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LONG-TERM RETENTION OF PARTICLES IN THE HUMAN RESPIRATORY TRACT*

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Abstract—Twelve healthy non-smoking male volunteers inhaled monodisperse 1 and 4 μm diameter fused aluminosilicate particles labelled with strontium-85 and yttrium-88, respectively. Retention was followed for at least a year (372–533 days). Approximately 7% of the initial lung deposit of 1 μm particles and 40% of that of the 4 μm particles were associated with a distinct rapid clearance phase. These figures correspond closely to the calculated tracheo-bronchial deposits, indicating insignificant rapid pulmonary clearance. Retention of the remaining material ($R(t)$) generally followed a two-component exponential function, the phases having half-times of the order of tens of days and several hundred days, respectively. At 350 days after inhalation, $R(t)$ averaged 46 ± 11% ($\bar{x} \pm$ SD) for the 1 μm particles and 55 ± 11% for the 4 μm particles. Retention of the 1 μm particles by each subject was correlated with that of 4 μm particles. Estimated lung dissolution rates based on urinary excretion were 7×10^{-4} and 2×10^{-4} per day for the 1 and 4 μm particles, respectively. The estimated rate of clearance of particles from the pulmonary region to the gastro-intestinal tract fell from an initial value of 4×10^{-3} per day to about 1×10^{-3} per day at and beyond 200 days after inhalation.

INTRODUCTION

Knowledge of the rates at which particles deposited in the respiratory tract are cleared is essential for the evaluation of radiation doses incurred when radioactive materials are inhaled. Most particles deposited in the conducting airways (nasal passages and tracheo-bronchial tree) are removed by muco-ciliary action within a day or two. The clearance of insoluble material from the pulmonary region (the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli) is, however, a much slower process, the mean retention time being of the order of a year. In the lung model adopted by the International Commission on Radiological Protection (ICRP) for determining Annual Limits of Intake for inhalation of radionuclides by workers (ICRP Lung Model), it is assumed that 40% of the pulmonary deposit of a relatively insoluble (Class Y) material is removed with a half-time of one day, and the rest with a half-time of 500 days (ICRP, 1979). There have however been few long-term experimental studies of particle retention in the human lung to substantiate these values (Bailey *et al.*, 1982). Measurements following accidental or occupational exposures are more plentiful (e.g. Watts, 1975), but rarely are the exposure conditions sufficiently well known, and the number of people involved sufficiently large, to enable conclusions of general applicability to be drawn.

The objectives of the experiment described here were to determine the pattern of particle retention in the human lung up to a year after inhalation, the effect on retention of particle size (for particles larger than 1 μm), and the degree of variation between individuals. Details of the experimental procedures and preliminary findings have been reported (Bailey *et al.*, 1982; Bailey, 1983; Bailey and Fry, 1983; Fry *et al.*, 1983). This paper provides a summary of the study and presents its final results.

MATERIALS AND METHODS

Pulmonary retention in the human lung was initially studied in a Group of 7 subjects (Group I). Because so much variation was found between them, a second Group (II),

consisting of five new subjects and one (A) from Group I was subsequently studied to increase the sample size. All were males with no history of any lung disorder. Seven had never smoked and the rest had ceased smoking at least six years previously (Table 1).

Monodisperse fused aluminosilicate particles (FAP; specific gravity 2.26 (Raabe *et al.*, 1971)) with nominal diameters of 1 and 4 μm, labelled with strontium-85 (half-life 65 days) and yttrium-88 (half-life 107 days), respectively, were prepared using the method described by Bailey and Strong (1980). Sufficient material of each size for all the subjects in a group was prepared in a single batch. The characteristics of the particles are given in Table 2. The particles were washed in distilled water and stored in ethanol prior to administration.

The subjects inhaled particles of both sizes under closely controlled conditions designed to give initial pulmonary deposits of about 18.5 kBq strontium-85 and 2.4 kBq yttrium-88, sufficient to enable retention to be followed for a year, and giving rise to a committed effective dose equivalent to each volunteer of about 0.2 mSv. The aerosol administration system has been described (Bailey *et al.*, 1982; Bailey and Fry, 1983). Briefly, for each exposure, about 25 μl of the suspension of FAP in ethanol was dispersed in a 25-l capacity polythene container using a compressed-air nebulizer. The subject inhaled the aerosol through a mouthpiece at a rate he controlled himself (15 l/min). The tidal volume was fixed by solenoid valves at 1.5 l (giving an average inhalation time about 6 s per breath), with a 4 s pause between inhalation and exhalation to promote particle deposition in the pulmonary region. The subject took about 10 such breaths, then rinsed out his mouth. The strontium-85 labelled particles were inhaled about 30 min after the yttrium-88 labelled particles. The fraction of inhaled activity which was deposited in the respiratory tract was determined for subjects in Group II, who exhaled through a low-impedance filter (Whatman GFA 150 mm). At the end of the series of exposures, activity deposited between the mouthpiece and exhalation filter was measured to correct for particle losses.

Measurements of particle retention in the thorax were made by external counting of the γ-rays emitted using an array of six side-shielded NaI(Tl) detectors placed around the subject's chest in a low-background enclosure. The arrangement maximized the detection efficiency for particles in the lungs and minimized changes in efficiency due to redistribution within the chest. Pulse-height spectra were accumulated with an on-line computer system, and activities determined by reference to known amounts of the radionuclides in appropriate phantoms. The activity in the chest was measured as quickly as possible after inhalation of the particles (within about 5 min), and then at appropriate intervals for at least a year.

To estimate the dissolution rate of the particles, 24-hr urine samples were collected during the first few days after inhalation, and subsequently occasional 72-hr samples were obtained from some of the subjects. Strontium and yttrium were precipitated as phosphates, and strontium-85 and yttrium-88 were measured with a germanium detector.

Table 1. Details of subjects

Group	Subject	Age (yr)	Weight (kg)	Height (m)	Circumference of chest (m)	Time since smoker (yr)	FEV* (l)	FVC† (l)
I	A‡	37	78	1.79	1.03	—	4.15	5.25
	B	57	61	1.76	0.88	20	2.8	
	C	34	79	1.76	0.98	6	4.0	5.2
	D	44	66	1.68	0.91	—	3.85	4.15
	E	54	91	1.76	1.08	22	3.65	4.35
	F	42	70	1.79	0.88	—	3.9	4.6
	G	57	67	1.72	0.96	30	3.0	4.1
II	H	54	65	1.72	0.97	10	3.7	4.65
	I	38	67	1.76	0.96	—	4.0	4.7
	J	43	78	1.74	0.99	—	4.2	5.8
	K	71	88	1.81	1.05	—	3.9	4.7
	L	35	65	1.76	0.87	—	3.7	4.5

* Forced Expiratory Volume in 1 s.
† Forced Vital Capacity.
‡ Subject A was also a member of Group II at age 39.

RESULTS

Initial deposition and clearance

Total deposition in the respiratory tract as a fraction of the activity inhaled for subjects in Group II averaged $86 \pm 3\%$ ($\bar{x} \pm$ SD) and $97.5 \pm 2\%$ for the 1 and 4 μm particles, respectively.

During the first week after inhalation, $8 \pm 3\%$ ($\bar{x} \pm$ SD, $n = 13$) and $43 \pm 8\%$ of the 1 and 4 μm particles, respectively, were cleared. There was a distinct rapid phase, completed within about two days, (Bailey *et al.*, 1982). This phase is generally attributed to muco-ciliary clearance of particles deposited in the ciliated conducting airways. The fraction of the initial lung deposit associated with the rapid phase, given by the difference between the intercept of the fitted long-term retention curve (see below) and the activity measured in the chest immediately after inhalation, was $7.1 \pm 3.4\%$ ($\bar{x} \pm$ SD) and $43 \pm 8\%$ for the 1 and 4 μm particles, respectively. These figures correspond closely to the amounts calculated to have deposited in the ciliated conducting airways with the particle sizes and breathing manoeuvres employed (Bailey *et al.*, 1982). Thus no significant rapid pulmonary clearance was observed.

Long-term retention

Material not associated with the rapid clearance phase is here termed the retained deposit ($R(t)$ at time t after inhalation). It is considered to consist mainly of particles retained in the pulmonary region, but may also include particles deposited in the conducting airways which were not cleared rapidly by mucociliary action, and material transferred to lymph nodes.

Multi-component exponential functions were fitted to the measurements of activity (corrected for radioactive decay) retained in the chest of each subject beyond 5 days after inhalation using a weighted least-squares multi-component fitting program (Hebden, 1973):

$$R(t) = \sum_{i=1}^{n} A_i \exp(-\lambda_i t) \qquad t > 5. \tag{1}$$

Initial retained deposits, $R(0)$, given by the intercepts of the fitted retention curves averaged 16 ± 3 kBq ($\bar{x} \pm$ SD) strontium-85 and 2.6 ± 0.9 kBq yttrium-88, corresponding to masses of 5 μg FAP for Group I and 12 μg for Group II.

The parameters of the fitted curves and the time after inhalation at which the last measurement on each subject was made (T_f) are given in Table 3. In some cases a single exponential function was found to represent retention satisfactorily, i.e. it did not over- or under-estimate a long series of consecutive data points. In most cases, however, two-component functions were required; the minor component having a half-life of tens of days, and the major component a half-life of several hundred days. This suggests that there are two phases of clearance of the retained deposit, here termed 'intermediate' and 'slow', respectively, since it is customary to refer to muco-ciliary clearance from the conducting airways as the 'rapid' phase of lung clearance. Both the exponents and amplitudes of the fitted functions are very variable. Some scatter is due to intersubject variation, but the standard errors on the values of the parameters of the fitted two-component exponential functions are generally large. This does not mean that the retention curves are not well defined—the standard error on the value of the fitted retention at any time is usually less than 2% of that value. It is a feature of multi-exponential curve fitting, that unless very marked changes in slope occur, it

Table 2. Characteristics of FAP used to study pulmonary retention in man

Group	Count median diameter (μm)	Geometric standard deviation	Specific activity (Bq/ng)
I	1.22	1.12	7
I	3.9	1.11	1
II	1.30	1.10	2
II	4.0	1.08	0.5

may well be possible to vary the value of one of the parameters over a wide range, and by adjusting the other parameters appropriately, make little change to the shape of the curve over a fixed interval. Thus, while such a function may provide a concise and accurate description of retention, the values of individual parameters may have little significance.

The fitted functions were used to calculate retention as a fraction of the initial retained deposit $R(t)/R(0)$ for each subject, and thence the mean retention, at 25 day intervals. Two-component exponential functions fitted to these values of mean retention were for the 1 and 4 μm particles respectively:

$$R(t)/R(0) = 0.145 \exp -0.0183t + 0.855 \exp -0.00172t \quad (2)$$

$$R(t)/R(0) = 0.275 \exp -0.0139t + 0.725 \exp -0.00079t. \quad (3)$$

Mean retention of each particle size is shown in Fig. 1. For comparison, the ICRP Lung Model's predicted retention of the pulmonary deposit of a relatively insoluble (Class Y) material (including material transferred from the pulmonary region to the lymph nodes) is also shown. The postulated rapid clearance of 40% of the pulmonary deposit was not observed, but the 500 day half-time for the slow phase is of the right order. Retention of the 1 μm particles was on average greater than that of the 4 μm particles between 25 and 125 days after inhalation, but was less thereafter. The difference was significant at the 5% level (two-tailed t-test) between 200 and 500 days after inhalation.

In Fig. 2 fractional retention of the 1 μm particles is plotted against that of the 4 μm particles in each subject. At 50 days after inhalation (Fig. 2a) retention of the 1 μm particles was greater than that of the 4 μm particles in half the subjects, but at 350 days (Fig. 2b) retention of the 4 μm particles was greater in all the subjects. Retention of the two sizes in each subject was correlated, especially at the later time ($r = 0.66, r = 0.93$, respectively). There was considerable variation between subjects, the coefficient of variation in the fractional retention being about 7% at 50 days after inhalation and 20% at 350 days.

Multiple linear regression analysis was carried out to determine whether retention, represented by fractional retention of each size of particle at 50 and 350 days after inhalation, was related to any of the subject variables listed in Table 1, alone or in combination. The only relationship found to be significant at the 5% level was between height and retention of 4 μm particles at 50 days, but since height was not significantly related to any other measure of retention, this was considered to be a chance occurrence. The relationship of retention to another commonly used measure of lung function, the ratio of the subject's Forced

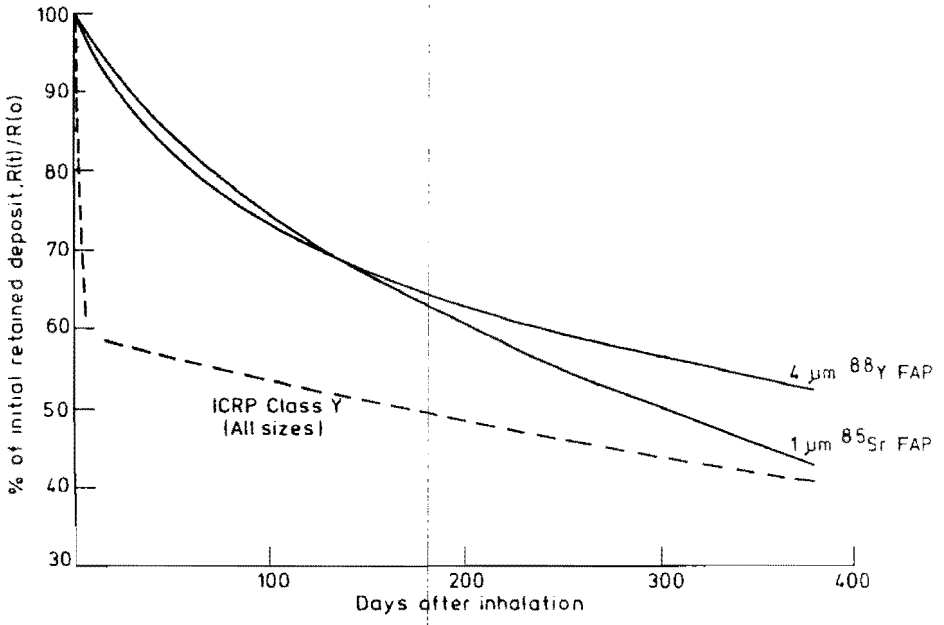

Fig. 1. Mean retention of FAP compared with that predicted by the ICRP lung model.

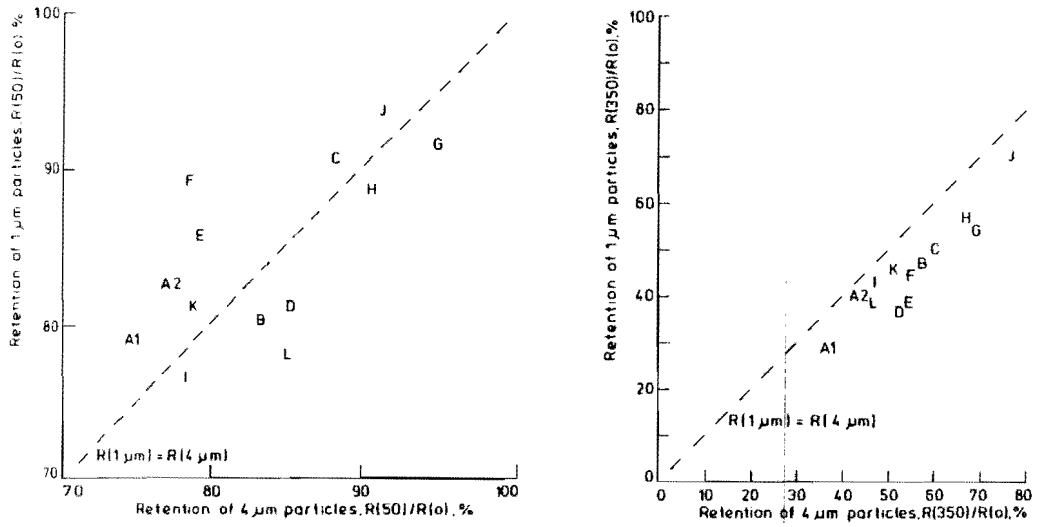

Fig. 2. Intersubject variation in retention. A1 and A2 are measurements made on subject A in Groups I and II, respectively. The broken line indicates equal retention of the two sizes.

Expiratory Volume in one second to his Forced Vital Capacity (FEV_1/FVC), was also investigated. FEV_1/FVC was negatively correlated with all four measures of retention, the relationship being significant at the 5% level for retention of 1 μm particles at 50 and 350 days, and at the 10% level for the retention of 4 μm particles at 50 and 350 days. The coefficients of the regression of retention on (FEV_1/FVC) are given in Table 4.

Table 3. Results of fitting exponential functions to retention beyond 5 days after inhalation

CMD (μm)	Group	Subject	Time of final measurement T_f (days)	Parameters of fitted functions (± SE) A_1 (%)	λ_1 ($\times 10^{-2}$ per day)	A_2 (%)	λ_2 ($\times 10^{-3}$ per day)
1.22	I	A	427	7.5 ± 3	4.22 ± 3	92.5 ± 2	3.39 ± 1.5
		B	391	12.3 ± 4	9.59 ± 5	87.7 ± 1	1.79 ± 0.09
		C	448	—	—	100 ± 0.9	1.96 ± 0.07
		D	427	7.8 ± 5	6.41 ± 6	92.2 ± 1.6	2.63 ± 0.1
		E	437	3.0 ± 3	4.33 ± 13	97.0 ± 3.5	2.60 ± 0.2
		F	372	—	—	100 ± 1	2.29 ± 0.1
		G	429	—	—	100 ± 1	1.75 ± 0.1
1.30	II	A	476	31.7 ± 9	0.97 ± 0.3	68.3 ± 10	1.56 ± 0.3
		H	454	7.2 ± 1	2.50 ± 0.9	92.8 ± 1	1.39 ± 0.05
		I	530	30.4 ± 3	1.89 ± 0.4	69.6 ± 4	1.40 ± 0.2
		J	533	2.0 ± 2	4.14 ± 7	98.0 ± 1	0.94 ± 0.04
		K	519	28.7 ± 2	1.41 ± 0.2	71.3 ± 3	1.26 ± 0.1
		L	484	34.3 ± 4	1.30 ± 0.2	65.7 ± 5	1.47 ± 0.2
3.9	I	A	427	33.9 ± 4	1.78 ± 0.3	66.1 ± 5	1.79 ± 0.3
		B	391	22.1 ± 2	1.81 ± 0.4	77.9 ± 3	0.90 ± 0.1
		C	448	26.2 ± 19	0.88 ± 0.6	73.8 ± 20	0.65 ± 0.7
		D	427	45.3 ± 14	0.73 ± 0.2	54.7 ± 15	0.27 ± 0.6
		E	437	46.3 ± 6	1.19 ± 0.2	53.7 ± 6	0.035 ± 0.3
		F	372	30.0 ± 5	2.06 ± 0.6	70.0 ± 5	0.69 ± 0.3
		G	429	—	—	100 ± 1	1.07 ± 0.07
4.0	II	A	476	32.1 ± 2	1.75 ± 0.2	67.9 ± 2	1.26 ± 0.1
		H	454	9.7 ± 2	1.76 ± 0.8	90.3 ± 2	0.84 ± 0.07
		I	530	37.3 ± 3	1.45 ± 0.2	62.7 ± 3	0.83 ± 0.1
		J	533	9.9 ± 1	2.18 ± 0.5	90.1 ± 1	0.45 ± 0.03
		K	519	35.0 ± 2	1.56 ± 0.2	65.0 ± 2	0.71 ± 0.1
		L	484	72.2 ± 20	0.48 ± 0.2	27.8 ± 22	−0.48 ± 1.2

Table 4. Coefficients (± SE) of the regression equation $R(t)/R(0) = a + b\ (FEV_1/FVC)$

CMD (μm)	Time (t) after inhalation (days)	a (%)	b (%)
1	50	138.0 ± 20.4	−65.1 ± 25.1
1	350	144.0 ± 40.1	−121.3 ± 49.4
4	50	134.4 ± 25.3	−61.9 ± 31.0
4	350	144.9 ± 43.7	−109.7 ± 53.7

Respiratory tract clearance rates

The rate at which material leaves the chest can be expressed as:

$$-\frac{dR(t)}{dt} = \lambda(t)\,R(t). \tag{4}$$

Respiratory tract clearance rates $\lambda(t)$ were determined for each subject from the fitted functions at 0, 10 and 25 days after inhalation, and then at 25 day intervals. Mean values for each particle size are given in Fig. 3. Clearance of the 4 μm particles was faster than that of the 1 μm particles between 10 and 50 days after inhalation, but not significantly; subsequently the 1 μm particles cleared faster, significantly (two-tailed t-test at the 5% level), from day 100 onwards. There was only a weak correlation between the clearance rate at 25 days after inhalation and that at 350 days: $r = 0.23$, 0.30 for the 1 and 4 μm particles respectively. Thus measurement of a subject's clearance over a short period cannot be used to predict his long-term clearance characteristics reliably.

Loss of material from the chest results from dissolution, here taken to mean the transfer of radioactivity from the particles to the body fluids regardless of the mechanisms involved, and from mechanical transport, i.e. the movement of particles via the conducting airways to the gastrointestinal tract. (Movement of particles from the pulmonary region to the lymph nodes would not have been observed.) Assessment of the contribution each made to clearance was based on the lung model proposed by Cuddihy *et al.* (1979) (Fig. 4), i.e. it was assumed that the two processes act independently on the material in each compartment, and that the dissolution rate $S(t)$ was the same in all regions of the respiratory tract and the lymph nodes.

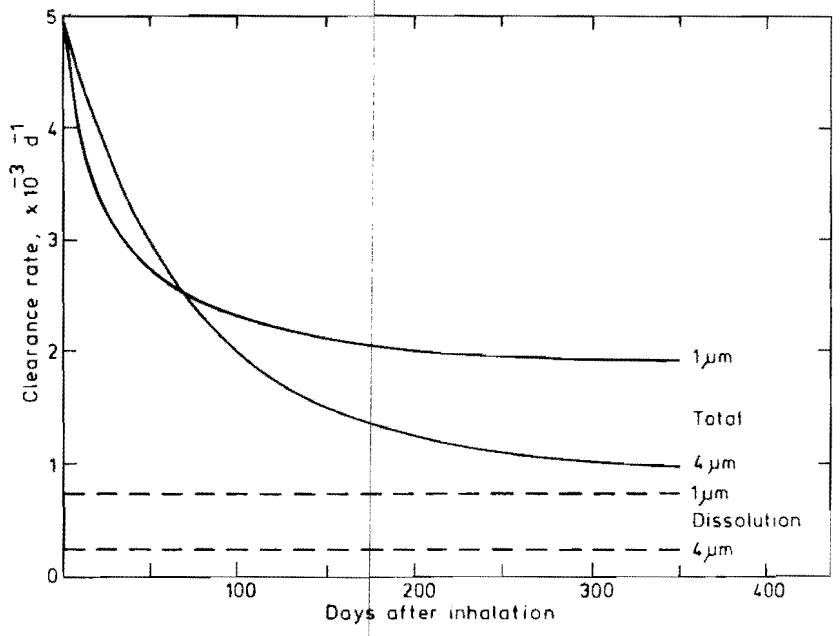

Fig. 3. Lung clearance rates of FAP in man.

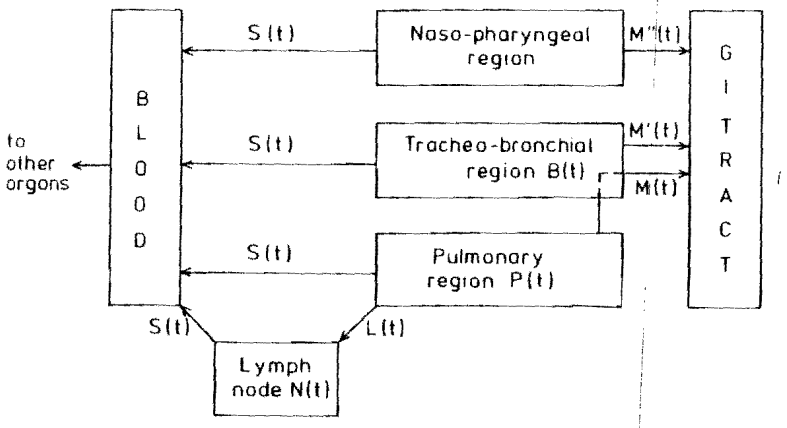

Fig. 4. Clearance model for the respiratory tract (Cuddihy *et al.*, 1979). $S(t)$ is the clearance rate by dissolution. $M(t)$, $M'(t)$ and $M''(t)$ are mechanical transport clearance rates, and $L(t)$ is the clearance rate from the pulmonary region to the lymph nodes. $B(t)$, $P(t)$ and $N(t)$ are the amounts of material in the tracheobronchial region, the pulmonary region and the lymph nodes, respectively.

Thus, referring to Fig. 4:

$$R(t) = B(t) + P(t) + N(t)$$

$$\frac{-\mathrm{d}R(t)}{\mathrm{d}t} = \lambda(t)R(t) = S(t)R(t) + M'(t)B(t) + M(t)P(t). \tag{5}$$

Muco-ciliary clearance of particles deposited in the tracheo-bronchial region is considered to be complete within about a day, giving:

$$\lambda(t)R(t) = S(t)R(t) + M(t)P(t)$$

$$M(t) = (\lambda(t) - S(t))\,(R(t)/P(t)). \tag{6}$$

Estimation of dissolution rates

Urinary excretion of the labels was used to estimate the dissolution rates of the particles in the respiratory tract. Strontium-85 was measurable in all samples collected up to 200 days after inhalation. The urinary excretion rate, $U(t)$, i.e. the fraction of the remaining chest activity excreted in the urine per day, showed considerable variation between samples, but no apparent difference between subjects or trend with time after the first few days. The results were therefore pooled as shown in Table 5. Strontium metabolism in adult man has been well characterized, and the ratio of urinary to faecal excretion of intravenously administered strontium is 4 : 1 (ICRP, 1973). A compartment model was constructed to predict $U(t)$ for a given dissolution rate. Activity in the respiratory tract was represented by two compartments

Table 5. Urinary excretion of radionuclide labels for inhaled FAP

		Urinary excretion rates ($\times 10^{-4}$ per day)		
		Strontium-85		Yttrium-88
Period (days)	Number of samples	Observed ($\bar{x} \pm$ SD)	Modelled*	Observed Range
1	11	3.6 ± 1.6	5.9	0.5–2.1
2	9	5.5 ± 2.1	5.3	0.4–2.1
3	7	4.8 ± 2.0	4.8	0.6–1.8
4–6	4	4.9 ± 1.1	4.2	
7–49	14	3.7 ± 1.1	3.6	0.4–0.9
50–99	8	3.9 ± 1.8	3.9	
100–200	6	3.3 ± 2.3	4.0	

* Fraction transferred immediately $f = 0.005$.
Fractional dissolution rate $s = 6.9 \times 10^{-4}$ per day.

corresponding to the components of the function describing mean retention of the 1 μm particles (equation 2). Retention of systemic strontium was represented by compartments corresponding to a three-component exponential function fitted to whole-body retention given by ICRP (1973) for the period 1–316 days after intravenous injection:

$$0.53\exp -0.31t + 0.15\exp -0.46t + 0.21\exp -0.107t.$$

The simplest assumptions about the dissolution rate which gave a predicted $U(t)$ in agreement with that observed, were that a fraction, f, of the initial lung deposit dissolved immediately after inhalation, and that subsequently the dissolution rate was a constant, s. $U(t)$ could be satisfactorily predicted with $f = 0.005$, $s = 6.9 \times 10^{-4}$ per day (Table 5). The latter figure corresponds to a dissolution rate constant, k (Mercer, 1967), of 3.3×10^{-8} g/cm^2/d, which is similar to values determined for FAP in the lungs of dogs, and in lung serum simulant *in vitro* (Kanapilly *et al.*, 1973).

Yttrium-88 was detectable in only one-third of the urine samples. On the assumption that $U(t)$ was the same for all subjects and independent of time over the periods 3–6 and 7–200 days after inhalation, a lower limit on its value was obtained by taking all the activities which could not be measured to be zero, and an upper limit by assuming them them all to be equal to the detection limit. On this basis $U(t)$ was between 4 and 9×10^{-5} per day after the first week (Table 5). No human data to relate systemic uptake of yttrium to urinary excretion could be found. In adult rats (Bailey *et al.*, 1978), 21% of intravenously injected yttrium-88 was excreted in the urine within 10 days. Applying the same fraction to man gives a dissolution rate between 2 and 5×10^{-4} per day. Because of the great uncertainties in this approach, the dissolution rate was calculated on the assumption that the dissolution rate constant for FAP in the human lung determined above for strontium-85 labelled 1 μm particles could be applied to the yttrium-88 labelled 4 μm particles. This gave a fractional dissolution rate of 2.2×10^{-4} per day, which lies within the range estimated directly.

These dissolution rates are compared in Fig. 3 with the total respiratory tract clearance rate. Dissolution makes a significant contribution to clearance especially after the first 100 days.

If respiratory tract retention can be represented by an exponential function (equation 1), and the dissolution rate is a constant, s, then retention in the absence of dissolution is given by:

$$R_m(t) = \sum_{i=1}^{n} A_i \exp -(\lambda_i - s)t. \tag{7}$$

Thus, taking the functions representing mean retention (equations 2 and 3), and the dissolution rate estimated above, retention of the 1 and 4 μm particles, respectively in the absence of dissolutuion is given by:

$$R_m(t)/R_m(0) = 0.145\exp -0.0176t + 0.855\exp -0.00103t \tag{8}$$

$$R_m(t)/R_m(0) = 0.275\exp -0.0137t + 0.725\exp -0.00057t. \tag{9}$$

Mechanical transport from the pulmonary region

Assessment of the rate of clearance from the pulmonary region by mechanical transport ($M(t)$, equation 6) requires estimation of the proportion of the retained fraction associated with the pulmonary region $P(t)/R(t)$, which in turn requires estimates to be made of the amounts of material in the tracheobronchial region $B(t)$, and in the lymph nodes $N(t)$. For neither, however, are there applicable human data. Some particles deposited on the ciliated conducting airways may not be cleared rapidly, but in rodents the fraction of the initial deposit on the major airways retained for more than a few days was less than 1% (Patrick and Stirling, 1977; Bailey *et al.*, 1984). The initial deposits on the airways were estimated to be about 8 and 60% of the initial retained deposits for the 1 and 4 μm particles, respectively. On this basis it is unlikely that more than about 1% of the retained fraction would have been associated with the airways at any time, and this small amount was ignored.

Transfer to the pulmonary lymphatic system is generally regarded as a slow, steady process. For FAP in dogs the rate of transfer $L(t)$ (Fig. 4) was estimated to be 1×10^{-4} per day by Cuddihy *et al.* (1979), and 2×10^{-4} per day by Snipes *et al.* (1983). In the ICRP Lung Model it is assumed, principally on the basis of studies on dogs, that for a Class Y material, 25 % of the long-term pulmonary burden, i.e. that associated with a half-time of 500 days, is cleared to the lymph nodes and thus that $L(t) = 3.5 \times 10^{-4}$ per day. The implications of these three values were examined.

A compartment model was set up to determine the contents of the pulmonary region, $P(t)$, and of the lymph nodes, $N(t)$; assuming that retention in the pulmonary region could be described by a two-component exponential function, that the transfer rate $L(t)$ was constant, and that the dissolution rate in the lymph nodes was that the derived for the respiratory tract above. By an iterative process parameters were found for the pulmonary retention functions which gave total respiratory tract retention in agreement with that observed. The parameters of the pulmonary retention functions are given in Table 6, together with those for total retention (which equals pulmonary retention when $L(t) = 0.0$). The effect of increasing $L(t)$ is principally to increase the decay constant of the slow phase, λ_2. Also given in Table 6 is the proportion of the material in the respiratory tract associated with the lymph nodes at a year after inhalation, which is just over 4 % for $L(t) = 1 \times 10^{-4}$ per day and increases roughly in proportion to $L(t)$.

Mechanical transport rates from the pulmonary region were calculated using equation (6) and the pulmonary retention functions given in Table 6. Results for $L(t) = 0.0$ and $L(t) = 3.5 \times 10^{-4}$ per day are shown in Fig. 5. Since activity in the lymph nodes is included in that measured in the chest (equation 5), an increase in the assumed value of $L(t)$ results in a decrease in the fraction of the activity in the chest considered to be in the pulmonary region $P(t)/R(t)$, and therefore an increase in the estimated value of $M(t)$ for given values of $\lambda(t)$ and $R(t)$ (equation 6). Changing the value of $L(t)$ within the range considered does not affect the overall pattern predicted for $M(t)$: for both sizes it decreases from an initial value of

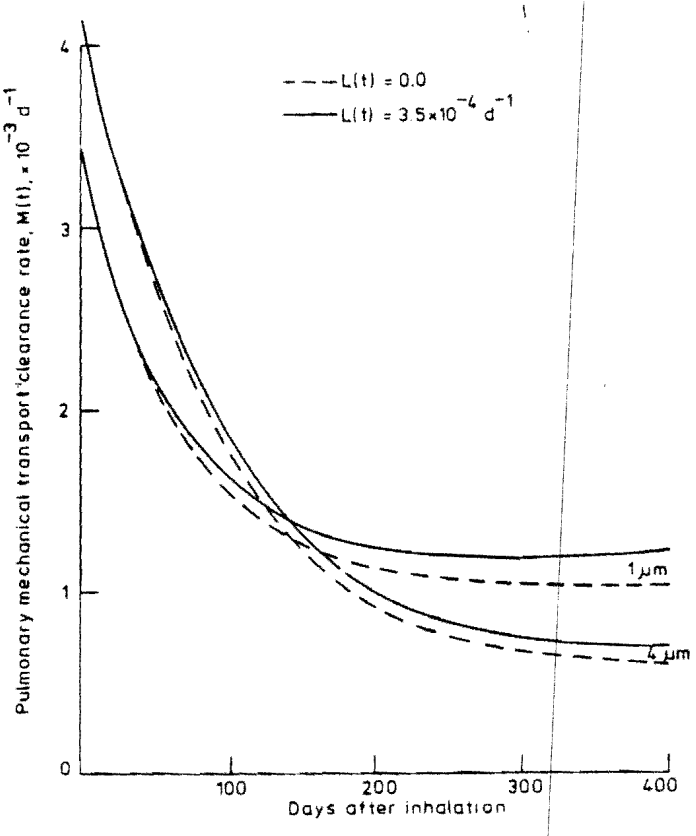

Fig. 5. Estimated pulmonary mechanical transport clearance rates $M(t)$ in man.

Table 6. Parameters of exponential functions representing pulmonary retention according to the assumed rate of transfer to lymph nodes

CMD (μm)	Rate of transfer to lymph nodes $L(t)$ ($\times 10^{-4}$ per day)	Proportion of retained fraction in lymph nodes at 1 yr $N(t)/R(t)$, (%)	Parameters of fitted pulmonary retention functions			
			A_1 (%)	λ_1 ($\times 10^{-2}$ per day)	A_2 (%)	λ_2 ($\times 10^{-3}$ per day)
1	0	0.0	14.54	1.834	85.46	1.723
	1	4.5	14.29	1.864	85.71	1.857
	2	8.7	13.81	1.890	86.19	2.002
	3.5	14.9	13.16	1.920	86.84	2.217
4	0	0.0	27.48	1.387	72.52	0.789
	1	4.3	27.47	1.388	72.53	0.910
	2	8.4	27.43	1.390	72.57	1.032
	3.5	14.3	27.02	1.425	72.98	1.237

about 4×10^{-3} per day to about 1×10^{-3} per day at 200 days, with little change thereafter. Although the results shown in Fig. 5 indicate that $M(t)$ is greater for 4 μm particles that for 1 μm particles up to 100 days, and greater for 1 μm particles beyond 200 days, in view of the uncertainties in the estimated dissolution rates, these differences cannot be regarded as significant.

CONCLUSIONS

Respiratory tract retention of 1 μm strontium-85 labelled FAP and 4 μm yttrium-88 labelled FAP was followed for more than a year (372–533 days) after inhalation by 12 healthy non-smoking male volunteers. Approximately 7% of the initial respiratory tract deposit of 1 μm particles and 40% of the 4 μm particles were associated with a distinct rapid clearance phase, completed within about 2 days after inhalation. These figures correspond closely to the amounts calculated to have deposited in the ciliated conducting airways under the conditions of aerosol administration. No significant rapid pulmonary clearance was observed. This finding is at variance with the current ICRP Lung Model, which assumes that 40% of the pulmonary deposit of a relatively insoluble material is cleared via the ciliated airways with a half-time of 1 day, but is consistent with recent observations made elsewhere (Lippmann, 1971; Foord *et al.*, 1977; Stahlhofen *et al.*, 1980).

In most subjects retention of particles of both sizes followed two-component exponential functions over the period of measurement, the two phases having half-times of the order of tens of days (intermediate phase), and several hundred days (slow phase), respectively. The mean retention observed for the group of subjects had a greater fraction associated with the intermediate phase for the 4 μm particles (28%) than for the 1 μm particles (15%).

There was considerable intersubject variation in retention, the coefficient of variation increasing from 7% at 50 days after inhalation to 20% at 350 days. A significant negative correlation was found between retention and the subject's FEV_1/FVC. A low value of FEV_1/FVC may be indicative of relatively high airway resistance (Cotes, 1975), and therefore of changes in the airways, but the values determined for the subjects studied here (72–93%) are consistent with the distribution of values reported by Kory *et al.* (1961) (82.0% ± 8.7%; $\bar{x}$ ± SD) for normal adult males. Retention of the two sizes of particles in each subject was strongly correlated, indicating that retention is a characteristic of an individual. There was only a weak correlation between the rate of clearance at 25 days after inhalation and that at 350 days, and therefore a subject's long-term clearance characteristics cannot be predicted reliably from measurements made over a short period.

Dissolution of the 1 μm particles was estimated from measurements of strontium-85 in urine samples, which was detectable up to 200 days after inhalation. The simplest dissolution model consistent with the observed excretion was immediate dissolution of 0.5% of the initial lung deposit followed by constant dissolution at a rate of 6.9×10^{-4} per day, corresponding to a dissolution rate constant of 3.3×10^{-8} g cm^{-2} per day for FAP in the human lung.

Dissolution of the 4 μm particles could not be assessed satisfactorily from urinary excretion of yttrium-88, and was therefore estimated on the assumption that they had the same dissolution rate constant as the 1 μm particles. Although dissolution did not dominate clearance from the respiratory tract, for both sizes its contribution was significant and difficult to assess, especially after the first 100 days. The development of a test aerosol with the qualities of FAP (low toxicity, ease of labelling, homogeneous composition), but a lower dissolution rate would greatly benefit studies of respiratory tract retention, especially if smaller particles or longer periods of measurement than used here, are to be employed.

Assessment of clearance by mechanical transport from the pulmonary region required estimates to be made of the fraction of the long-term retained activity associated with the conducting airways and the lymph nodes. These could not be based on observations in this or any other human study. The results of rodent studies suggested that the former would be no more than 1 % while estimate of rates of transfer from pulmonary lung to lymph nodes based on dog studies indicated that the latter could be 5–15 %. Values within this range do not affect the overall pattern of the estimated mechanical transport rates from the pulmonary region which for both sizes fell from an initial value of about 4×10^{-3} per day to about 1×10^{-3} per day at 200 days, and decreased relatively slowly thereafter.

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