airways (all other factors normal) would be expected to have higher deposition efficiencies. Also, if all other factors are normal, people with either unusually large or unusually small airway radii would be expected to have enhanced tracheobronchial deposition. Our analysis implies that in an individual both bronchoconstriction and bronchodilation would tend to increase tracheobronchial deposition efficiency for particles larger than 1 micrometer in diameter.

Air flow rate is one of the important determinants of predicted particle deposition. Thus, it should be known with an accuracy of about $\pm 5\%$ in order to predict particle deposition within $\pm 10\%$ for small particles.

Our sensitivity analysis sheds some light on the controversy over whether variations in airflow or variations in airway sizes produce the variability of particle deposition seen in humans. With respect to tracheobronchial deposition both parameters are about equally important for small particles; and airway geometry appears to be more important in the 10 micrometer diameter size range for adults.

Implications for Lung Morphometry

When airway dimensions are measured for use as parameters in particle deposition models, how accurate must the measurements be? The sensitivity analysis indicates that inaccuracies of $\pm 10\%$ in airway radii can lead to differences in predicted particle deposition of about 10%. Therefore, tube radii should be measured by morphometrists to $\pm 5\%$ of their true values in order to produce an uncertainty in particle deposition of less than 10%. For airway lengths, branch angles and gravity angles, an accuracy of $\pm 10\%$ in measurement is apparently sufficient to provide deposition predictions that are well within $\pm 10\%$ of their true values. It is important to note that some investigators use 60° for the average gravity angle (based on theoretical considerations) and others use 45° (based on extrapolation of measurements in larger airways) (Phalen et al., 1985). Although these values lead to different deposition predictions, the correct value is not known.

Limitations of the Analysis

Our sensitivity analysis was performed using a simplified model and some assumptions that may not be met in real-world circumstances. Our anatomical model is idealized and does not have the heterogeneity of the human airways. We considered only inhalation, so the effect of pulmonary deposition is neglected. Deposition in the head and larynx is ignored. Also, our model particles were spherical and had a uniform distribution in the inhaled air. Our consideration of particle density is limited to particles whose density is near that of water: other interesting cases exist. As has been pointed out by

Ferron et al. (1985) essentially all of the computational models for tracheobronchial deposition may overestimate the deposition as derived from studies on breathing humans. On the other hand, we believe that the relative sensitivity of calculated deposition to the parameters studied is likely to be a good estimator for the relative sensitivity of deposition to these same parameters in humans.

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APPENDIX (DEPOSITION EQUATIONS)

Deposition by Diffusion

For laminar flow

$$P_D = 1 - 0.819e^{-7.315x} - 0.0976e^{-44.61x} - 0.0325e^{-114x} - 0.0509e^{-79.31y}$$

$$x = \frac{LD}{2R^2\bar{v}} \quad y = x^{2/3}$$

For turbulent flow

$$P_D = \frac{2(Dt)^{1/2}(1-2(Dt)^{1/2} + \dots)}{R} = 2.828x^{1/2}(1 - 0.314x^{1/2} + \dots)$$

Deposition by Sedimentation

$$P_S = 1 - \exp\left[-\frac{4gCpr^2pL \cos\phi}{9\mu R\bar{v}}\right]$$

Deposition by Inertial Impaction

$$P_I = 1 - \frac{2\cos^{-1}(\theta St)}{\pi} + \frac{1\sin\{2\cos^{-1}(\theta St)\}}{\pi} \text{ for } \theta St \leq 1$$

$$P_I = 1 \text{ for } \theta St \geq 1$$

$$St = \text{Stokes' number} = \frac{Cpr^2\bar{v}}{9\mu R}$$

Nomenclature

P_D = diffusion deposition probability
 P_S = sedimentation deposition probability

