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LUNG DEPOSITION OF LABELLED MONODISPERSE SUBMICRONIC PARTICLES

U.S. NAVAL RADIOLOGICAL DEFENSE LABORATORY

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ADMINISTRATIVE INFORMATION

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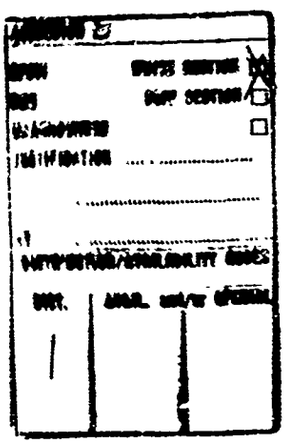

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ABSTRACT

Aerosol deposition in the rat lung has been determined as a function of particle size between 0.034 and 1.2 μ aerodynamic diameter. ^{22}Na-Labeled aerosol was produced as monodisperse particles by a modified version of the Sinclair-LaMer glycerol generator. Particle size was determined by light scattering and was verified by light and electron microscopy. Anesthetized rats were fitted with a tracheal tube, thus avoiding oral or nasal influences on lung deposition. Respiratory minute volume as determined with this surgical preparation was 97 ± 3 ml/min. This value and the breathing pattern were practically identical to those found in nontracheotomized rats, similarly maintained at a body temperature of 37.5 C (colon). For particles between 0.6 and 1.2 μ, lung deposition varied from 14% to 20%. Fifteen minutes after inhalation, organ distribution of ^{22}Na outside the lung was similar at two different particle sizes and in agreement with other studies based on intraperitoneal injection. Critical comparison of present lung deposition values in the rat with existing data on man showed close agreement with those studies in man giving low lung deposition values (20%), for particles with aerodynamic diameter between 0.6 and 1.2 μ. Particles less than 0.14 μ in size showed lung deposition values of 7 to 8 %; this may be a particular characteristic of the rat.

SUMMARY

The Problem:

Hazard evaluation of inhaled radioactive particles depends on the fraction of particles deposited in the respiratory tract. This fraction, expressed as "percent deposition", usually refers to how much of the material in the inspired air remains behind in the entire respiratory tract after expiration. Pulmonary or "lung deposition" refers to how much of the material in the inspired air remains in the lung after expiration. After 25 years of experimentation recent reports indicate that human lung deposition values, because of wide variance, are still a matter of dispute. The intention of the present study was to identify factors responsible for these variations by critically comparing our lung deposition values, which were obtained with the more important variables under control, with existing data on man. Two factors which have been responsible for ambiguity in interpretation of data in studies on man were: polydispersity of particle sizes, and mode of breathing.

The Findings:

The present study used a glycerol aerosol generator which was designed to make submicronic monodisperse particles. To resolve the point involving the mode of breathing anesthetized rats were fitted with a tracheal tube, thus avoiding oral or nasal influences on lung deposition. For particles between 0.6 and 1.2 μ diameter, results were in close agreement with studies showing low lung deposition values in man. For smaller particles lung deposition in the rat decreased, unlike the curves usually depicted for man.

INTRODUCTION

Hazard evaluation of inhaled radioactive particles depends on the fraction of particles deposited in the respiratory tract. This fraction, expressed as "percent deposition", usually refers to how much of the material in the inspired air remains behind in the entire respiratory tract after expiration (1). Pulmonary or lung deposition will refer to how much of the material in the inspired air remains in the lung after expiration. Recent reports (2,3) indicate, after 25 years of experimentation, that human lung deposition values, because of wide variance, are still a matter of dispute. Data from 5 independent studies fell into 2 ranges, 2 groups of workers obtaining much higher values for deposition than the other three, for particles between 0.5 and 1.5 μ in aerodynamic* diameter. The intention of the present study is to identify factors responsible for these variations by critically comparing our animal lung deposition values, which were obtained with the more important variables under control, with existing data on man. Over the aerodynamic size range considered, oral and nasal deposition in humans is small.

Dautrebande lists many factors which may be responsible for these variations (4), and among these is polydispersity of particle size. For polydispersed aerosols, deposition values obtained have limited use, as they can be compared quantitatively only to another aerosol with the same size distribution and equivalent particle density. With a monodisperse aerosol and a particular species of animal, if a relation between deposition and particle size can be obtained at each size, then this relation can be used to predict percent deposition for any size distribution using the same aerosol and animal species. In the present study, monodisperse glycerol particles were produced using a modified Sinclair and LaMer type generator (5).

Variation in lung deposition values has also been ascribed to the method of breathing. Dennis indicates that mouth breathing in man gives a lower percentage deposition than nasal breathing (3). To resolve this point, in the present study, rats were fitted with a tracheal tube (tracheotomized), thus avoiding oral or nasal influences. During aerosol transport to the lung, deposition within the tracheal tube did not change concentration significantly. Also, deposition on the larger bronchi was possible, although deposition values reported in the literature would indicate that these values are small compared to pulmonary values (6). There appear to be no other lung deposition studies with the rat in which the respiratory minute

*the diameter of a unit density sphere with the same settling velocity as the particle in question (6).

was measured. Our results, while not in agreement with certain other animal data (7), were in close agreement with studies showing low lung deposition values in man (8, 9. 10).

METHODS

Aerosol Generation and Size Measurement Monodisperse (high degree of size uniformity) particles were produced using a modified version of a Sinclair-LaMer generator, similar to those described elsewhere in the literature (5). The general process of aerosol production was as follows: glycerol (analytical reagent grade) was heated to produce vapor, which was then allowed to cool slowly while condensing on vaporized salt crystal "nuclei" (Figure 1). Under proper conditions, monodisperse particles resulted. In the present experiment, glycerol vapor was condensed on ^{22}Na-labelled NaCl "nuclei". Relative humidity of the gas used for aerosol production was approximately 5 percent. For earlier experiments air was used to generate and transport the aerosol, but for all later work nitrogen (N_2) of 99% purity was used to generate the aerosol stream. Note that oxygen (O_2) was metered into the nitrogen stream (containing cooled aerosol) beyond the heated chambers; partial pressure of O_2 was monitored by a paramagnetic analyzer. Use of nitrogen in the generator suppressed tar formation, at the same time eliminating an unidentified volatile factor which caused curling of 12 day-old leaves of the bean plant, Phaseolus vulgaris. The plant leaf provided an extremely sensitive means for detecting the presence of this factor, which presumably might be toxic to animals, too, if it was produced at high concentrations.

Settling characteristics of the aerosol indicated that the aerosol was uncharged. Aerosol size was determined by measuring the scattering of light as a function of angle using the "owl" as described by Sinclair (11). Particle sizes were verified by light and electron microscope studies. As a measure of aerosol monodispersity, the Standard Error of Mean(SEM)was established by light microscopic measurement of 2 sizes generated during 2 different aerosol runs. Results were: 1.2 μ diam. ± .04 (SEM) and 1.5 μ diam. ± .03 (SEM). Figure 2 is an electron micrograph of glycerol particles for sizes smaller than those measureable by the owl. The particles were initially allowed to settle on silicone-treated glass slides. The slides were then dipped into a parlodion-amylacetate solution and allowed to drain. The resulting film was found to have glycerol particles embedded in it. Particles were readily distinguishable from background.

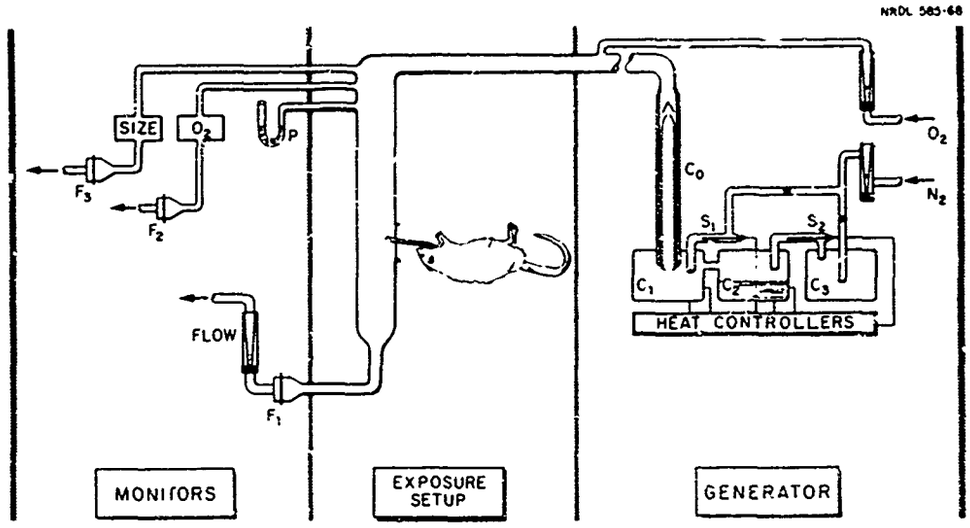

Figure 1. Schematic outline of aerosol exposure equipment: glycerol vapor from C_2 condenses on NaCl crystals volatized at S_1 and/or S_2 to form aerosol particles at C_1; C_2 and C_3 are glycerol and nitrogen thermal conditioning chambers; growth in particle size is regulated by cooling rate in C_0, based on metered flow rate of N_2. Particle size, partial pressure of O_2, and total inside pressure (measured by differential manometer at P) are continuously monitored and kept at 0.6 μ, 160 mm Hg, and 760 mm Hg (ambient), respectively; Final filter, F_1, is assayed for specific activity of ^{22}Na-glycerol; negligible activity is removed at F_2 and F_3.

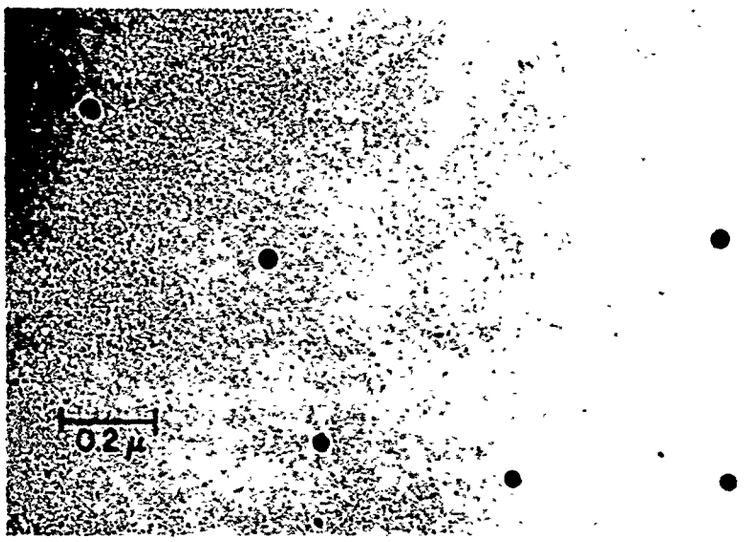

Figure 2. Electron micrograph of glycerol particles embedded in parlodian.

Animal Preparations Prior to Exposure Female rats, six months old, were used from the laboratory strain (Sprague-Dawley). These weighed between 240-260 grams and were fasted for 24 hours prior to inhalation experiments. For anesthetic, intraperitoneal injections of sodium pentobarbital were given. An initial injection of 9 mg was followed by booster injections of not more than 0.3 mg after 1 hour. No more than 2 booster injections were given. During all procedures colon temperature was maintained at 37.5 ± 0.5 by use of an electrically heated pad. This temperature, as measured by Hunt, is considered normal for non-anesthetized rats of this strain (12). By controlling body temperature, respiratory rate remained quite constant during the inhalation period.

Immediately before the 1-hour inhalation period each rat was tracheotomized as follows: An incision approximately 3 cm long was made directly below the larynx and over the trachea. The trachea was bared by blunt dissection through the fascia, soft tissue, and overlying muscle. Special care was taken to avoid disturbing the nerve trunks. The trachea was sectioned midway between two cartilaginous rings. An 8 cm piece of polyethylene tubing (intramedic, No. PE 240/S12 ID 0.066 in OD 0.095 in.) was inserted into the trachea to a depth approximately one cm short of the bifurcation.

Minute-volumes reported in Table I were obtained for 250 g rats using an air-tight plethysmographic chamber setup similar to that of Thomas (13). The equipment is shown in Figure 3. Except for the pressure transducer (PM 197 by Statham Instrument, Inc., Los Angeles, California) the components were: Gage Control Module 902641, Accudata 104-10C amplifier, and Visicorder 906-C (Minneapolis-Honeywell; San Francisco, Calif.). The rat was enclosed in the plethysmograph in a supine position. Its tracheal tube or head was exposed to outside air through a point opening in a taut rubber wall at one end of the chamber. Change in thoracic volume with each respiratory movement caused a linear pressure change within the chamber. The change in pressure was electrically transduced, amplified and recorded. The system was calibrated by injecting an exact volume of dry air and measuring the pressure change at constant temperature. In the situation where a rat was allowed to breathe through both its nose and mouth an air-tight seal around its neck was necessary. This was accomplished by shaving the neck, lubricating it with vaseline, and inserting the head through the thumb section of a surgical glove with the tip of the thumb cut off. Care was taken so that the rubber collar formed in this way was very slightly larger in size than the neck of the rat. An air-tight seal was then effected by sealing the space between the collar and the rat's neck with more

TABLE I

RESPIRATORY PARAMETERS FOR ANESTHETIZED RATS

PREPARED FOR AEROSOL INHALATION

RAT CONDITIONS	NO OF RATS	TIDAL VOL (ml)	RESP RATE (min^{-1})	MEAN MINUTE VOLUME ± SEM ml/min
Tracheotomized	29	1.30 ± .04	75 ± 2	97 ± 3
Intact	6	1.33 ± .04	69 ± 2	93 ± 3

Gas volumes at 26 C; Body temperature (colon) 37.5 C

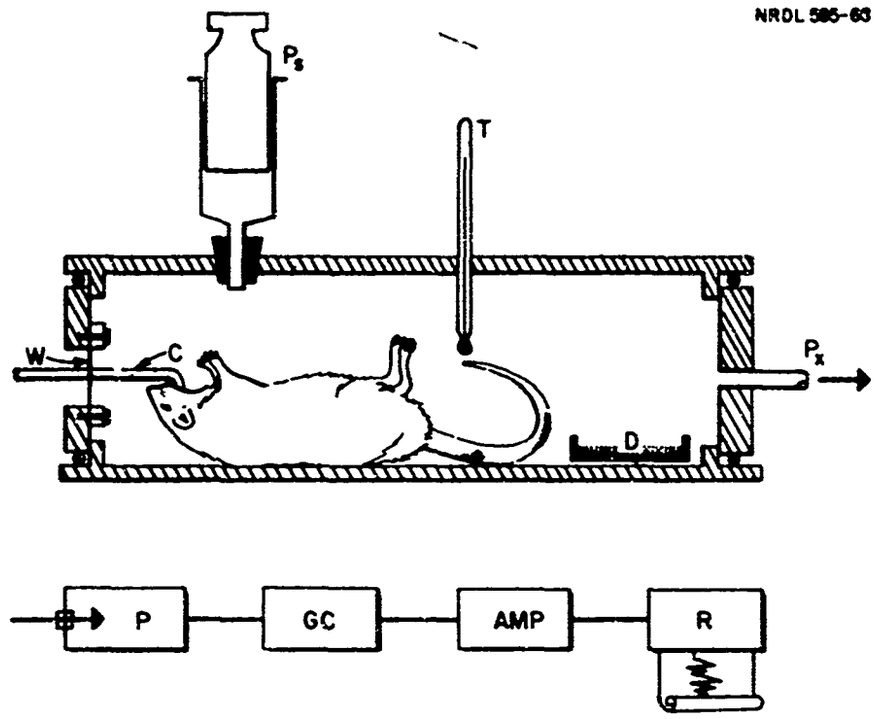

Figure 3. Plethysmographic Assembly; showing surgically prepared rat in position with tracheal catheter (C) piercing taut rubber wall (W). Ends are o-ring sealed, with temperature (T) held constant at 26 C, pressure transduced at (P_x), and dessicant at (D). Also indicated are calibration syringe, gauge controls, amplifier and high speed recorder (P_s,GC, AMP and R). Chamber volume was 2.5 liters.

vaseline. In these cases the rubber was stretched quite taut, preventing any change in plethysmograph volume as a consequence of respiratory movement.

Inhalation Setup and Procedure ^{22}Na-labelled glycerol particles were generated monodispersely, in sizes ranging from 1.03 to 0.03 μ diameter. The amount of inspired radioactivity, necessary for deposition calculations, was obtained as will be shown later, from activity values on the final filter, aerosol flow rate, and respiratory minute volume. Only tracheotomized rats were used for deposition studies, and the radioactive aerosol was administered directly through the tracheal cannula. The sharpened tip of the tracheal cannula pierced through a smaller hole in a rubber wall stretching across a lateral opening in the aerosol duct (Figure 1). Thus no part of the rat was exposed to the aerosol except the lung and trachea. A water manometer was used to measure pressure differential between the inside the outside of the aerosol duct. Possible pressure differences were kept at zero, since a pressure difference of 1 or 2 cm of water could substantially alter both respiratory minute volume and breathing patterns. Body (colon) temperature was maintained at 37.5 C throughout the one hour period of inhalatory exposure.

Dissection and Counting Procedures Fifteen minutes after separating the rat from the aerosol duct its abdomen was opened, and 2 ml of blood was withdrawn from the vena cava. The rat was then killed by puncturing its pleural cavity. The trachal tube and remaining trachea were next removed. The entire carcas was then placed in a close fitting lucite container to fix counting geometry, and the container was positioned between two opposing four-inch sodium iodide crystals, spaced 3 inches apart. Using a 100 channel pulse height analyzer, the 1.28 Mev peak of ^{22}Na was counted between 1.15 and 1.41 Mev. Counting efficiency was 7% of total radioactivity, as established in other animals injected with ^{22}Na prior to killing. Whole body counts were taken on 54 animals and subsequent lung deposition values were calculated. In cases where organ distribution of radio activity was determined, care was taken to avoid cross-contamination. Upon removal of the organ from the carcass, excess blood was blotted, and the organ was then placed in a Petri dish for counting. Fresh tissue weights were taken before organs were counted.

EXPERIMENTAL RESULTS AND DISCUSSION

Respiratory Pattern Estimates of respiratory minute volume ($\dot{v}$) can lead to large errors in deposition calculations. This would be

especially true when, for example, the body temperature of anesthetized rats is not maintained during the inhalation period. For the rat, minute-volume determinations by Guyton (14) involved ether anesthesia, a practice possibly undesirable from the standpoint of the early excitatory action of ether. Since in present experiments, rats were given sodium pentobarbital and also had tracheotomies, it was deemed desirable to re-investigate the respiratory pattern under our conditions. Data reported in Table I clearly show that the tracheotomy procedure itself had no significant effect on the respiratory pattern; also, it had no effect on the minute volume. On the other hand, tracheotomized and intact rats, anesthetized in both cases, showed lower minute volumes, 97 and 93 ml/min, respectively, than 130 ml/min; a value for 250 gram rats calculated from Guyton's empirical formula, $\dot{v} = 2.1\ (\text{weight})^{3/4}$. Guyton's data may not be however, strictly comparable, because temperature was not stated and because of possible anesthetic differences. In our work, particular care was taken to maintain body temperature, to avoid protracted anesthesia and to avoid leaving the anesthetized rat in one given postural position for longer than necessary to complete the determinations of respiratory pattern and inhalation exposure. These precautions stabilized respiratory minute volume at a remarkably constant level for periods of 1 - 1/2 hours. They also precluded disturbances caused by variation in heat loading and maintained the metabolic state. Individual $\dot{v}$ measurements were not obtained for deposition experiments involving sizes 0.63 and 1.15 μ diam. In these groups of animals, the mean value of 97 ml/min was used for calculation of % lung deposition.

Organ-Distribution of Inhaled Label Distribution of ^{22}Na, shown in Table II, resulted from nine standard aerosol runs, four at the 0.63 μ size and five at the 1.15 μ diam. size. The relative amounts of ^{22}Na among individual organs agreed quite well with results reported for intraperitoneal injection of ^{22}Na in rats (15), thus supporting the view that for a soluble radioelement, distribution is independent of route of entry. One should note also that all organs showed increased radioactivity per gram, as one would expect from lung deposition results. The nine exposures have been standardized to the same final filter activity, corresponding to 10,000 picocuries in inspired air (because of unavoidable variation in evolution of ^{22}Na-Cl from the seeder, from one run to another). Femur samples, as reported in the table, were scraped free of muscle prior to weighing and counting.

Aerosol Deposition Fraction Deposition data are shown in Table III. For these determinations rats were subjected individually to glycerol aerosol at each stated size. From 0.6 to 1.2 μ lung deposition varied from 14 to 22% only. These results are generally in

TABLE II

DEPOSITION OF RADIOACTIVITY IN DIFFERENT TISSUES FOR TWO PARTICLE SIZES AS INHALED*

	0.63 μ picocuries g fresh	1.15 μ picocuries g fresh
lung	202	316
femur	72	101
kidney	58	93
heart	69	71
blood	63	77
GI tract	47	74
liver	41	64
spleen	36	69
skin sample	38	62
pelt	36	63
carcass residue	27	43
muscle sample	23	30
number of rats	(4)	(5)

*Mean values reported; values have been standardized for 10,000 picocuries in the inspired air; fifteen minutes after inhalation

TABLE III

NO OF RATS	AERODYNAMIC DIAMETER	RANGE OF LUNG DEPOSITION*	LUNG DEPOSITION
	(μ)	(%)	(%)
18	1.15	14.7 - 28.3	22.0 ± 0.7
17	0.63	10.5 - 17.6	14.0 ± 0.5
9	0.39	6.1 - 13.7	10.5 ± 0.9
1	0.14	——	7.0
2	0.094	7.2 - 11	9.1
1	0.07	——	8.2
1	0.04	——	7.0
1	0.034	——	8.0

*Mean ± SEM indicated

agreement with certain studies in man. Since studies in man often entail other considerations, they will be critically reviewed below. Data in Table III also show progressively lower lung deposition values with sizes smaller than 0.14 μ. This feature is unlike the rising curve usually depicted for man (6), and it may be characteristic of the rat. Presumably it is a consequence of the more rapid breathing rate of the rat, as compared to man. Dissection and counting of the excised lung, 15 minutes after the inhalation period, revealed that approximately 3% of the total body radioactivity was still in the lung, the remaining 97% of the radioactivity was distributed throughout the body. In the tracheotomized rat, ^{22}Na transport out of the lung could take place from functional regions only. Hence these observations indicate that deposition was almost totally within the pulmonary compartment as defined below. Considering that lung deposition values included the entire bronchial tree and that the aerosol concentration had not been decreased by nasal deposition, the values listed here also must represent maximum rat lung deposition for the breathing frequency and tidal volumes indicated. The expression for lung deposition was derived in the following way:

$$\% \text{ lung deposition} = \frac{\text{amount of material deposited in lung} \times 100}{\text{amount of material in total inspired air}}$$

Since tracheotomized animals were used, the material found in the body is entirely the result of lung deposition. Also, the amount of ^{22}Na radioactivity is directly proportional to the amount of aerosol material so that

$$\% \text{ lung deposition} = \frac{\text{total body activity} \times 100}{\text{activity in total inspired air}}$$

In terms of our experimental parameters,

$$\% \text{ lung deposition} = \frac{\text{total body activity} \times 100}{\frac{\dot{v}}{1} \cdot \frac{A_F}{k}}$$

K = gas flow rate through aerosol duct (L/min)

$\dot{v}$ = minute volume (L/min)

A_F = activity on final filter

A source of much confusion in aerosol inhalation literature has been the use of the words "deposition" and "retention". Our use of these words follows definitions suggested by the National Academy

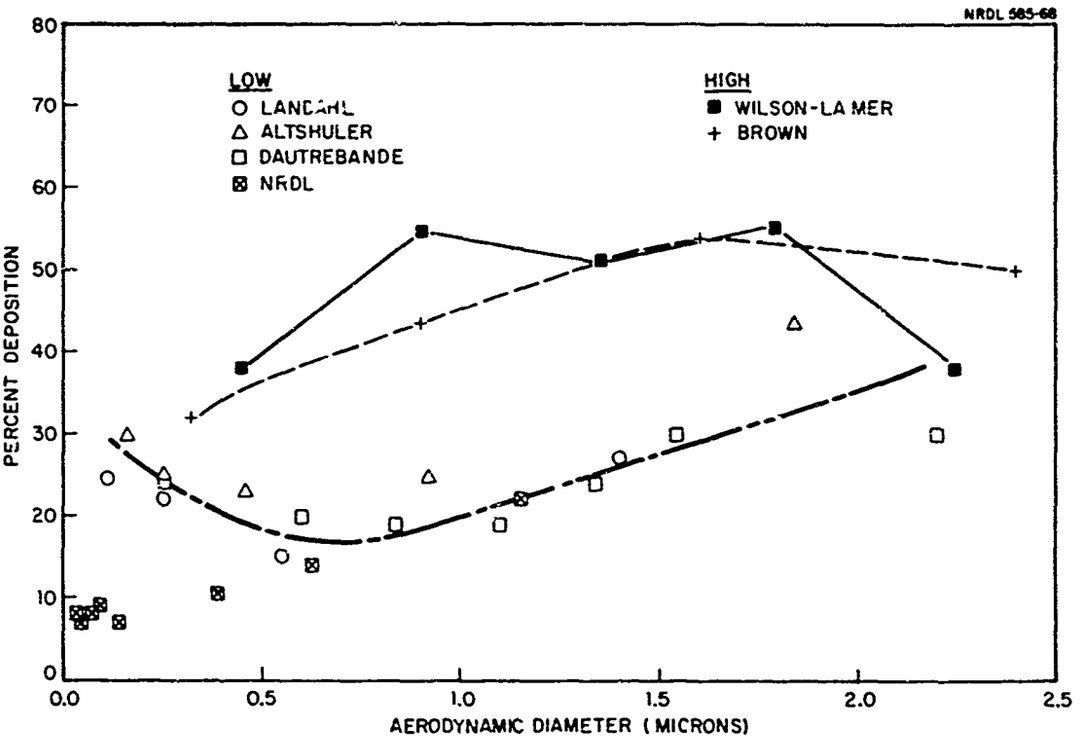

Figure 4. Lung deposition in anesthetized rats as a function of aerodynamic diameter; shown in comparison to other deposition studies

	% DEPOSITION	BREATHING MODE	BREATHING FREQUENCY min^{-1}	TIDAL VOLUME ml	AEROSOL	DENSITY
HIGH VALUES						
■ Lung	(Wilson and LaMer, 16)	mouth	5-1/2 to 20	?	glycerol-water	1.06
+ Lung	(Brown, et al.17)	nose	15	620 to 790	clay	1.6
LOW VALUES						
○ Total	(Landahl, et al.8)	mouth	15	450	triphenyl phosphate	1.15
△ Total	(Altshuler, et al.9)	mouth	15	450		1.15
□ Total	(Dautrebande, 10)	nose	32	414	coal	1.22
⊠ Lung	NRDL	tracheal tube	75	1.3	glycerol	1.12

(The Wilson and LaMer data were averaged at sizes as indicated; maximum deposition was taken as 55 percent).

of Sciences (1). "Deposition" refers to how much of the material in the inspired air remains behind after expiration, for example as based on comparisons of inhaled and exhaled gases. "Retention" refers to the fraction of deposited material remaining at a particular site at any given time, for example as determined directly by tracer. Hence, "percent total deposition" and "percent lung deposition" which occur in many other publications, refer to how much of the material in the inspired air remains behind after expiration in the entire respiratory tract, and in the lung, respectively. Another source of confusion arises when the experimental terms "lung", "pulmonary", and "alveolar" deposition are used without careful definition of the anatomical regions. The term "lung" as used here will refer to the "pulmonary compartment" as defined by the Task Group on Lung Dynamics; this is the region including respiratory bronchioles, alveolar ducts, atria, alveoli and alveolar sacs (6). The surface of this region consists of non-ciliated, moist epithelium and can be regarded as the functional area (exchange space) of the lungs. Insoluble particles deposited here may present a long-term hazard since this region does not have the ciliary clearance mechanism needed for particle removal.

CRITIQUE

Rat Deposition in Relation to Studies on Man: Lung deposition values for man are shown in Figure 4, in relation to present data for rats. Data from 5 independent studies on man fell into 2 groups: Two laboratories obtained much higher values for lung deposition than did the other three laboratories. Average particle sizes between 0.5 and 1.5 μ aerodynamic diameter were used in all cases. Note that our results closely agree with those of the group of workers who obtained low lung deposition values in man. Except for our data, the lower curve of Figure 4 represents total deposition, since insufficient information was available for calculation of lung deposition as we have defined it. From Landahl and from Altshuler, the data provide a good approximation of lung deposition, since their mouth-breathing procedures precluded nasal deposition and since tracheo-bronchial deposition is low over their size range, from 0.5 μ to 2.0 diameter. Obviously, when comparing the two groups of experiments done under similar conditions, lung deposition should be less than total deposition. Yet, as Figure 4 shows, the Landahl, Altshuler, and Dautreband values for total deposition are far below the values for lung deposition as actually determined by Wilson and LaMer, and by Brown (16,17).

To insure that the data compared in Figure 4 were obtained under similar experimental conditions, the following factors require consideration:

Aerosol parameters

1. median aerodynamic diameter (MAD)
2. hygroscopic nature of aerosol
3. electrical charge on the aerosol particles
4. particle size distribution

Physiological parameters

5. Tidal volume and respiratory rate
6. Method of breathing, nose vs mouth

The median aerodynamic diameter (MAD) is plotted on the abscissa in Figure 4. This diameter is the same as the "equivalent impaction diameter" (Landahl). For this particle size comparison diameters have been adjusted by a factor equal to the square root of particle density. The factor applies to particles obeying Stokes law, and for glycerol is 1.12. A 1 μ glycerol particle would then have a median aerodynamic diameter of 1.12 μ.

Can the differences between the high and low deposition values shown in Figure 4 be attributed to an error in the MAD determination? MAD errors can arise either because of size determination errors or because of irregular shape effects. Particles of 1 μ diam. present no measurement problem. Applying a density adjustment factor to irregularly shaped particles does not necessarily assure a settling velocity equivalent to a unit density sphere. Multiplying Brown's MAD by 4 would allow his data to complement the lower values. However, a difference in settling velocity by a factor of 4 due to a shape difference seems unreasonable. Also, Dautrebande's data with irregularly shaped NaCl particles agrees quite well with the lower values, so the difference between the high and low values is not likely due to MAD errors caused by shape. Besides, Wilson's data is still in disagreement with the lower values shown in Figure 4, and in his study MAD determinations present no problem.

The Task Group on Lung Dynamics has indicated that there may be an error in Wilson's MAD due to the hygroscopic nature of glycerol particles. If the hygroscopic glycerol particle enlarges in the lung to a greater degree than an insoluble, non-hygroscopic particle, then glycerol deposition values may not be comparable to other work. Experimental studies of particle enlargement under inhalation conditions are at variance with theoretical prediction. One micron particles of triphenyl phosphate, which are non-hygroscopic, were shown not to grow in wet atmosphere (9). Dautrebande obtained similar deposition values

when using hygroscopic and non-hygroscopic particles which were under 1 μ in diam (4). For Wilson's glycerol particles, consisting of 50% glycerol- and 50% water, equilibrium calculations of particle enlargement by the Task Group on Lung dynamics indicated a particle diameter growth factor of 2.5. Experiments in our own laboratory involved passing 1 μ diameter anhydrous glycerol particles through a water saturated atmosphere maintained at 37.5 C. Under aerosol flow conditions approximating both human and rat lung ventilation rates, particle growth was less than 15%. Since this would amount to a smaller correction than that to be predicted theoretically, we conclude that calculations of particle growth based on equilibrium assumptions are inappropriate for lung ventilation conditions. At 1 μ, the reported differences between high and low deposition values are most probably not attributable to hygroscopic growth.

Could electrically charged particles coagulate and enlarge by the time they traveled to the lung? If this were the case, Brown's curve in Figure 4 could be shifted to the right to complement the lower values as mentioned before. In Brown's case, this is a strong possibility, since the aerosol was heated during generation and "occasional flocks were observed" (17). This leaves us to explain the difference between the Wilson and LaMer data and the lower values. In the cases of Wilson and LaMer, of Altschuler, of Landahl, and of our own experiments, the same type of aerosol generator was used. During sedimentation studies in our own laboratory, aerosols showed characteristics typical of electrically neutral particles. Therefore, the disagreement between LaMer's deposition values and the lower values is not likely due to charge differences.

As Wilson and LaMer indicated, the characterization of a polydisperse aerosol by its mass median diameter can be ambiguous, since the size distribution is uncertain. If we were simply comparing Brown's data to Dautrebande's data, polydispersity could be given as a basis for the differences observed. But Wilson and LaMer's data and the lower values (except Dautrebande's) involved monodispersed aerosols, so the difference is still unresolved. Thus it seems most likely that the disagreement between high and low deposition values shown in Figure 4 is due to physiological variation.

Data other than those shown in Figure 4 clearly indicate that higher tidal volumes and lower breathing frequencies tend to increase percent total deposition (8, 9, 10). If one takes 10 respirations per minute as the lowest conceivable regular breathing frequency then examines deposition at the largest tidal volume, one would assess maximal average deposition values. Such data can be obtained from Dautrebande's study, namely values of 10 rpm and a tidal volume of 923 ml (10). Even at these rather extreme conditions, a comparison of total

versus lung deposition will show that the lung values of Wilson and LaMer and of Brown are inexplicably high. Again some basic difference in the sets of data seems to exist. It is interesting to note that another physiological case, as represented by our anesthesized, tracheotomized rats, the data compare quite well with the more normal, lower deposition values. This argues in favor of using such animals for inhalation studies with the thought of extropolation to man, especially in the size range of 0.5 to 2 μ diameter. For particles below 0.5 μ diam, the low rat deposition values are noteworthy. Reasons for this low deposition are not clear. Possibly, this is due to a higher breathing frequency in the rat as compared to man.

In conclusion, a recent opinion given by Dennis attributes the differences between the sets of data to the method of breathing (3). Although the title of his paper states lung deposition, he clearly dealt with total deposition. Dennis indicated that mouth breathing gave a lower percent (total) deposition than did nasal breathing, and no one would dispute this statement. The real question implied was: Does mouth breathing as compared to nasal breathing lead to lower percent lung deposition in the size range 0.5 to 1.5 μ diameter? Also, is this reason for the disagreement between the 2 sets of data? The answer would seem to be no, since Wilson and LaMer used mouth breathing, as did Altshuler, and Landahl. Furthermore, Dautrebande's data on nasal breathing as well as our own data on tracheotomized rats compare well with the Altshuler and the Landahl data.

Two important considerations for rejecting studies showing high lung deposition values are: absence of tidal volume information in the Wilson and LaMer Study and possible particle coagulation in the Brown Study. For the low deposition values, there appear to be no criticisms outstanding.

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13 ABSTRACT

Aerosol deposition in the rat lung has been determined as a function of particle size between 0.034 and 1.2 μ aerodynamic diameter. ^{22}Na-Labeled aerosol was produced as monodisperse particles by a modified version of the Sinclair-LaMer glycerol generator. Particle size was determined by light scattering and was verified by light and electron microscopy. Anesthetized rats were fitted with a tracheal tube, thus avoiding oral or nasal influences on lung deposition. Respiratory minute volume as determined with this surgical preparation was 97 ± 3 ml/min. This value and the breathing pattern were practically identical to those found in nontracheotomized rats, similarly maintained at a body temperature at 37.5 C (colon). For particles between 0.6 and 1.2 μ, lung deposition varied from 14% to 20%. Fifteen minutes after inhalation, organ distribution of ^{22}Na outside the lung was similar at two different particle sizes and in agreement with other studies based on intraperitoneal injection. Critical comparison of present lung deposition values in the rat with existing data on man showed close agreement with those studies in man giving low lung deposition values (20%), for particles with aerodynamic diameter between 0.6 and 1.2 μ. Particles less than 0.14 μ in size showed lung deposition values of 7 to 3%; this may be a particular characteristic of the rat.

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