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Intercomparison of Experimental Regional Aerosol Deposition Data

W. STAHLHOFEN,[1] G. RUDOLF,[2] and A.C. JAMES[3]

[1]*Gesellschaft für Strahlen- und Umweltforschung*
Institut für Biophysikalische Strahlenforschung
Paul-Ehrlich-Strasse 20
D-6000 Frankfurt am main, FRG
[2]*Institut für Biophysik*
Universität Frankfurt am Main
Paul-Ehrlich-Strasse 20
D-6000 Frankfurt am Main, FRG
[3]*Pacific Northwest Laboratory*
P.O. Box 999
Richland, WA 99352, USA

ABSTRACT

A critical review is presented of the available experimental data on regional aerosol deposition in man. The data agree well for nasal and extrathoracic deposition. For the fast and slow cleared components of thoracic deposition, however, agreement is less satisfactory. The different experimental techniques are critically evaluated, and possible reasons for the observed discrepancies are discussed. Additionally, a semi-empirical model is presented which takes this evaluation into account, and which enables regional deposition to be calculated as function of particle size and respiratory parameters without lengthy computer models. The proposed equations explain and eliminate some of the intra- and inter-individual scatter of the data, and some of the discrepancies between the data from different laboratories. Where these discrepancies could not be eliminated, an additional 'conservative' model for dose estimations is offered which takes account of the uncertainty inherent to the data. A summary of the model equations is given in the appendix.

NOMENCLATURE

a	coefficient of regional efficiency parameter R
B	efficiency parameter of the fast-cleared region
d/d_{ae}	geometric/aerodynamic particle diameter
D	diffusion parameter
DE	total deposition
DE_R	regional deposition (see 'subscripts')
$DE_{T(f)}'$, $DE_{T(f)}''$	see text
E_{ae}	extrathoracic deposition parameter
FRC	functional residual capacity
N_{ae}	nasal deposition parameter
p	pressure drop across the nasal passage

KEY WORDS: empirical model, regional deposition, review

q	power of regional efficiency parameter R
Q	volumetric flow rate
R	regional efficiency parameter
t_A	mean residence time in the alveolated region of aerosol entering this region
t_R	mean residence time in the respective region of aerosol passing this region (see 'subscripts')
V	tidal volume
V_R	aerosol volume coming to rest in the respective region at end-inspiration (see 'subscripts')
V_{B0}	tracheobronchial volume at the onset of inspiration
η	deposition or filtering efficiency
η_R	regional efficiency (see 'subscripts')
$\eta_{T(f)}'$	see text
$\phi_R = V_R/V$	fraction of tidal volume coming to rest in the respective region at end-inspiration (see 'subscripts')

subscripts:	A	alveolated region
	B	tracheobronchial region
	E	extrathoracic region
	L	larynx
	N	nose
	T(f)	fast-cleared thoracic region
	T(s)	slow-cleared thoracic region
	ae	aerodynamic particle size range (inertial and gravitational transport)
	th	thermodynamic particle size range (diffusional transport)

INTRODUCTION

The knowledge of aerosol deposition in the human respiratory tract is an important link between air pollution and respiratory toxicology. It is equally indispensable for an optimization of inhalational therapy, and it may even offer new possibilities regarding the diagnostics of respiratory disease. Consequently, regional aerosol deposition in man has been subject to many years of experimental and theoretical investigation. While numerous review papers have summarized the data, and some authors have presented statistical analyses using much of the available data (Yu et al. 1981, Miller et al. 1988), no comprehensive evaluation and representative modelling of the experimental data has been attempted so far. This paper tries to fill this gap. It reviews and compares the available data on regional deposition, tries to evaluate the experimental techniques applied, and explains some of the apparent discrepancies between the data from different laboratories.

Moreover, this paper offers a semi-empirical model of regional deposition which takes this evaluation into account. Contrary to models which calculate deposition by considering the motions of aerosol particles in morphometric models of the respiratory tract, it allows regional deposition to be calculated without lengthy computer programs. The human respiratory tract is treated as a series of four compartments or filters which the aerosol passes through during respiration. According to the experimental data available, these regions are

the nose,
the mouth and larynx (extrathoracic region),
the fast-cleared thoracic region,
the slow-cleared thoracic region.

The deposition, DE_R, in one of these regions denotes the number of particles deposited in this region divided by the number of particles inhaled. The deposition (or filtering) efficiency, η_R, of a region is the number of particles deposited in that region divided by the number of particles entering the region.

The deposition efficiencies of these regions and the depositions within them are given as functions of particle size and of the respiratory parameters (tidal volume, respiratory flow rate). The formulae cover the particle diameter range from 0.5 nm to 15 µm which, according to the predominant particle transport mechanisms, can be divided into the thermodynamic ($d < 0.1$ µm), transitional (0.1 µm $\leq d \leq 1.0$ µm) and aerodynamic size range ($d > 1.0$ µm) (Heyder 1982). They hold for the aerodynamic particle size given in µm, and the other parameters given in cgs. They are based on experimental data as far as such data were available; in some cases, where no such data were available, theoretical model calculations have been used. The model is a modification of an empirical model described previously (Rudolf et al. 1986, 1988) adapted to the experimental data reviewed.

NASAL DEPOSITION

For aerosols with particle diameters above 0.1 µm, a large number of authors have reported experimental studies on nasal deposition (e.g., Landahl & Black 1947, Dennis & Sawyer 1949, Landahl & Tracewell 1949, Pattle 1961, Lippmann 1970, Fry 1970, Hounam et al. 1971, Giacomelli-Maltoni et al. 1972, Märtens & Jacobi 1973, Rudolf & Heyder 1974). However, due to differing experimental techniques or evaluation procedures, not all of the data are intercomparable. Reviews have been given by Mercer (1975), Lippmann (1977), Yu et al. (1981), and Schlesinger (1985). Yu et al. (1981) have classified the data according to the experimental parameters used, and by statistical analysis they evaluated most of the existing data. Since nasal deposition of particles within the aerodynamic size range is due to impaction, reasonable agreement was found when the data were plotted as a function of d_{ae}^2Q. Yu et al. (1981) divided the range of d_{ae}^2Q values into four sections, and within each section approximated the aerodynamic inspiratory nasal deposition efficiency, η_{Nae}, by a linear function of the logarithm of d_{ae}^2Q, the approximation in the very small and large particle size range being $\eta_{Nae} = 0$ and $\eta_{Nae} = 1$, respectively.

It is, however, possible to represent the data by a unique function of d_{ae}^2Q. Figure 1 shows the same data as evaluated by Yu et al., together with the approximation

$$\eta_{Nae} = 1 - (3.0 \cdot 10^{-4}\ d_{ae}^2Q + 1)^{-1} \quad . \tag{1}$$

Such a unique function obviously fits the data better over the whole range of d_{ae}^2Q values, and the advantage of not having to be concerned with ranges of validity for the formulae is evident.

For nasal inspiration, aerodynamic nasal deposition, DE_{Nae}, is equal to the corresponding nasal efficiency η_{Nae}, because inertial deposition occurs mainly at the front or entrance of the nasal cavity, so that no 'dead space' has to be considered. This is different in the case of extrathoracic deposition during mouth breathing.

It is interesting to note that natural nose breathing (Lippmann 1970, Giacomelli-Maltoni et al. 1972, Märtens & Jacobi 1973, Rudolf 1975) consistently led to somewhat higher values than the artificial inspiration technique used in the first nasal deposition studies (Landahl & Tracewell 1949, Pattle 1961, Hounam et al. 1971), i.e., to pump the aerosol in through the nose and out through the mouth while the subject held his breath. By giving less weight to those data,

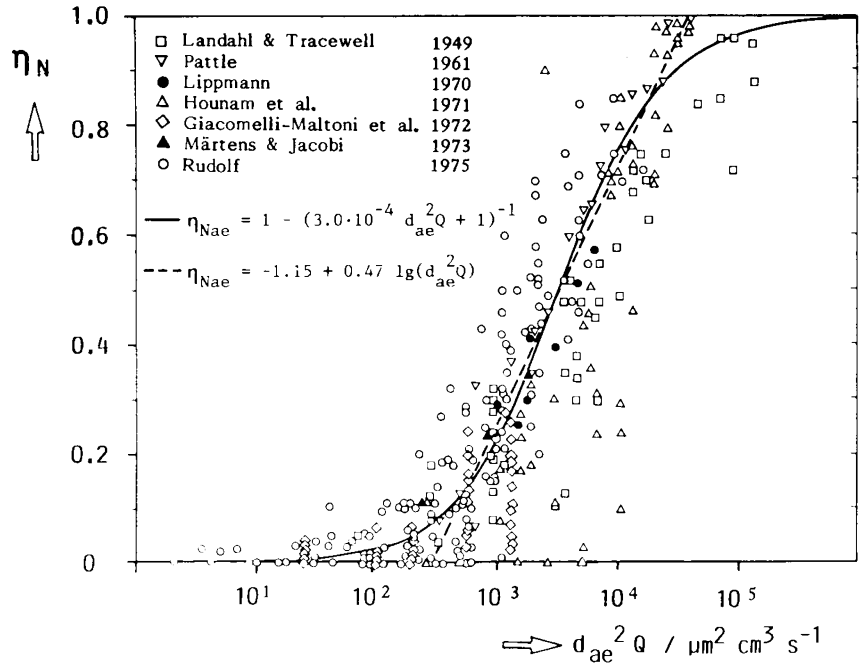

FIGURE 1. Inspiratory deposition efficiency of the human nose as function of d_{ae}^2Q. Experimental data, a hyperbolic approximation (solid curve) and a log-linear approximation which is valid for $2.8 \cdot 10^2 \leq d_{ae}^2Q/\mu m^2 cm^3 s^{-1} \leq 3.8 \cdot 10^4$ (broken line).

this has been accounted for in evaluating Equation 1. Consequently, this function or a log-linear approximation fitted to it (Figure 1) yields somewhat higher values than the approximation given by Yu et al. (1981); it is, however, identical with the approximation published by Heyder & Rudolf (1977), and only slightly larger than the approximation by Pattle (1961) which was later adopted by the ICRP Task Group on Lung Dynamics (1966).

The scatter of the data shown in Figure 1 results at about equal shares from the variability among the different collectives of subjects, from the interindividual scatter among the subjects within the collectives, and from intraindividual scatter. A more detailed analysis of the data (Rudolf 1975) shows that, for constant values of d_{ae}^2Q, the mean efficiencies obtained in the different studies increase with the mean flow rates applied. Correspondingly, in a study based on data of four subjects, a dependence on flow rate stronger than implied by the impaction parameter d_{ae}^2Q was found for flow rates above 400 cm^3s^{-1}, and in one subject even for lower flow rates (Rudolf 1975); also, when η_{Nae} is plotted versus d_{ae}^2Q, a considerable intersubject variability remains (Figure 2).

However, while the intersubject variability and the flowrate-induced intrasubject variability could not be eliminated by plotting η_{Nae} against any function of Q, both could be accounted for when η_{Nae} was plotted against a parameter containing the pressure drop across the nasal passage, p. This parameter has been evaluated to be

$$N_{ae} = d_{ae}^2 p^{2/3} \qquad (2)$$

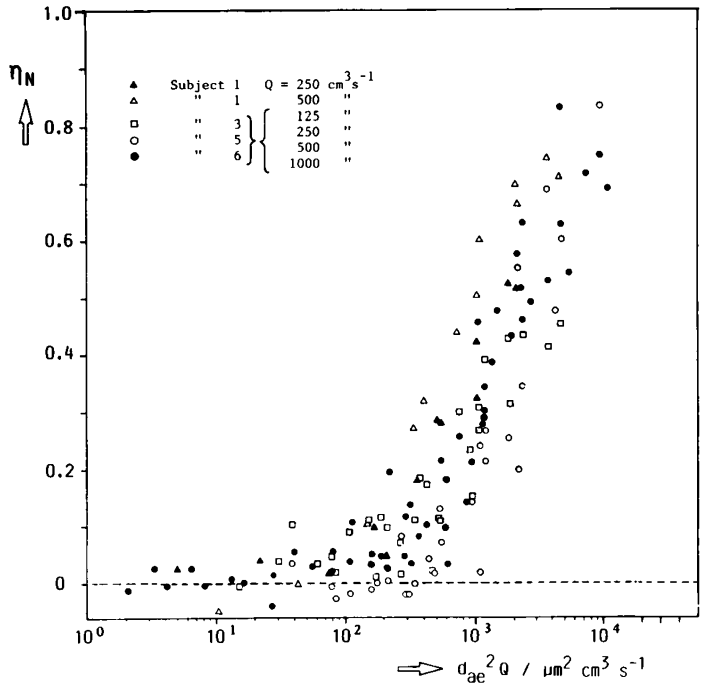

FIGURE 2. Inspiratory efficiency of the nose as function of d_{ae}^2Q. Experimental data of four subjects (Rudolf 1975).

(Rudolf 1975). The result is shown in Figure 3. The aerodynamic inspiratory nasal efficiency is then given by

$$\eta_{Nae} = 1 - (3.5 \cdot 10^{-3}\ d_{ae}^2 p^{2/3} + 1)^{-1} \quad . \tag{3}$$

Hence, it could be concluded that N_{ae} is a more universal parameter than d_{ae}^2Q to describe aerodynamic inspiratory deposition within the nose. Unfortunately, the nasal pressure drop of the subjects volunteering in the other studies is unknown; therefore it cannot be proved that this parameter would decrease or eliminate the variability among the different groups as well. It should do so if this scatter is due to normal intersubject variability. As mentioned above, the artificial inhalation technique used by Hounam et al. (1971) and the groups before adds to this variability, but the efficiency should still be correlated with p rather than with Q. This is, indeed, what Hounam et al. (1971) found.

More experimental work is necessary in order to determine whether N_{ae} is also capable of taking account of the variability in nasal deposition among different collectives, males and females, adults and children, different racial groups, etc. For the subjects examined, however, inspiratory nasal efficiency can be predicted more reliably by Equation 3 than by Equation 1, although Equation 1 may serve as a useful approximation to predict η_{Nae} when p is not known.

For the thermodynamic particle size range very few experimental data are available. Nasal deposition values derived from the experimental total deposition data of Schiller et al. (1986, 1988) suggest an inspiratory nasal efficiency of about 0.15 and 0.04 for particles of 0.005 µm and 0.01 µm in diameter, respectively. This is within the range of the data obtained in a nasal cast by

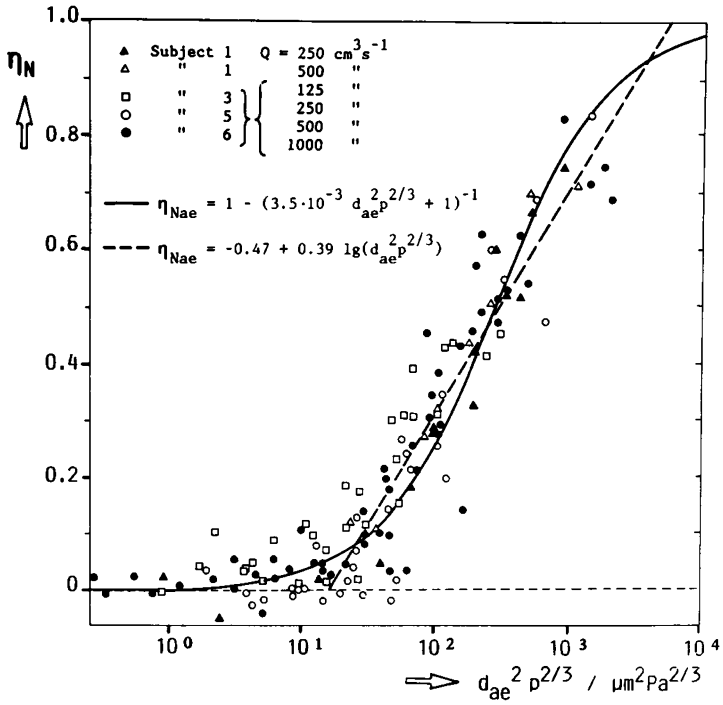

FIGURE 3. Inspiratory deposition efficiency of the nose. The same data as shown in Figure 2 are plotted as a function of $N_{ae} = d_{ae}^2 p^{2/3}$ (p is the pressure drop across the nasal passage). Intraindividual as well as interindividual scatter is reduced as compared to Figure 2. A hyperbolic approximation (solid curve) and a log-linear approximation valid for $1.6 \cdot 10^1 \leq d_{ae}^2 p^{2/3} / \mu m^2 Pa^{2/3} \leq 5.9 \cdot 10^3$ (broken line) are shown.

Strong & Swift (1987), while Cheng et al. (1988) obtained distinctly higher values in their cast study. The data have been modelled by James et al. (1987) in terms of the particle diffusion coefficient D,

$$\eta_{Nth} = 6.5\ (Dt_N)^{1/2} = 45\ (D/Q)^{1/2}\ . \qquad (4)$$

t_N is the residence time of the inspired particles in the nasal passage (see Appendix). For the entire particle size range, inspiratory nasal efficiency η_N and nasal deposition DE_N are obtained by

$$DE_N = \eta_N = (\eta_{Nth}^2 + \eta_{Nae}^2)^{1/2}\ . \qquad (5)$$

Expiratory nasal efficiency has been evaluated for the aerodynamic domain by Heyder & Rudolf (1977). Due to deposition in the lower respiratory tract, however, expiratory nasal deposition is throughout negligible compared to inspiratory deposition.

In setting $DE_N = \eta_N$, we have also assumed that not only aerodynamic, but also thermodynamic nasal deposition concentrates at the front of the nasal passage which introduces a negligible mistake.

In the following sections, expressions for laryngeal and thoracic deposition fractions are derived assuming oral breathing. These formulae are easily adapted to nasal breathing conditions by multiplying them by $(1-\eta_N)$.

EXTRATHORACIC DEPOSITION AT MOUTH BREATHING

Like thoracic deposition, deposition in the head during mouth breathing is experimentally less easy to measure than nasal deposition. Correspondingly, fewer authors have reported such studies. All the available data have been obtained from experiments in which radioactive labelled particles above 0.1 µm in diameter were inspired through a tube held in the mouth (Lippmann & Albert 1969, Lippmann 1977, Foord et al. 1978, Chan & Lippmann 1980, Emmett et al. 1982, Stahlhofen et al. 1980, 1981, 1983). Again, due to differing experimental techniques, direct comparison of the data is not always possible. Reviews have been given by Chan & Lippmann (1980), Yu et al. (1981), and Stahlhofen (1984). Chan & Lippmann (1980) and Yu et al. (1981) have attempted to model the data empirically. These approximations are incorporated in Figure 4 where the same extrathoracic deposition (DE_E) data as evaluated by these authors are shown, supplemented by later experimental data (Stahlhofen et al. 1980, 1981, 1983, Emmett et al. 1982). Also, for a tidal volume of 1000 cm^3, the approximation of DE_E derived in this section is shown.

For the breathing technique used in the reported studies, i.e. breathing through a tube in the mouth, and for d_{ae}^2Q values up to 10^5 $\mu m^2 cm^3 s^{-1}$, evidence was found that the bulk of aerodynamic extrathoracic deposition during mouth breathing occurs in the larynx, namely on the upper side of the vocal chords (Rudolf 1984, 1985). This is in agreement with the gamma scanning results by Emmett et al. (1982), and is also supported by the data of Stahlhofen

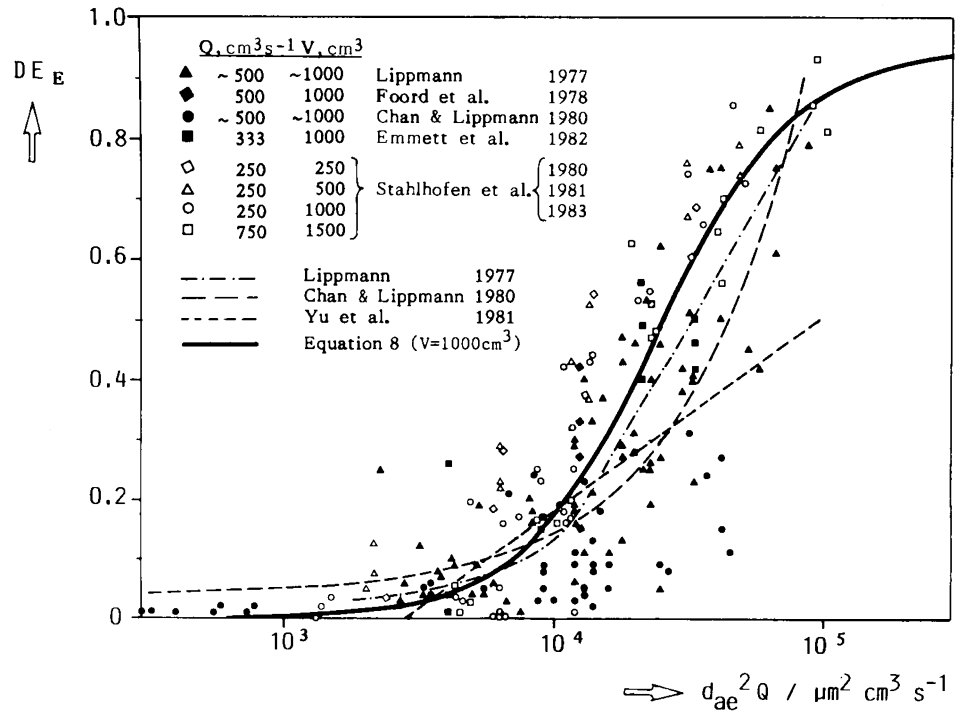

FIGURE 4. Extrathoracic deposition during mouth breathing as function of d_{ae}^2Q. Experimental data, and various approximations proposed in the literature including the one derived in this section (Equation 8) for V = 1000 cm^3.

et al. (1984) which show an increased extrathoracic deposition in larynx carcinoma patients.

There is evidence that during natural mouth breathing (without a tube in the mouth) deposition in the mouth is enhanced compared to these results (Dennis 1961, Bowes & Swift 1986). It can, however, be expected that oral deposition at natural breathing is very sensitive to the degree to which the mouth is opened. The mouth opening, on the other hand, depends on the respiratory parameters (flow rate, breathing frequency) which have not been controlled in these studies.

Hence it must be concluded that little is known about deposition in the mouth and oropharynx; and that the data summarized in Figure 4 give an estimate primarily of laryngeal deposition. Then, for variable tidal volumes, a better correlation of the data with d_{ae}^2Q is expected if instead of extrathoracic deposition, DE_E, the extrathoracic efficiency η_E is considered.

Expiratory deposition in the head can be neglected compared to inspiratory deposition. Then, supposing oral deposition to be negligible as compared to laryngeal deposition, the relationship between laryngeal or extrathoracic inspiratory efficiency, η_E, and extrathoracic deposition, DE_E, may be expressed as

$$DE_E = (1 - V_E/V)\eta_E = \phi_T\eta_E \qquad (6)$$

where V is the tidal volume, V_E the extrathoracic airway volume which has been determined to be about 50 cm^3 (Rudolf et al. 1983), and ϕ_T the fraction of tidal volume that reaches the thorax. The η_E data obtained this way are shown in Figure 5, together with the approximation for the aerodynamic domain,

$$\eta_{Eae} = 1 - (3.5\cdot10^{-8}(d_{ae}^2Q)^{1.7} + 1)^{-1} \ . \qquad (7)$$

Thermodynamic deposition in the extrathoracic region for mouth-breathing is estimated to be negligible for particles above 0.5 nm in diameter. Then, combining equations (6) and (7), an approximation of DE_E is obtained,

$$DE_E = (1 - V_E/V)(1 - (3.5\cdot10^{-8}(d_{ae}^2Q)^{1.7} + 1)^{-1}) \ . \qquad (8)$$

This approximation with V = 1000 cm^3 (ϕ_T = 0.95) is included in Figure 4.

The full advantage of considering η_E instead of DE_E is only realized if the data are plotted as a function of a parameter which takes the influence of the respiratory motions of the vocal chords on laryngeal deposition into account. These motions depend on the respiratory parameters (flow rate, tidal volume, breathing frequency). Such a parameter has been found to be (Rudolf et al. 1983)

$$E_{ae} = d_{ae}^2Q^{2/3}V^{-1/4} \ . \qquad (9)$$

When the η_E data are plotted vs. E_{ae}, the scatter among the data obtained with different breathing parameters is markedly reduced, which is seen when the data of Stahlhofen et al. (1980, 1981, 1983) in Figure 6 are compared to those in Figure 5. Obviously the influence of the respiratory parameters upon η_E is accounted for, and only inter-individual scatter remains. Moreover, also the discrepancies among the data from the different laboratories are reduced. In contrast with Figure 5, in Figure 6 the data by Stahlhofen et al. (1980, 1981, 1983) fall completely within the range of the data by Lippmann (1977) and Chan & Lippmann (1980) (indicated by dashed lines).

It must be concluded, therefore, that the intergroup discrepancies which appear when the data are plotted vs. d_{ae}^2Q partly originate in the different breathing parameters applied. The remaining discrepancy and scatter of the data by Stahlhofen et al. (1980, 1981, 1983) is most likely due to intersubject

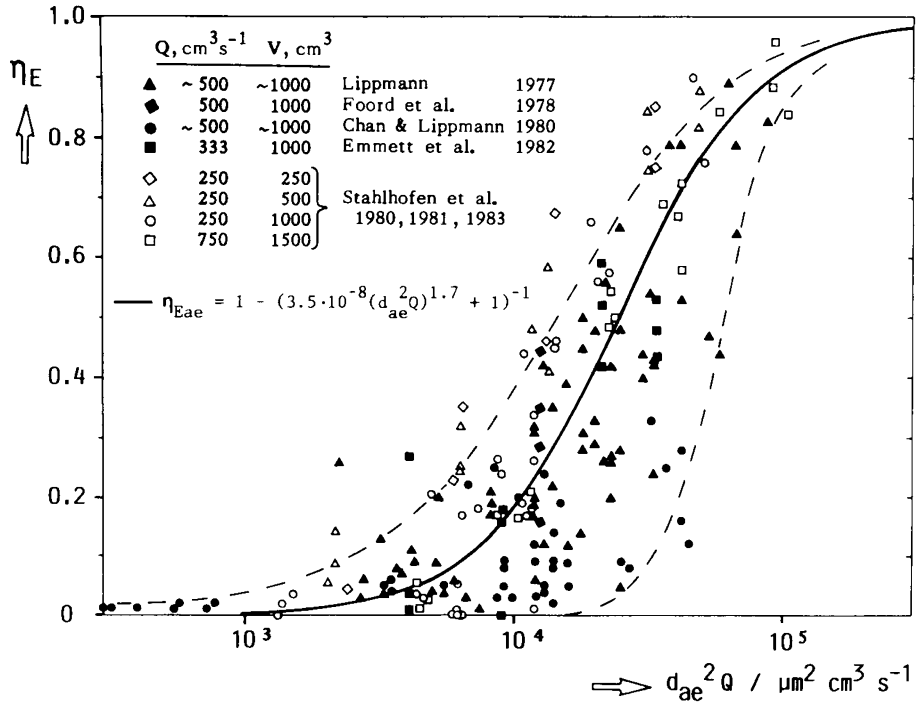

FIGURE 5. Inspiratory extrathoracic deposition efficiency during mouth breathing as function of $d_{ae}^2 Q$. Same experimental data as shown in Figure 4, together with the hyperbolic approximation (Equation 7). The dashed curves indicate the approximate range of the NYU data.

differences in airway geometry. Because the individual breathing parameters of the experiments by Lippmann (1977) and Chan & Lippmann (1980) were not reported, only the mean parameters could be applied in evaluating E_{ae} and hence, for these data, no reduction of intragroup scatter could be achieved.

According to Figure 6, the inspiratory aerodynamic extrathoracic efficiency is best approximated by

$$\eta_{Eae} = 1 - (1.5 \cdot 10^{-5}(d_{ae}^2 Q^{2/3} V^{-1/4})^{1.7} + 1)^{-1} \quad . \tag{10}$$

The corresponding extrathoracic deposition is obtained by Equation 6. Since this deposition occurs mainly in the larynx, an expression of laryngeal deposition during nasal breathing can be obtained by multiplying Equation 6 by $(1-\eta_N)$ (see Appendix). Equations 6 and 10 have been verified experimentally for particle diameters up to 15 µm.

FAST-CLEARED THORACIC DEPOSITION

Like the extrathoracic deposition data for mouth breathing, all the available thoracic deposition data have been obtained from experiments with radioactive labeled particles above 0.1 µm in diameter. Measuring the amount of activity retained in the thorax as a function of time, generally a fast (half-lives of several hours) and a slow (half-lives of tens to hundreds of days) clearance component can be distinguished which have been identified as mucociliary and macrophage clearance. Since ciliated epithelium has been found exclusively in the

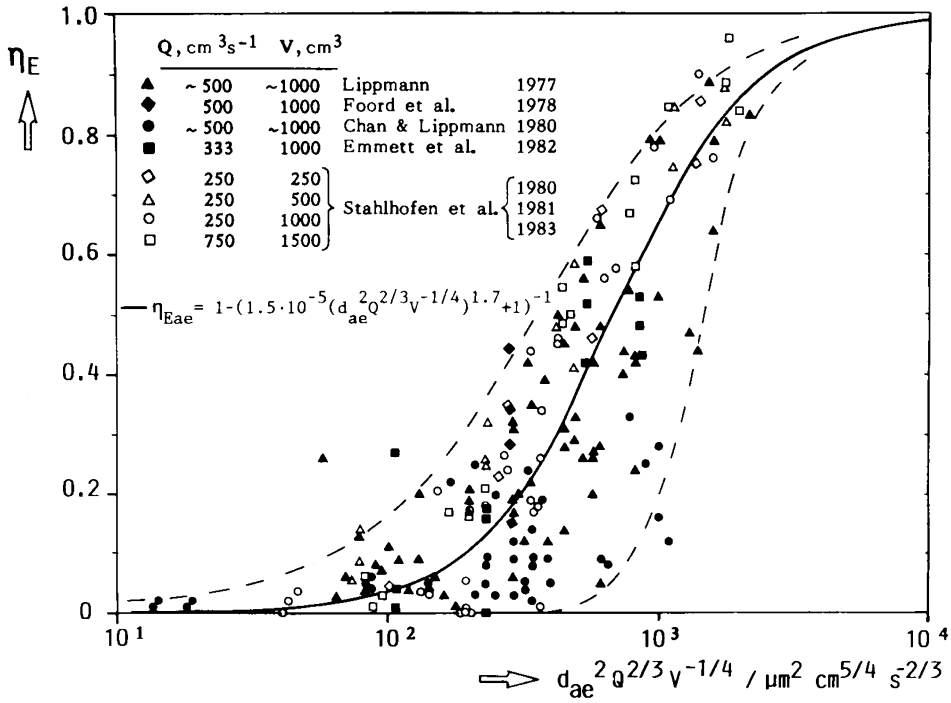

FIGURE 6. Inspiratory extrathoracic deposition efficiency during mouth breathing. Same data as in Figure 5, however plotted as function of $E_{ae} = d_{ae}^2 Q^{2/3} V^{-1/4}$, together with the corresponding approximation (Equation 10). Both intraindividual and interindividual scatter are reduced as compared to Figures 4 and 5.

tracheobronchial tree, it has become usage to consider the rapidly (slowly) cleared fraction of initial activity as a measure of the amount of material deposited in the tracheobronchial (alveolar) region.

However there have been early indications that a significant fraction of the material deposited in the tracheobronchial airways may be retained there for much longer than 24 hrs and be cleared eventually by macrophages (Patrick & Stirling 1977). Later evidence has confirmed these findings (Stahlhofen et al. 1986a, 1986b, Scheuch & Stahlhofen 1988, Smaldone et al. 1988). This may in part be due to the fact that not all of the tracheobronchial airway surface is lined with ciliated epithelium (Hilding 1957) or, that not all of the ciliated epithelium is covered with mucus all the time (Van As 1977, Lumsden et al. 1984). The latter circumstance may also explain the finding that significant numbers of particles have been found trapped in the periciliary fluid underneath the mucus gel-phase (Geiser et al. 1988, 1989), or ingested by macrophages which were buried in or passing through the airway epithelium (Stirling & Patrick 1980). "We have arbitrarily described mucociliary transport and macrophages as two distinct systems"; instead, "it seems likely that the two systems overlap and work cooperatively" (Brain 1988). Instead of arbitrarily interpreting the experimental data as tracheobronchial and alveolar deposition, we have, therefore, used the simple terms 'fast-cleared' and 'slow-cleared thoracic deposition'.

Again, differing experimental techniques, evaluation methods, and modes of presentation make comparison of the data difficult. Several retention studies have focussed on determining the fast- and slow-cleared fractions of material deposited in the thorax only and failed to determine extrathoracic and total deposition

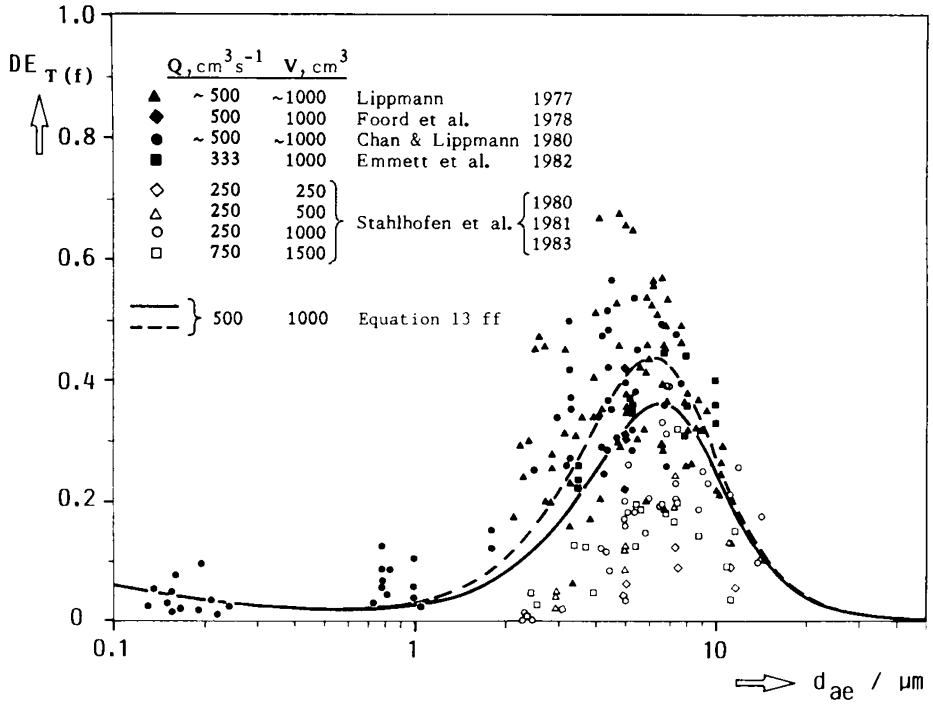

FIGURE 7. Fast-cleared thoracic deposition as function of aerodynamic particle diameter. The solid curve represents the approximate mean of all the experimental data (Equation 13 with 15); the broken curve gives a 'conservative' approximation (mean of the NYU data; Equation 13 with 18) for tissue dose estimations. Both curves are valid for Q = 500 cm^3s^{-1} and V = 1000 cm^3.

(Lourenco et al. 1971, Camner & Philipson 1978, Garrard et al. 1981, Svartengren et al. 1984). Their results cannot be expressed in terms of regional deposition as defined in this paper, but only, e.g., as the ratio of fast- to slow-cleared deposition. These values are comparable to those reviewed here and are therefore not considered in detail.

Figure 7 summarizes the available data on fast-cleared thoracic deposition during mouth breathing ($DE_{T(f)}$) as function of the aerodynamic particle diameter. $DE_{T(f)}$ is defined as the fast-cleared fraction of the inhaled aerosol. Lippmann (1977) and Chan & Lippmann (1980) gave their fast-cleared deposition data in terms of what they named 'fraction deposited of aerosol entering the trachea' (see below) which is here termed $\eta_{T(f)}'$ and is defined by

$$\eta_{T(f)}' = DE_{T(f)}/(1-DE_E) \quad . \tag{11}$$

We have converted these data into $DE_{T(f)}$ using their own predicted extrathoracic deposition results (Figure 4). Figure 7 shows that the data of Lippmann (1977) and Chan & Lippmann (1980) (NYU data) and the data of Stahlhofen et al. (1980, 1981, 1983) (FFM data) differ considerably. The latter show consistently lower values that the former. The British data (Foord et al. 1978, Emmett et al. 1982) range between those from the continents.

This general discrepancy is also seen in Figure 8 where mean curves of the same data are shown. (The empirical functions included in Figure 7 are introduced below.)

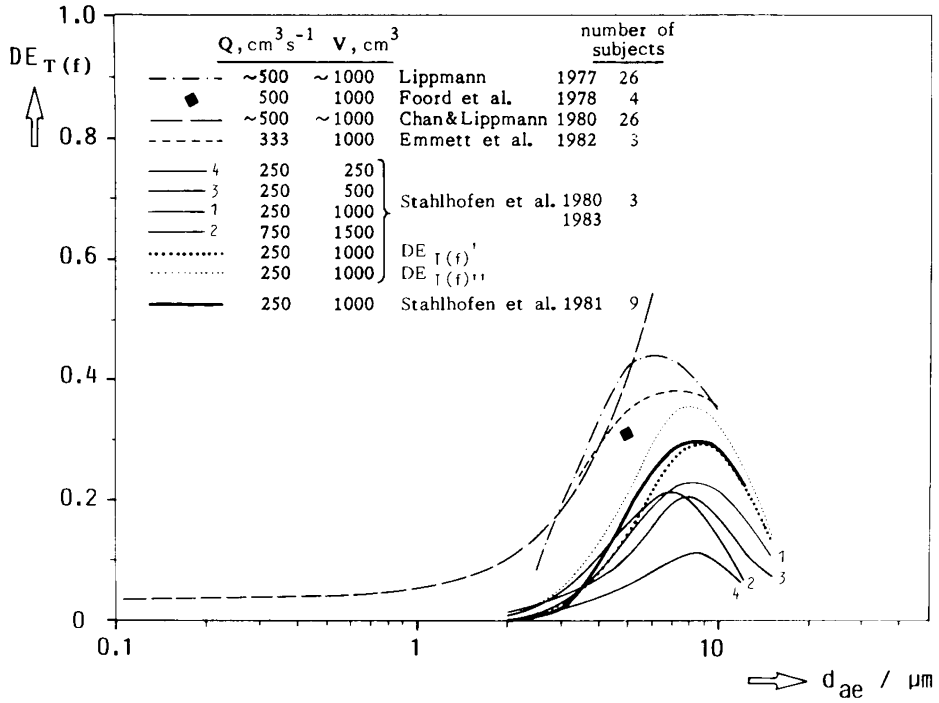

FIGURE 8. Fast-cleared thoracic deposition as function of aerodynamic particle diameter. Mean curves and approximations representing the experimental data from Figure 7. Included are also $DE_{T(f)}'$ and $DE_{T(f)}''$ (see text).

Several reasons may explain this discrepancy, but none of them appears to explain it alone. It seems to be a combined effect due to several causes.

(1) One of the reasons for the discrepancy may be natural biological variability. In fact, the 9-subject study by Stahlhofen et al. (1981) confirmed the 3-subject data (Stahlhofen et al. 1980, 1983) as far as total and slow-cleared deposition are concerned; however, it yielded, on average, lower DE_E, and larger $DE_{T(f)}$ values than the 3-subject study. The intersubject variability being very large, it is possible that part of the discrepancy between the FFM and NYU mean data is also due to biological variability.

It is interesting to note that the difference in mean fast-cleared deposition between the 3- and the 9-subject FFM studies can be completely explained by the difference in extrathoracic deposition between the two groups. We have, therefore, re-calculated the 3 subjects' mean fast-cleared deposition, $DE_{T(f)}(3)$, using the mean extrathoracic efficiency of the larger group, $\eta_E(9)$, obtaining

$$DE_{T(f)}'(3) = DE_{T(f)}(3)\ (1-\eta_E(9))/(1-\eta_E(3))\ . \qquad (12)$$

As can be seen in Figure 8, $DE_{T(f)}'(3)$ is nearly the same as $DE_{T(f)}(9)$, the 9 subjects' mean fast-cleared deposition. This confirms the representativeness of $DE_{T(f)}(9)$ and makes it appear unlikely that the whole discrepancy between the NYU and FFM data is due to biological variability. This discrepancy is only halved if instead of $DE_{T(f)}(3)$, $DE_{T(f)}'(3) = DE_{T(f)}(9)$ is compared to the NYU data. Even if $DE_{T(f)}(3)$ is raised by the whole difference in DE_E between the two FFM groups, so as to keep total and slow-cleared deposition constant (these data agree between the two FFM groups), resulting in $DE_{T(f)}''(3)$, $DE_{T(f)}''(3)$ would not match the NYU data (Figure 8).

(2) Another, possibly preponderant, portion of the discrepancy may be due to the different breathing patterns applied; i.e., so-called 'academic breathing' at a constant flow rate without pauses between the breaths (Stahlhofen et al. 1980, 1981, 1983, Emmett et al. 1982) vs. 'natural breathing' with only the breathing frequency and an approximate tidal volume preset (Lippmann 1977, Foord et al. 1978, Chan & Lippmann 1980). Studies of deposition in glass tube models of airway bifurcations (Kim et al. 1988) and replicate hollow casts of the upper human bronchial tree (Schlesinger et al. 1982, Gurman et al. 1984a, 1984b, Cohen 1987) were conducted to compare inertial and diffusional deposition under cyclic and constant flow conditions. Depending on particle size, flow rate and generation number, cyclic flow resulted in equal or up to three times higher deposition as compared to constant flow. These data urgently need to be confirmed in vivo.

(3) Another, non-negligible portion of the difference may originate in the different definitions used of fast-cleared deposition. Depending on particle size and breathing parameters, the period after which fast clearance terminates was found to range between 2 hrs (Lippmann & Albert 1969) and 40 hrs (Stahlhofen et al. 1980). Hence, adopting the 22- or 24-hr clearance value as a measure of fast-cleared deposition (Lippmann 1977, Foord et al. 1978, Chan & Lippmann 1980, Emmett et al. 1982) introduces an uncertainty avoided by observing clearance for several days and extrapolating the slow component back to the time of inhalation (Stahlhofen et al. 1980, 1981, 1983).

(4) The measuring procedure is another source of variability. Probably the most critical point is the method by which interference of activity between the different regions is accounted for. Neglecting the activity from the lowest part of the lungs in order to avoid a possible contribution from the stomach (Lippmann 1977) probably underestimates the contribution from the peripheral airways and overestimates that from the central airways. On the other hand, using the stomach measurement only as a control in order to eliminate those experiments that show any stomach burden (Lippmann 1977), does not account for a possible contribution from the esophagus and may also overestimate deposition in the central airways. This is avoided by additionally measuring the activity in the stomach before and after clearing the esophagus by eating, and by taking the time-dependent interference factors into account which could be determined at an accuracy of about 20% (Stahlhofen et al. 1980). Again, different techniques have been applied by the other authors.

(5) Furthermore, it is not known whether in all of the reported studies hygroscopic growth of the inhaled particles has been prevented by properly hydrolysing the colloidal Fe_2O_3 solution. Growth of the particles during inhalation would favour deposition in the tracheobronchial region. Also, possible leakage of activity from the particles must be considered.

It may be seen from this short discussion that it is impossible to assign a single reason for the observed discrepancy, or to determine which ones predominate. More experimental work, or a more detailled intercomparison study taking account of differences in experimental techniques would help to elucidate this point.

The fast-cleared deposition related to aerosol entering the trachea, or deposition efficiency of the fast-cleared region, $\eta_{T(f)}$, is shown in Figure 9. It is related to $DE_{T(f)}$ by

$$DE_{T(f)} = \phi_T(1-\eta_E)\eta_{T(f)} = (\phi_T - DE_E)\eta_{T(f)} \quad . \tag{13}$$

Hence, by definition $\eta_{T(f)}$ and $\eta_{T(f)}'$ differ by a factor of $(1-DE_E)/(\phi_T-DE_E)$. In other words, they differ more as DE_E approaches ϕ_T, or as η_E approaches unity. This is shown by one example in Figure 9 (indicated by arrows). The NYU $\eta_{T(f)}$ data shown in Figure 9 have again been obtained using the NYU mean DE_E functions shown in Figure 4.

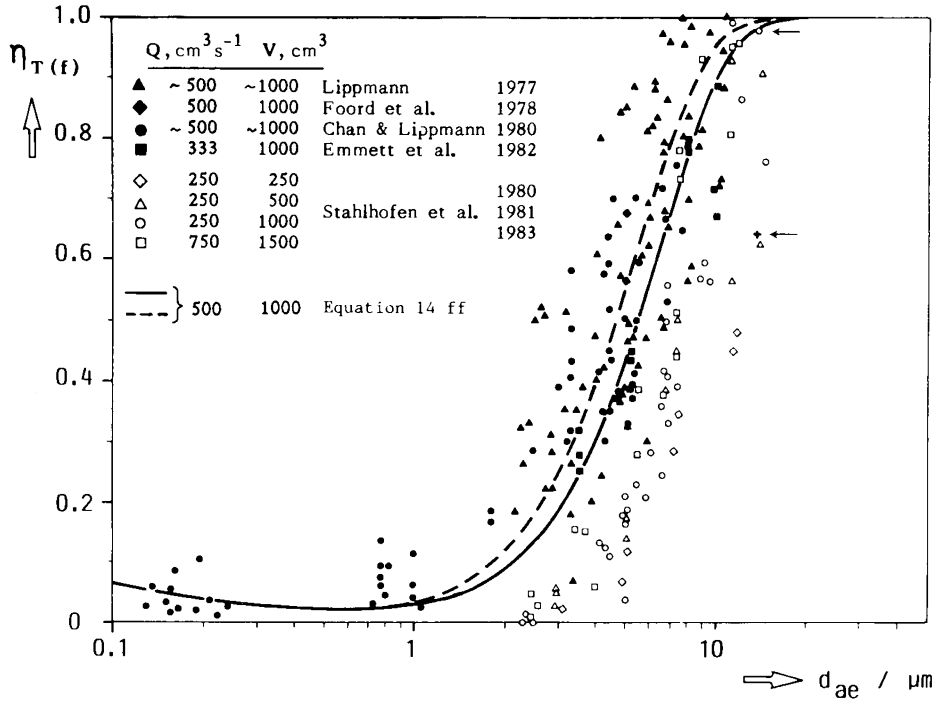

FIGURE 9. Inspiratory deposition efficiency of the fast-cleared thoracic region (or, fast-cleared deposition related to aerosol entering the trachea) as function of aerodynamic particle diameter. Same experimental data as shown in Figure 7. One example of the difference between $\eta_{T(f)}$ (o) and $\eta_{T(f)}'$ (+) is shown (indicated by arrows). The solid curve represents the approximate mean of the data (Equation 15), the broken curve gives a 'conservative' approximation (mean of the NYU data; Equation 18). Both curves hold for Q = 500 $cm^3 s^{-1}$ and V = 1000 cm^3.

Figure 9, like Figures 7 and 8, illustrates the discrepancy between the FFM and NYU data. At present, the most reliable way to model the data consists in merely averaging the data. This is done by the function shown in Figure 9 which holds for Q = 500 $cm^3 s^{-1}$ and V = 1000 cm^3 (solid curve). It is a special case of a function which holds for any combination of breathing parameters and is given by

$$\eta_{T(f)} = (\eta_{T(f)th}^2 + \eta_{T(f)ae}^2)^{1/2} \qquad (14)$$

with the aerodynamic term

$$\eta_{T(f)ae} = 1 - \exp(-3.4 \cdot 10^{-5}\, d_{ae}^2 Q - 0.023\, d_{ae}^2 t_{T(f)}) \; . \qquad (15)$$

$t_{T(f)}$ is the mean residence time in the fast-cleared thoracic region of aerosol passing this region during inspiration. However, since morphometric data of the fast- and slow-cleared thoracic regions are completely lacking, in this model the volumes of these regions are approximated by the volumes of the tracheobronchial and alveolar regions as given by Weibel (1963), scaled down to an FRC of 3000 cm^3 (see Appendix). Because the coefficients in the $\eta_{T(f)}$ and

$\eta_{T(s)}$ functions were chosen to fit the experimental data, this may introduce only slight artifacts regarding the dependence of these functions on the respiratory parameters. Hence,

$$t_{T(f)} = t_B = 110\ cm^3\ (2 + V/3000\ cm^3)/2Q\ . \qquad (16)$$

Up to now, no experimental data on thermodynamic deposition in the fast- and slow-cleared thoracic regions are available. Therefore we approximate these data by theoretical data of deposition in the tracheobronchial and alveolar regions (James 1988, Egan & Nixon 1989). This thermodynamic tracheobronchial efficiency can concisely be represented by

$$\eta_{T(f)th} = \eta_{Bth} = 1 - \exp(-50\ (Dt_B)^{1/2})\ . \qquad (17)$$

The artifact introduced by setting $\eta_{T(f)th} = \eta_{Bth}$ and $\eta_{T(s)th} = \eta_{Ath}$ can only be quantitated by future experimental data.

Because of the uncertainty inherent to the experimental $DE_{T(f)}$ data, in order to estimate lung tissue doses a more conservative approach may be desirable. Such a function may be fitted to the NYU data and is given by

$$\eta_{T(f)ae} = 1 - \exp(-4.8 \cdot 10^{-5}\ d_{ae}^2 Q - 0.032\ d_{ae}^2 t_{T(f)})\ . \qquad (18)$$

This fit is also shown in Figure 9 for $Q = 500\ cm^3 s^{-1}$ and $V = 1000\ cm^3$ (broken curve).

$DE_{T(f)}$ is obtained from $\eta_{T(f)}$ using Equations 10 and 13. The $DE_{T(f)}$ functions obtained this way are incorporated in Figure 7 for $Q = 500\ cm^3 s^{-1}$ and $V = 1000\ cm^3$. As in Figure 9, they represent the mean of the available data (solid curve), and a conservative estimation equal to the mean of the NYU data (broken curve).

SLOW-CLEARED THORACIC DEPOSITION

The slow-cleared thoracic deposition data for mouth-breathing, $DE_{T(s)}$, are compiled in Figure 10. These data, from the same studies as evaluated in the previous sections (Figures 4 through 9), show better agreement than is the case for $DE_{T(f)}$. However, some significant discrepancies appear to exist between the data from the different laboratories.

As mentioned before, the 3-subject FFM $DE_{T(s)}$ data agree well with those of the 9-subject study. This suggests that, again, the difference between the FFM and NYU data is not mainly due to intersubject variability. The fact that the difference in $DE_{T(s)}$ is the opposite of that in $DE_{T(f)}$ while the DE_E data are in agreement between the two laboratories, suggests that this difference is caused by the different experimental techniques and evaluation methods discussed in the previous chapter. However, this can only be verified by an experimental intercomparison study.

Slow-cleared thoracic deposition is given by

$$DE_{T(s)} = (V_{T(s)}/V)(1-\eta_E)(1-\eta_{T(f)})\eta_{T(s)} \qquad (19)$$

where $V_{T(s)}$ is the aerosol volume coming to rest in the slow-cleared airways at end-inspiration. As mentioned above, due to the lack of appropriate data, $V_{T(s)}$ is approximated by the volume of the alveolar region after Weibel (1963),

$$V_{T(s)} = V_A = 0.963\ V - 160\ cm^3 \qquad (20)$$

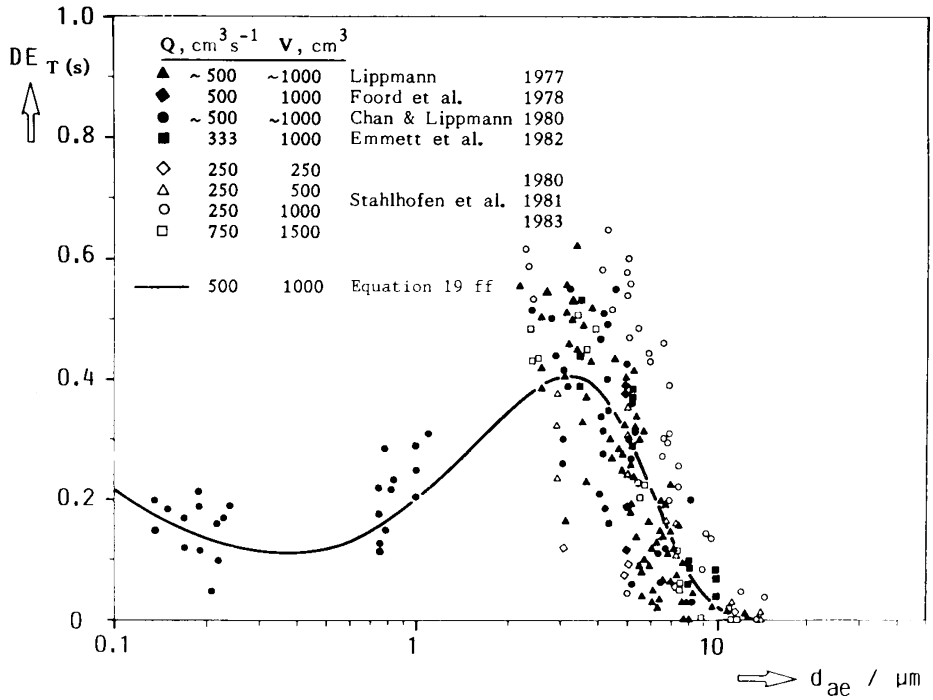

FIGURE 10. Slow-cleared thoracic deposition as function of aerodynamic particle diameter. Experimental data, together with the approximation (Equations 19-22) for Q = 500 cm^3s^{-1} and V = 1000 cm^3.

(see Appendix). $\eta_{T(s)}$ is given by

$$\eta_{T(s)} = (\eta_{T(s)th}^2 + \eta_{T(s)ae}^2)^{1/2} \quad (21)$$

with

$$\eta_{T(s)ae} = 1 - \exp(-0.25\ (d_{ae}^2 t_{T(s)})^{0.6}) \quad (22)$$

and

$$\eta_{T(s)th} = \eta_{Ath} = 1 - \exp(-95\ (Dt_A)^{1/2}) \ . \quad (23)$$

As in the case of the efficiency of the fast-cleared region, the aerodynamic term has been fitted to the experimental data, and the thermodynamic term to the model calculations mentioned above.

$$t_{T(s)} = t_A = (V - 160\ cm^3)/Q \quad (24)$$

is the mean residence time of the aerosol that enters the slow-cleared, or alveolar, region. Figure 10 shows the approximation given by Equations 19 through 24 for Q = 500 cm^3s^{-1} and V = 1000 cm^3.

It is worth mentioning here that both fast and slow cleared thoracic deposition are not monotonic functions of the respiratory parameters but exhibit minima ($DE_{T(f)}$) and maxima ($DE_{T(s)}$) particularly as a function of flow rate. This means that deposition estimates assuming 'mean' breathing parameters do not necessarily result in 'mean' deposition data but may well deliver minimum or maximum values (Rudolf 1985).

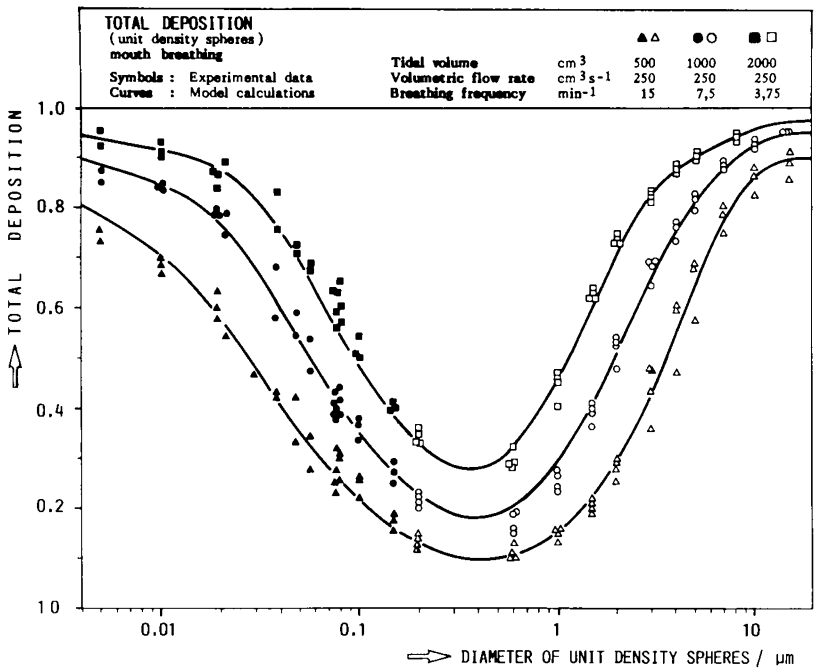

FIGURE 11. Total deposition as function of the diameter of unit density spheres, for variable tidal volume and breathing frequency. Experimental data by Heyder et al. (1986) and Schiller et al. (1988). The curves represent the sum of the approximations of the mean regional depositions derived in this paper.

TOTAL DEPOSITION

Due to the fact that total deposition is much easier to determine experimentally than regional deposition, total deposition in the human respiratory tract is well documented today. The wealth of data has already been extensively reviewed (Mercer 1975, Lippmann 1977, Chan & Lippmann 1980, Raabe 1982, Stahlhofen 1984, Schlesinger 1985), and reasonable agreement is found between the data from different laboratories. Therefore only some representative data are shown here. Figure 11 demonstrates the influence of particle size, tidal volume and breathing frequency upon total deposition (data of Heyder et al. 1986, Schiller et al. 1989). In Figure 12, total deposition is shown for two selected breathing patterns typical for quiet breathing ($Q = 250\ cm^3s^{-1}$, $V = 1000\ cm^3$) and breathing during physical work ($Q = 750\ cm^3s^{-1}$, $V = 1500\ cm^3$).

The curves shown in Figures 11 and 12 represent the sums of the mean functions of the regional deposition data presented in this paper, with the extrathoracic efficiency given by Equation 10.

SUMMARY AND CONCLUSIONS

The available experimental data on regional aerosol deposition in the human respiratory tract have been reviewed and the different experimental techniques were discussed in an effort to evaluate the variability observed in the data. In addition, mathematical expressions of regional deposition as a function of particle size and respiratory parameters were derived.

Good agreement is found for the aerodynamic extrathoracic deposition data

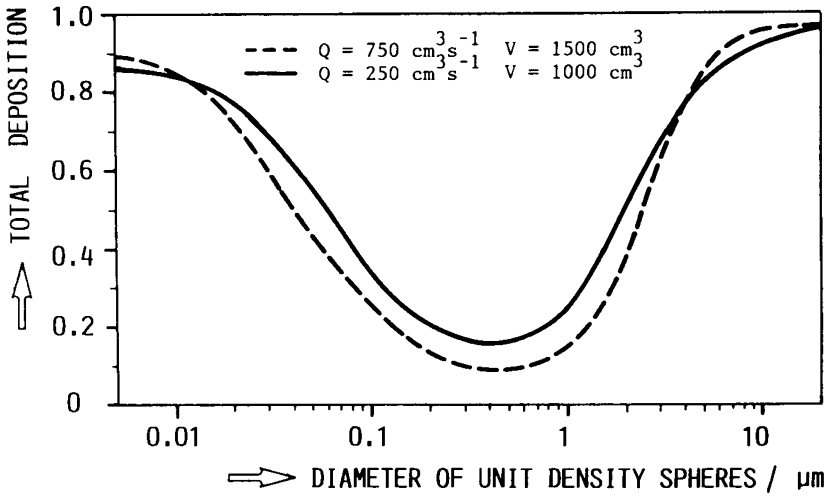

FIGURE 12. Total deposition as function of the diameter of unit density spheres, for two distinct breathing patterns representing quiet breathing ($Q = 250\ cm^3s^{-1}$, $V = 1000\ cm^3$), and breathing under physical work conditions ($Q = 750\ cm^3s^{-1}$, $V = 1500\ cm^3$). The curves represent the sum of the approximations of the mean regional depositions derived in this paper.

for both oral and nasal breathing, and for total deposition. The agreement could be improved, and the inter- as well as the intra-individual scatter of the data can be reduced in some cases by plotting the data as a function of particular physiological parameters. Concerning thoracic regional deposition, however, agreement is less satisfactory, and a number of possible reasons for this discrepancy have been suggested. Further investigation of the differences would require an experimental intercomparison study between the different laboratories, with a careful assessment of effects of the different experimental techniques applied. To take account of this uncertainty, in addition to the mean function, a 'conservative' model is proposed for fast-cleared thoracic deposition. Also, more experimental work is necessary in order to verify the proposed regional deposition functions for the thermodynamic particle size range which are largely based on theoretical data.

The data summarized in this paper are confined to healthy adults. Very few experimental data exist on particle deposition in children and in diseased lungs. Both extrathoracic and total deposition appear to be enhanced in children compared to adults (Becquemin et al. 1989, Roy et al. 1988), but the data are by far not sufficient to derive according empirical expressions as a function of age.

The parameters of the mathematical expressions developed in this paper may be modified to account for any other desired approach, such as to represent the minimum or maximum deposition found experimentally, or to develop a statistical model of the data for any region of the respiratory tract. This is of particular interest in determining limits of intake for airborne toxicants and radionuclides and will be the subject of a subsequent paper.

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APPENDIX

(d_{ae} in μm, all other units in cgs)

Mouth Breathing	Nose Breathing
Regional Deposition	
$DE_E = \phi_T \eta_E$	$DE_N = \eta_N$
	$DE_L = \phi_T (1-\eta_N) \eta_E$
$DE_{T(f)} = \phi_T (1-\eta_E) \eta_{T(f)}$	$DE_{T(f)} = \phi_T (1-\eta_N)(1-\eta_E) \eta_{T(f)}$
$DE_{T(s)} = \phi_A (1-\eta_E)(1-\eta_{T(f)}) \eta_{T(s)}$	$DE_{T(s)} = \phi_A (1-\eta_N)(1-\eta_E)(1-\eta_{T(f)}) \eta_{T(s)}$
Total Deposition	
$DE = DE_E + DE_{T(f)} + DE_{T(s)}$	$DE = DE_N + DE_L + DE_{T(f)} + DE_{T(s)}$

Efficiencies

$\eta_R = (\eta_{Rth}^2 + \eta_{Rae}^2)^{1/2}$; η_{Nae}, η_{Eae}: $\eta = 1 - (aR^q + 1)^{-1}$

η_{Nth}, η_{Eth}: $\eta = aR^q$

$\eta_{T(f)ae}$, $\eta_{T(f)th}$, $\eta_{T(s)ae}$, $\eta_{T(s)th}$: $\eta = 1 - \exp(-aR^q)$

	η_{Nth}	η_{Eth}	$\eta_{T(f)th}$	$\eta_{T(s)th}$	η_{Nae}	η_{Eae}	$\eta_{T(f)ae}$	$\eta_{T(s)ae}$
a	6.5	0	50	95	$3.0 \cdot 10^{-4}$	$1.5 \cdot 10^{5}$	1	0.2
R	$(Dt_N)^{1/2}$	-	$(Dt_B)^{1/2}$	$(Dt_A)^{1/2}$	$d_{ae}^2 Q$	$d_{ae}^2 Q^{2/3} V^{-1/4}$	B	$d_{ae}^2 t_A$
q	1	-	1	1	1	1.7	1	0.6

mean: $B = 3.4 \cdot 10^{-5}\, d_{ae}^2 Q + 0.023\, d_{ae}^2 t_B$

conservative: $B' = 4.8 \cdot 10^{-5}\, d_{ae}^2 Q + 0.032\, d_{ae}^2 t_B$

Volumes and Mean Residence Times

$V_E = 50\ cm^3$, $t_N = V_E/Q$, $FRC = 3000\ cm^3$, $V_{B0} = 110\ cm^3$

$V_B = V_{B0}(1 + V/FRC)$, $t_B = (V_{B0}+V_B)/2Q = V_{B0}(2 + V/FRC)/2Q$

$V_A = V - V_E - V_B = 0.963\ V - 160\ cm^3$, $t_A = (V - V_E - V_{B0})/Q = (V - 160\ cm^3)/Q$

$\phi_T = 1 - V_E/V$, $\phi_A = V_A/V$

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Reviewed by:
John Agnew
Dieter Hochrainer

Address reprint requests to:
Dr. Gerhard Rudolf
Institut für Biophysik
Universität Frankfurt am Main
Paul-Ehrlich-Strasse 20
D 6000 Frankfurt am Main
Federal Republic of Germany