

Deposition and clearance of particles in the human lung

by Lena Låstbom & Per Camner

The upper respiratory tract consists of the nose, mouth, pharynx, and larynx. For particles with diameters larger than around 1 μm , the nose is a much more efficient filter than the mouth. During physical exercise, breathing occurs to a great deal via the mouth. Also at low physical activity, quiet breathing via the mouth may occur to some extent, especially when people are talking (1). The PM_{10} concept is based on the assumption that mouth breathing occurs (2). During the determination of the PM_{10} (particulate matter <10 μm in diameter) fraction in air, the mass of particles which penetrate a preseparator is measured. The deposition characteristics of this preseparator are similar to those of the mouth and throat. Another important function of the respiratory tract, besides acting as a filter of inhaled particles, is to warm and humidify the air. Already in the subglottic space, the relative humidity during inspiration is 98–99% during nasal breathing and around 90% during oral breathing (3). Therefore particles of soluble materials will take up water and grow, a phenomenon called hygroscopic growth. The diameter of a particle can increase several times, and the growth is rapid as the relative humidity increases from around 95% to 100%, especially during the increase from 99% to 100%.

Traditionally, the lung has been divided into a tracheobronchial region of conducting airways with a ciliated epithelium and an alveolar region of respiratory bronchioles, alveolar ducts, and alveoli without a ciliated epithelium. Until some years ago, there was a consensus that only smaller fractions of particles are retained for more than 24 hours in the tracheobronchial region in healthy persons. In recent years, this idea has been questioned, and there are experimental data supporting the fact that particles, especially in small ciliated airways, are, to a great extent, retained after 24 hours. There are therefore reasons for discussing larger airways (trachea and bronchi) and small ciliated airways (bronchioles) separately. The deposition and clearance of particles in the human lung have recently been exhaustively reviewed by a task group of the International Commission on Radiological Protection (ICRP) (4) and also by the Institute of Environmental Medicine (5).

Deposition

The deposition of particles in the respiratory tract is a function of particle size, inhalation and exhalation flow patterns, and the anatomy of the respiratory tract. The most important mechanisms for the deposition of particles are impaction, sedimentation, and diffusion. Parti-

cles are deposited by impaction when the airstream changes direction and the particles continue in their original direction due to their momentum. Impaction is of importance for the upper airways and in larger airways of the lung. Its effect increases with air velocity and particle size, and it is important for particles down to 1 or 2 μm . Particles are deposited by sedimentation when they fall because of gravitational force. This mechanism is valid for the entire respiratory tract, but it is generally the most important for the alveolar region, where the dimensions are small and the transition time long. Deposition increases with particle size and with decreasing air velocity and is important for particles down to around 0.5 μm in size. Diffusion denotes the mechanism by which particles move randomly because they collide with gas molecules. Deposition by this mechanism is important only for particles less than 0.5 μm , and the effect increases with decreasing size. Therefore there is a minimum deposition in the respiratory tract around the size of 0.5 μm . The mechanism is important for deposition in the entire respiratory tract. Impaction and sedimentation are dependent on the aerodynamic diameter of the particles, which is determined by the density, geometric size, and shape of the particles. Diffusion is not dependent on the density of the particles and therefore depends on the true geometric rather than the aerodynamic diameter of particles.

Theoretical models for the deposition of particles generally agree fairly well with the results from experimental studies. Figure 1 shows the deposition in various regions of the respiratory tract as a function of particle size, calculated with the theoretical model that was developed for particle deposition in the lung in 1994 by the ICRP (4). It can be seen from the figure that deposition of submicron particles increases markedly with decreasing size due to the effect of diffusion. In real life, size distributions of aerosols are usually very broad and often lognormal. However, deposition in the respiratory tract can fairly well be described by the mass median aerodynamic diameter of aerosols, for which impaction and sedimentation are the major deposition mechanisms.

Tracheobronchial and bronchiolar clearance

Mucociliary clearance

The airways in human lung have ciliated epithelium down to and including the terminal bronchioles. There was previously a consensus that the large majority of particles deposited in the ciliated region cleared within 24 hours, although small fractions of particles were

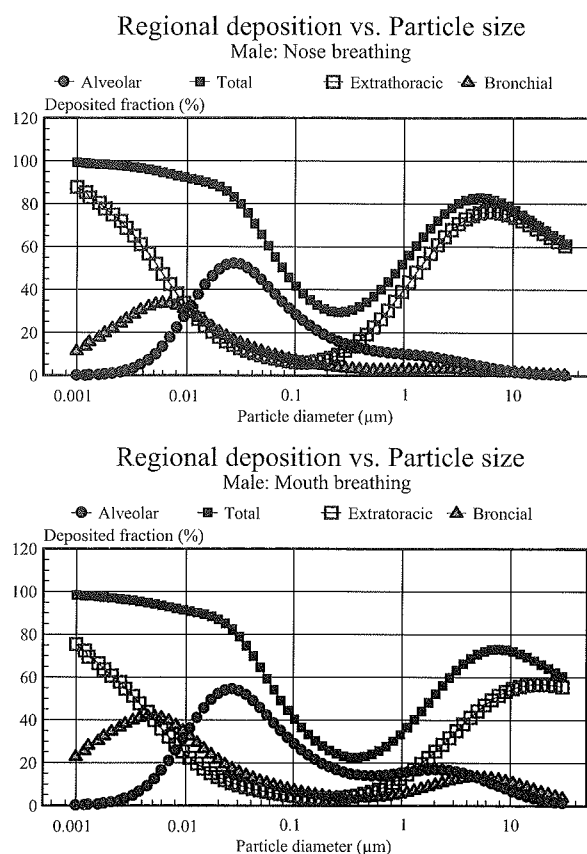


Figure 1. Deposition of particles during nose breathing (a) and during mouth breathing (b).

known to be retained for more than 24 hours (6–8). However, Stahlhofen and his co-workers (9–12) found that a large fraction of particles inhaled as a bolus with a penetration depth of less than the dead space was retained after 24 hours. The results of these bolus experiments have had a large impact on the ICRP Human Respiratory Tract Model for Radiological Protection (4). However, such a large retained fraction in large airways is contradictory to results from studies of the retention of particles inhaled in normal volumes in the human lung, because the 24-hour retention in these studies is often well below 50% (13–16). To handle these conflicting data, the ICRP model assumes that the slow clearing fraction of particles deposited in the tracheobronchial tree decreases with increasing geometric particle size, as proposed by Stahlhofen et al (17). However, the results of the bolus studies can also be interpreted in another way. The particles may in fact have penetrated deeper than the estimated penetration depth and deposited in the alveolar region or in the small ciliated airways with incomplete mucociliary transport. This latter explanation has some support from the results of Scheuch et al (12).

Recently, a method was developed for determining the clearance of particles in the bronchiolar region (18). Rather large particles, 6 μm, are inhaled at an extreme-

ly slow inhalation flow, 0.05 l/s. Deposition by impaction in large airways is reduced due to the slow inhalation flow, and the majority of the particles deposit by sedimentation before they reach the alveolar region. Calculations with several theoretical models for particle deposition in the lung, including the ICRP model, all show that the majority of the particles are deposited in the bronchiolar region and only relatively small fractions are found in the bronchial and alveolar regions (19). Particles 6 μm in size and inhaled at 0.5 l/s mainly deposit in the bronchial and alveolar regions and only to a small extent in the bronchiolar region. Camner et al (19) calculated that the large majority of particles deposited in the most peripheral part of ciliated airways is retained after 24 hours. This figure should be compared with the around 20% retained in generations 0–12, which include both large and small ciliated airways. The 24-hour retention of these extremely slowly inhaled particles was measured to be 50% in healthy subjects. In order to evaluate whether or not this high fraction of particles in fact could be due to deposition in the alveolar region, as has been suggested for particles inhaled in boli, Falk et al (20) followed the clearance of 6-μm particles inhaled by healthy subjects over a period of 1 month at both 0.5 l/s and 0.05 l/s. The particles inhaled with the extremely slow inhalation cleared with a half-time of 45 days, which was significantly faster than when particles were inhaled at 0.5 l/s, for which the half-time was 190 days, and much slower than the bronchial mucociliary transport, which is considered to be finished within 24 hours. The large retained fraction at 24 hours in the experiments with the 6-μm particles, inhaled extremely slowly, can thus not be explained by assuming that all these particles have been deposited in the alveolar region.

Roth et al (21) studied human clearance of inhaled ultrafine ^{111}In -labeled indium oxide particles. The count median diameter of the aerosol was 18 nm, and the mass median diameter was 27 nm. During the first few days, 7% of the particles deposited in the lungs were cleared. This is a considerably lower value when compared with the percentage that the ICRP model predicted would be deposited in the tracheobronchial region (figure 1). The study indicates that a considerable fraction of the ultrafine particles deposited in the tracheobronchial region is not cleared within a few days.

Cough

Coughing is also an important mechanism for the clearance of particles deposited in the tracheobronchial region, at least for the trachea and bronchi. There must be an increased amount of secretion in the airways for coughing to be effective. Patients with chronic bronchitis have a severely impaired mucociliary transport, and patients with immotile cilia syndrome have more or less absent mucociliary transport. However, both these

groups of patients have been shown to eliminate 6- μm particles inhaled at 0.5 l/s efficiently (22, 23). The fast tracheobronchial clearance phase was not completely finished until after 72 hours, which should be compared with the 24 hours determined for healthy subjects. As previously mentioned, 6- μm particles inhaled at 0.5 l/s mainly deposit in the large airways and in the alveolar region and only minimally in the bronchioles. The total cross areas of the airway generations in the bronchial part (generations 0–8) are rather small, and therefore the air velocity can be high during coughing, and the effect of coughing is important.

Groups of patients with chronic bronchitis and immotile cilia syndrome have also inhaled 6- μm particles with an extremely slow flow, 0.05 l/s (24, 25). Although, the retention measured at 24, 48, and 72 hours was significantly higher for the patient groups than for healthy subjects, the differences were rather moderate. One explanation for this rather efficient clearance also from the bronchiolar region in patients with impaired or absent mucociliary transport may be that coughing is an important elimination mechanism also in this region. On the other hand, the total cross-sectional area in this region is large, and therefore the air velocity during coughing should be low. A better explanation may be that mucociliary transport is of little importance for particles deposited in this region, at least the fraction of particles retained after 24 hours, and that clearance, both in healthy subjects and in patients with lung diseases, occurs by a mechanism other than mucociliary transport and cough. The idea that mucociliary transport is not important in the bronchiolar region is supported by the fact that exposures to cholinergic and adrenergic compounds, which are known to stimulate mucociliary clearance markedly in large airways, have no effect on bronchiolar clearance (26, 27).

Alveolar clearance

Studies of mechanical clearance (clearance of entire particles) from the human alveolar region require extremely insoluble particles firmly labeled with long-lived radionuclides, and it is not surprising that only a few such studies have been made. The retention of inhaled radiolabeled particles of polystyrene (28), fused clay (29), and TeflonTM (30) in the thoracic region has been studied for periods of about 1 year. In these studies, a minor fraction of the particles cleared with biological half-times of tens of days, while a major fraction cleared with a much longer half-time of one or several years. In the study by Bohning et al (28), no information about the leakage of radionuclides from the particles was given, but the leakage reported in the two other studies was not negligible considering the long half-time. In a more

recent study on healthy persons, Philipson et al (31) studied mechanical alveolar clearance of extremely firmly radiolabeled 5.3 μm Teflon particles for almost 3 years. For the first 250 days after the exposure, the half-time averaged 740 days. Between day 250 and day 900, the average half-time was 1750 days (almost 5 years) of the radioactivity over the thorax region. All the particles that cleared from the thoracic region left the body via the feces. This extremely slow clearance of highly insoluble material should have relevance to ambient air particles, which, to a considerable extent, consist of extremely insoluble carbon.

However, the particles are not only mechanically cleared from the alveolar region. Alveolar macrophages phagocytize particles deposited in this region. Several *in vitro* studies with alveolar macrophages, including human alveolar macrophages, have shown that these cells efficiently dissolve metal particles that are generally considered insoluble in water (32–36). One mechanism behind this ability of the macrophages is the acid milieu in the phagolysosomes in the cells (35). The pH in these phagolysosomes has been found to be around 5 in macrophages from several species (37–39).

There is also a slow transport of particles from the alveolar region to the regional lymph nodes. Such a clearance route has been seen in animal experiments, especially for highly toxic particles (eg, quartz and plutonium oxide particles) (40, 41). Also in animal experiments with very high lung burdens of rather innocuous particles such as titanium dioxide, the transport to the lymph nodes has been found to increase (42). In more recent experiments, in which rats have been exposed via inhalation to aggregates of ultrafine and fine titanium dioxide particles, the ultrafine particles have been found to be translocated to a much higher extent to the lymph nodes than the fine titanium dioxide particles are at similar lung burdens (43, 44). A possible explanation for the more efficient transport to the lymph nodes in all these cases may be that the particles are located to a relatively large extent outside the alveolar macrophages.

Summary and concluding remarks

Deposition of particles in the airways is dependent on their size, density, and shape. Particles of soluble material can take up water in the airways and grow considerably, hygroscopic growth. Deposition is also dependent on the respiration pattern, including mouth or nose breathing. In the alveolar region there is a maximum deposition, about 50%, for 20–30 nm particles (ie, ultrafine particles).

Particles deposited in large ciliated airways (bronchi) seem to clear within 24 hours. However, for small ciliated airways (bronchioli), there is a strong

indication of large retained fractions after 24 hours, and these fractions seem to clear with a half-time with a magnitude of tens of days.

Clearance by coughing is also an important mechanism in larger airways in the lung, but its importance in small ciliated airways is uncertain. An increased amount of secretion in the airways is necessary for coughing to be efficient.

Mechanical clearance (ie, clearance of whole particles) from the alveolar region in humans is extremely slow with a half-time of 5 years for the majority of particles. Mechanical clearance should be relevant for the carbon skeleton of ambient particles. However, particles of materials that are usually considered to be insoluble in water, for example, many metal oxides, can be cleared at a much faster rate because they are dissolved in the acid milieu (pH 5) in the phagolysosomes of the alveolar macrophages.

Particles deposited in the alveolar region can be transported to the regional lymph nodes. This is especially the case for highly toxic particles, for example, quartz particles, for ultrafine particles, and also for rather large inert particles when the inhaled amount is extremely high. A common explanation for all these three cases may be a considerable number of particles outside alveolar macrophages.

Acknowledgments

We are grateful to Mr Rolf Falk for calculating the deposition data for the new ICRP model and to Ms Ulla Bergsten for her editorial contributions.

References

- Camner P, Bakke B. Nose or mouth breathing? *Environ Res* 1980;21:394—8.
- Fed Reg 1984; 49(55).
- Ingelstedt S. Studies on the conditioning of air in the respiratory tract. *Acta Otolaryngol* 1956;suppl 131.
- International Commission on Radiological Protection (ICRP). Human respiratory tract model for radiological protection. Oxford: Elsevier Science Ltd, 1994:1—3. ICRP publication 66 Ann ICRP 24.
- Camner P, Johansson A, Boström CE, Nyqvist G. Health effects of particles in the ambient air. Stockholm: Swedish Environmental Protection Agency, 1994. Report 4261.
- Patrick G, Stirling C. Measurement of mucociliary clearance from the trachea of conscious and anaesthetised rats. *J Appl Physiol* 1977;43:451—5.
- Svartengren M, Widtskiöld-Olsson K, Philipson K, Camner P. Retention of particles on the first bifurcation and the trachea of rabbits. *Clin Respir Physiol* 1981;17:87—91.
- Bailey MR, Fry FA, James AC. The long-term clearance kinetics of insoluble particles from the human lung. *Ann Occup Hyg* 1992;26:273—90.
- Stahlhofen W, Gebhart J, Rudolf G, Scheuch G, Philipson K. Clearance from the human airways of particles of different sizes deposited from inhaled aerosol boli. In: Israel G, editor. *Aerosols: formation and reactivity*. Oxford: Pergamon Press, 1986:192—196.
- Stahlhofen W, Scheuch G, Bailey MR. Measurement of the tracheobronchial clearance of particles after aerosol bolus inhalation. *Ann Occup Hyg* 1994;38:suppl 1:189—96.
- Scheuch G, Kreyling W, Haas F, Stahlhofen W. The clearance of polystyrene particles from human intrathoracic airways. *J Aerosol Med* 1993;6(suppl):47.
- Scheuch G, Philipson K, Falk R, Anderson M, Svartengren M, Stahlhofen W, et al. Retention of particles inhaled in boli with and without induced bronchoconstriction. *Exp Lung Res* 1995;21:901—16.
- Svartengren M, Philipson K, Camner P. Individual differences in regional deposition of 6 µm particles in humans with induced bronchoconstriction. *Exp Lung Res* 1989;15:139—49.
- Svartengren M, Anderson M, Bylin G, Philipson K, Camner P. Regional deposition of 3.6 µm particles and lung function in asthmatics. *J Aerosol Med* 1990;3:197—207.
- Svartengren M, Anderson M, Bylin G, Philipson K, Camner P. Regional deposition of 3.6 µm particles and lung function in asthmatic subjects. *J Appl Physiol* 1991;71(6):2238—43.
- Bailey M, Birchall A, Cuddihy RG, James AC, Roy M. Respiratory tract clearance model for dosimetry and bioassay of inhaled radionuclides. *Radiat Prot Dosim* 1991;38:153—8.
- Stahlhofen W, Koebrich R, Rudolf G, Scheuch G. Short-term and long-term clearance of particles from the upper human respiratory tract as function of particle size. *J Aerosol Sci* 1990;21:suppl 1:S407—S410.
- Anderson M, Philipson K, Svartengren M, Camner P. Human deposition and clearance of 6 µm particles inhaled with an extremely slow flow rate. *Exp Lung Res* 1995;21:187—95.
- Camner P, Anderson M, Philipson K, Bailey A, Hashish A, Jarvis N, et al. Human bronchiolar deposition and retention of 6, 8 and 10 µm particles. *Exp Lung Res* 1997;23:517—35.
- Falk R, Philipson K, Svartengren M, Jarvis N, Bailey M, Camner P. Clearance of particles from small ciliated airways. *Exp Lung Res* 1997;23:495—515.
- Roth C, Scheuch G, Stahlhofen W. Clearance measurements with radioactively labelled ultrafine particles. *Ann Occup Hyg* 1994;(suppl 1):101—6.
- Ruusa J, Svartengren M, Philipson K, Camner P. Tracheobronchial particle deposition and clearance in immotile cilia syndrome patients. *J Aerosol Med* 1993;6:89—98.
- Ericsson CH, Svartengren K, Svartengren M, Mossberg B, Philipson K, Blomquist M, et al. Repeatability of airway deposition and tracheobronchial clearance rate over three days in chronic bronchitis. *Eur Respir J* 1995;8:1886—93.
- Svartengren K, Philipson K, Svartengren M, Camner P. Clearance in smaller airways of inhaled 6-µm particles in subjects with Immotile-cilia syndrome. *Exp Lung Res* 1995;21:667—82.
- Svartengren K, Ericsson CH, Svartengren M, Mossberg B, Philipson K, Camner P. Deposition and clearance in large and small airways in chronic bronchitis. *Exp Lung Res* 1996;22:555—76.

26. Svartengren K, Philipson K, Svartengren M, Camner P. Effect of adrenergic stimulation on clearance from small ciliated airways in healthy subjects. *Exp Lung Res* 1998;24:149—58.
27. Svartengren M, Svartengren K, Aghaie F, Philipson K, Camner P. Lung deposition and extremely slow inhalations of particles: limited effect of induced airway obstruction. *Exp Lung Res* 1999;25:353—66.
28. Bohning DE, Atkins HL, Cohn SH. Long-term particle clearance in man: normal and impaired. *Ann Occup Hyg* 1982;26:259—71.
29. Bailey M, Fry FA, James AC. Long-term retention of particles in the human respiratory tract. *J Aerosol Sci* 1985;16:295—305.
30. Philipson K, Falk R, Camner P. Long-term lung clearance in humans studied with Teflon particles labelled with ⁵¹Cr. *Exp Lung Res* 1985;9:31—42.
31. Philipson K, Falk R, Gustafsson J, Camner P. Long-term lung clearance of ¹⁹⁵Au labelled Teflon particles in humans. *Exp Lung Res* 1996;22:65—83.
32. Lundborg M, Lind B, Camner P. Ability of rabbit alveolar macrophages to dissolve metals. *Exp Lung Res* 1984;7:11—22.
33. Lundborg M, Johard U, Johansson A, Eklund A, Falk R, Kreyling W, et al. Phagolysosomal morphology and dissolution of cobalt oxide particles by human and rabbit alveolar macrophages. *Exp Lung Res* 1995;21:51—66.
34. André S, Métivier H, Lenfenois G, Boyer M, Nolibé D, Masse R. Beryllium metal solubility in the lung: comparison of metal and hot-pressed forms by *in vitro* and *in vivo* dissolution bioassays. *Hum Toxicol* 1987;6:233—40.
35. Marafante E, Lundborg M, Vahter M, Camner P. Dissolution of two arsenic compounds by alveolar macrophages. *Fundam Appl Toxicol* 1987;8:382—9.
36. Kreyling WG, Godleski JJ, Kariya ST, Rose RM, Brain JD. *In vitro* dissolution of uniform cobalt oxide particles by human and canine alveolar macrophages. *Am J Respir Cell Molec Biol* 1990;2:413—22.
37. Nyberg K, Johansson A, Camner P. Intraphagosomal pH in alveolar macrophages studied with fluorescein-labelled amorphous silica particles. *Exp Lung Res* 1989;15:49—62.
38. Nyberg K, Johansson A, Camner P, Johard U, Eklund A. Phagolysosomal pH in alveolar macrophages from smokers and non-smokers. *Hum Exp Toxicol* 1994;13:175—9.
39. Kreyling K, Nyberg K, Nolibé D, Collier CG, Camner P, Heilmann P, et al. Interspecies comparison of phagolysosomal pH in alveolar macrophages. *Inhalation Toxicol* 1991;3:91—100.
40. Bair WI. Deposition retention, translocation and excretion of radioactive particles. In: Davies CN, editor. *Inhaled particles and vapours*. London (England): Pergamon press, 1961:122—208.
41. Klosterkötter W, Gono F. Long-term storage, migration and elimination of dust in the lungs of animals, with special respect to the influence of polyvinyl-pyridine-n-oxide. In: Walter WH, editor. *Inhaled Particles*. Surrey (England): Unwin Bros Ltd, 1972:273—80.
42. Ferin J. Effect of particle content of lung on clearance pathways. In: *Pulmonary macrophage and epithelial cells*. Springfield (VA): Technical Information Center Energy Research and Development Administration, 1977:414—23. ERDA symposium series 43.
43. Ferin J, Oberdörster G, Penney DP. Pulmonary retention of ultrafine and fine particles in rats. *Am J Respir Cell Mol Biol* 1992;6:535—42.
44. Oberdörster G, Ferin J, Lehnert BE. Correlation between particle size, *in vivo* particle persistence, and lung injury. *Environ Health Perspect* 1994;102(suppl 5):173—9.