Particle deposition and clearance from the respiratory tract

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Abstract: Epidemiological studies have repeatedly associated high levels of ambient particulate matter with increased hospital admission and daily mortality. The adverse health effects have especially been linked to fine and ultra fines (<0.1µm) from combustion sources. Despite the fact that hazardous exposure to ultra fine particulates has clearly been reported, it is still under investigation which exact particle characteristics underlie the health effects. The rapid growing field of nanotechnology might be another source of exposure to potential harmful nano sized particulates. Better understanding of the particle characteristics that are related to adverse effects will help in addressing regulation strategies. In this thesis I will explain how regional particle deposition in the respiratory tract and clearance mechanisms are influenced by physical and chemical particle properties such as particle size, density and shape. Moreover I show how particle deposition site and particle clearance mechanisms are related to pulmonary and extra-pulmonary health effects.

Author: Gillina F.G. Bezemer, B.Sc.
Institute for Risk assessment Sciences,
University of Utrecht, the Netherlands,
Email: G.F.G.Bezemer@uu.nl
Telephone: +31-624728801

Supervisor: Dr. R.H.H. Pieters
Institute for Risk assessment Sciences,
University of Utrecht, the Netherlands
Email: R.H.H.Pieters@uu.nl
Telephone: +31-30-2533565

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1 Introduction

1.1 Ambient particulate matter

Epidemiological studies have repeatedly linked high levels of ambient particulate matter to increased hospital admission and daily mortality (Dockery et al. ,1993;Dockery et al., 1989;Pope et al., 1995;Brunekreef and Holgate, 2002;Seaton et al., 1995;Utell and Frampton, 2000). Frequently has been concluded that fine (< 2.5 µm) and especially ultra fines (<0.1 µm). from combustion sources, have a stronger association with adverse health effects than coarse particles (Oberdorster et al., 2002;Oberdorster, Oberdorster, and Oberdorster, 2005;Peters et al., 1997;Samet et al., 2000;Utell and Frampton, 2000;Nel, 2005). Fine and ultrafine particulate exposure has consistently been related to respiratory effects like asthma and COPD. (Dockery and Pope, 1994;Peters et al., 1997;Schwartz and Neas, 2000). Cardio vascular mortality and morbidity have also been repeatedly associated with episodes of (ultra)fine particulate air pollution (Seaton et al., 1995;Donaldson et al., 2001;Nemmar et al., 2001;Pope et al., 1999;Schwartz and Morris, 1995;Utell and Frampton, 2000). More recently has been suggested that even the central nervous system (CNS) may be a target for ultrafine particulates (Oberdorster and Utell, 2002). Some investigators have already reported that air pollution may play an important role in neurodegenerative diseases like Alzheimer and Parkinson (Oberdorster and Utell, 2002;Calderon-Garciduenas et al., 2002).

Ambient particulate matter (APM) is a poly-disperse dynamic mixture of aerosols. An aerosol is defined as a collection of solid or liquid particles suspended in a gas (Hinds, 1999). It is thus a two-phase system consisting of the particles and the gas in which they are suspended. The gases that form air are from highest to lowest concentration: Nitrogen (N_2), Oxygen (O_2), Argon, Carbon dioxide (CO_2), Neon, Helium, Methane (CH_4), Krypton, Hydrogen (H_2O) and Xeon. Particles in the environment originate from natural and anthropogenic sources (Figure 1-1). The natural particles, which have always been present, originate from volcanoes, dust storms, vegetation, forest fires and sea spray. Humans have always been exposed to these natural ultrafine particles; however the exposure to particles has increased enormously due to anthropogenic sources. The particles that are found in the lowest kilometer of the atmosphere over cities originate predominant from anthropogenic sources. Exposure levels to these types of particles have increased enormously since the industrial revolution. During this period and in the beginning of the 20th century many fog episodes took place that were linked to dramatic increases in mortality (Anderson et al, 1996.). The 1952 London smog disaster is one of the greatest episodes that has encountered for approximately 13000 excess deaths with maximum of 900 per day during the peak exposures in the cold December days (Laskin, 2006). Pollution originated from factories and from the burning of coal for heating purposes with smoke concentrations up to 4.5 mg per m^3. The act of 1954 and the Clean Air Acts of 1956 and 1968 establishing mass based emission standards starting with banning of the emission of black smoke by reducing coal burning. Nowadays the aerosol mass concentration in urban areas still varies under different conditions. Maximum concentrations however are much lower. They range between approximately 10 ug up to 1 mg per m^3 (Hinds, 1999). Factors that influence concentration levels are emission-rates but also weather and geographical conditions. Time spend close to emission sources also influences particle exposure

concentrations. In occupational settings high levels of aerosol exposure can occur for example to paint spray, welding fumes, coal dust and oil smoke.

1.2 Particle size distributions

Particle size distributions are commonly presented by nuclei- (≤0.1µm), accumulation- (0.1-2.5µm), and coarse particle-mode (2.5-100µm). The nuclei mode consists of primary and secondary particles that are usually found close to their emission sources like highways. Examples of these primary pollutants are carbonaceous dusts and sulphur dioxide (SO_2) (Hinds, 1999). The nuclei particles either rain/washout or end up relatively quickly into the accumulation mode due to gas to particle conversion and by coagulation with other aerosols. Due to the diversity of primary particles and the different chemical processes the secondary particles have an enormous mixture in characteristics and reactivity. Ozone (O_3) and H_2SO_4 are examples of secondary formed pollutants. In the accumulation mode particles remain suspended for about one to two weeks. Particle coagulation still occurs in the accumulation mode; however particles do not become big enough to end up in the coarse mode. The main removal mechanisms in the accumulation mode are rain-, and washout. The particles in the coarse mode have different origin than the nuclei-, and accumulation-particles. Examples of coarse particles are coal-, cement-, and agriculture-dust and sea salt particles. These relatively large particles usually settle out within a few hours. In literature particle size ranges are often classified as course (>2.5 microns in diameter), fine (< 2.5 µm) and ultra fines (0.001-0.1 µm). Figure 1-1 summarizes aerosol origins and size distributions.

1.3 Nanotechnology

The rapid growing field of nanotechnology might also be a source of exposure to nano sized particulates (Oberdorster, Oberdorster, and Oberdorster, 2005). One nanometer is equivalent with 10^{-3} µm and 10^{-9} meter. Engineered materials with sizes up to 100nm are usually not referred to as ultra-fines but as nano particles (NPs). In contrast to the polydisperse nature of APM, NPs often have a monodisperse size distribution. The worldwide market of products produced using nanotechnology is estimated to reach one trillion US dollars in 2015. It is considered to be the biggest engineering innovation since the industrial revolution (Gwinn and Vallyathan, 2006). Examples of NPs can be found in biomedical applications (quantum dots, dendrimers, fullerenes, colloid gold) and in electronic applications (semiconductors, nano spheres, tubes, wires). They are also used in consumer products such as cosmetics and in all kind of coatings. Human exposure may occur during a products manufacturing or use. Despite the fact that nanotechnology is rapidly growing it is still unknown to which extends these laboratory generated NPs form a hazard.

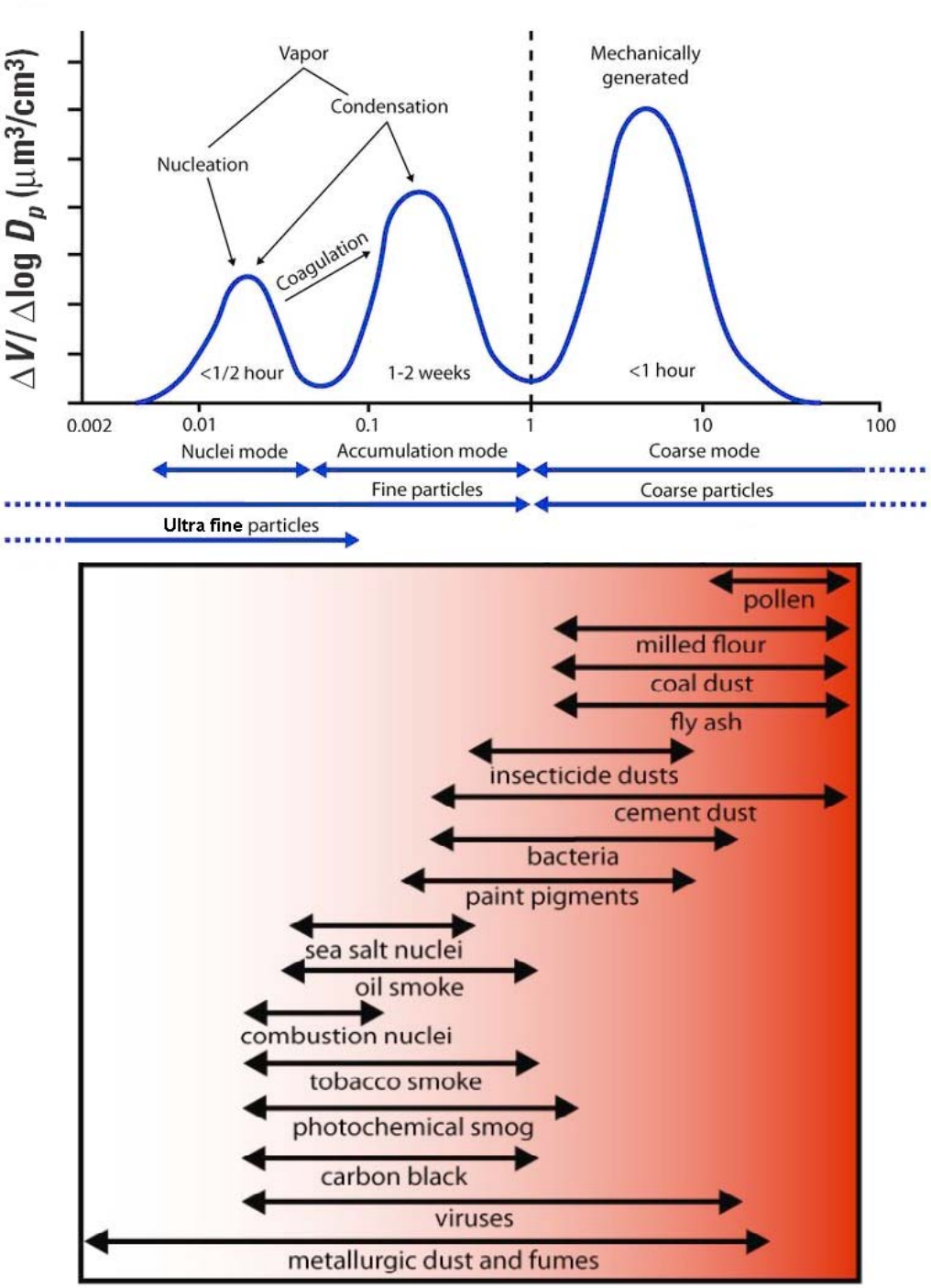

Figure 1-1 Adapted from: "Aerodynamic behavior of aerosols" and "particle size and deposition within the respiratory tract" Available at: http://ocw.jhsph.edu. Copyright © Johns Hopkins Bloomberg School of Public Health. Creative Commons BY-NC-SA.

2 Modeling respiratory deposition

The fraction of particles that enters the nose or mouth is called the inhalable fraction (IF). Factors influencing inhalability are the size and density of the particle and the wind velocity and direction. Wind tunnels with mannequins that are connected to a breathing machine are used to experimentally determine the IF. Upon inhalation, particles can either deposit somewhere along the respiratory tract or they can be exhaled. The fraction of inhaled particulates that deposit in the respiratory tract is called “respiratory tract deposited fraction” (DF). Human in vivo experiments are used to calculate the DF under different conditions; however regional deposition doses cannot be obtained using this technique. Moreover there are restrictions in the particles that can be used for human exposure. The site of deposition within the respiratory tract influences the effects of particles within the organism. Regional dosimetry is important for assessing the potential hazard of inhaled particles. Mathematical models have been developed to predict regional particle deposition. These models are based on (1) lung morphometry, (2) physical and chemical particle properties, (3) gas and vapor properties of the air and (3) breathing patterns (Rostami, 2009). These elements will be discussed in the following chapters.

2.1 Whole lung deposition models

The Human Respiratory Tract Model (HRTM) and the multiple path particle dosimetry model (MPPD) are two examples of widely used whole lung deposition models, which are based on a combination of computational and experimental data. The HRTM model was designed by the International Commission on Radiological Protection in 1966 and was further improved into the 1994 ICRP model (ICRP publication 66). It was first designed to facilitate the prediction of inhaled radioactive particle deposition, retention and clearance. It is now used for the prediction of deposition and clearance of mono- and poly-disperse particles ranging between 0.005 and 100 μm. Five regions represent the ICRP lung morphometry and it allows correcting for different breathing patterns. The MPPD model was developed as a user-friendly software package by the Chemical Industry Institute of Toxicology (CIIT) and the RIVM to extrapolate deposition doses, retention and clearance values between humans and laboratory animals. The multiple path lung geometry is a model that incorporated available data on asymmetries in the airways. It calculates the deposition and clearance of mono- and poly-disperse aerosols from ultra fine to coarse mode in the respiratory tract of humans and rats. Like the ICRP model it allows to study the impact of breathing patterns on regional deposition (RIVM report 650010018, 1999).

2.2 Local deposition models

Unlike the whole-lung deposition models, the local deposition models or computational fluid dynamics (CFD) -based models rely exclusively on theoretical and computational equations not on experimental data. Local deposition models are most suitable to study the oro-nasal and upper airways. These models use detailed airway geometry and are therefore complex to develop and to validate. The semi-empirical whole lung models are still considered more reliable than the purely theoretical local models (Rostami, 2009). More information on computational tools and approaches can be found in Rostami’s recent review of the history and the current status of computational modeling of aerosol deposition (Rostami, 2009).

3 Human respiratory tract

3.1 Three compartment model

The human airway anatomy can be divided into three-compartments (Hinds 1999). Figure 3-1 shows the three regions of the respiratory tract. **(1)** The head airways include the nasal passages, mouth, pharynx and larynx. This site is also referred to as the nasopharyngeal region. The main function of the nasal passages is olfaction and heating, humidifying and filtering of the inhaled air. **(2)** The conducting airways include the trachea which bifurcates at the carina, behind the sternum into the two main bronchi of which each leads to a lung. In the lung the bronchus divides further into a sequence of smaller and smaller airway bronchi and bronchiole which have a diameter of about 0.5 mm. The first approximately 16 bifurcations belong to the conducting airways. The tracheobronchial region is another name for the conducting airways. The main function of this region is to further humidify and filter air and conduct it from the head to the gas exchange region. **(3)** The alveolar gas-exchange region includes the terminal- and respiratory-bronchioles and the alveolar ducts and sacs. The bronchioles bifurcate about 7 times further until they reach the alveolar ducts, which have a diameter of approximately 0.2 mm. The ducts lead the air into the alveoli sacs where gas exchange takes place. The total gas exchange surface area is about 72m2 (Weibel and Gomez, 1962). We pump approximately 30 m^3 of air through our respiratory system per day. The alveoli are surrounded by millions of pulmonary capillaries. Venous blood, which is pumped through these capillaries, takes up oxygen and expels CO^2 in the gas exchange region due to diffusion gradients between the blood and the inspired air.

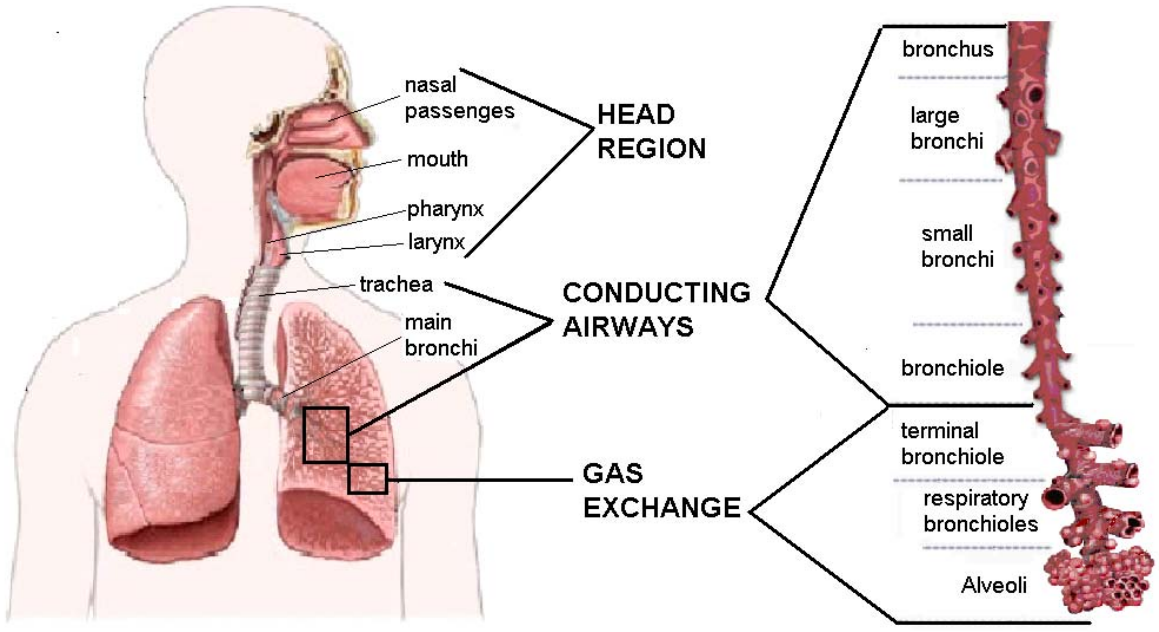

Figure 3-1 The respiratory tract. Adapted from Dr. D. Eidelman, lecture 12. Pulmonary ventilation. http://www.mcgill.ca/mmimediasampler2002/images/eidelman-12no3.gif

3.2 Weibels geometrical lung model

The first publication of the morphometry of the human lung is described in Science in 1962 by Weibel and Gomez (Rostami, 2009;Weibel and Gomez, 1962). For this study Weibels task was: “To do anything on the structure of the lung that is of interest to physiology.” (Weibel, 2001). While working in close collaboration with physiologists, pulmonary physicians and with the mathematical physiologist Gomez, Weibel developed a completely new geometrical approach to study the lung structures. Highly critiqued by classical anatomists, this work was very well recognized by physiologists who needed quantitative data on lung anatomy for the calculation of for example the total gas exchange area. By examining human lung material, Weibel et al described that the 23 dichotomous generations of airways divide following a systematic rule. The bronchial diameter decreases with each generation according to Murray’s law of optimal design. Every generation branches into two identical daughter generations with equal diameter and lengths thereby increasing the number of airways by a factor 2 at every bifurcation. According to this law there are at the twenty-third generation 2^{23}= 8,288,608 identical alveolar sacs (Rostami, 2009;Weibel and Gomez, 1962). Table 3-1 summarizes the characteristics of selected regions of a typical adult lung based on Weibel’s model.

Table 3-1 Characteristics of selected regions of the lung (Hinds, 1999)

	generation	Diameter (mm)	Length (mm)	Total cross Section (cm2)	Velocity (mm/s)	Residence time[a] (ms)
Trachea	0	18	120	2.5	3900	30
Main bronchus	1	12	48	2.3	4300	11
Terminal bronchiole	16	0.6	1.6	180	54	31
Alveolar sac	23	0.41	0.5	72000	0.9	550

[a] At a steady flow rate of 3.6 m3/hr [1.0 L/s]

Weibel based models are nowadays still widely used for computational purposes.
Several investigators have been working on improving the 23 generation model by including asymmetry, branching angles, gravitation angles and a stochastic distribution of the parameters (Rostami, 2009). Such improvements have already been incorporated in the whole lung prediction models such as the IRCP and the MDDP model.
Most recent work in modeling airway geometry experiments has been done using sophisticated imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT). These techniques visualize solid, liquid or hyperpolarized gas filled regions in a human body or cadaver. These techniques are mostly used for local deposition models.

4 Five particle deposition mechanisms

Computational models use calculations that are based on the mechanisms by which particles can deposit. It is therefore needed to first introduce the five mechanisms by which aerosol particles can deposit (Figure 4-1). I will explain these mechanisms based on Hinds' book Aerosol technology and the reviews of Stuart and Rostami (Rostami, 2009;Stuart, 1976).

4.1 Inertial impaction

Inertial impaction occurs when airflow changes direction and the particle, which happens to be close to the airway wall, follows it's original direction instead of adjusting to the airflow. The probability of deposition by impaction depends on the ratio of particle stopping distance to airway dimensions at an airstream's velocity. The stopping distance is equal to the velocity before the change in current, times the relaxation time, which is the time required for a particle to adjust its velocity to a new condition. The higher the particle mass and its mobility, the more difficult it is for the particle to adjust for a curving air stream. Large particles have a higher relaxation time compared to small particles (Table 4-1). The Stokes number (Stk) is used to predict impaction driven impaction. It combines all parameters that are important for inertia (Equation 4-1). When the size of a particle approaches the mean free path of air its properties change because of "slip" at its surface. This error becomes significant for particles less than 1 µm. The slip correction factor (Cc) is inserted in the deposition equations to correct for this error (Table 4-1, Equation 4-1, 4-2, 4-3).

$$Stk = \frac{U\rho_p {d_p}^2 C_c}{9\eta D_j}$$

$U = flowvelocity$
$\rho_p = particledensity$
$d_p = particlediameter$
$C_c = slipcorrection\,factor$
$\eta = airvis\cos ity$
$D_j = airwaydiameter$

Equation 4-1

The Stk number shows that the probability of a particle to deposit due to impaction is directly proportional to particle density, diameter^2 and flow velocity whereas it is inversely proportional to the distance to the surface (the airway diameter). Thus: deposition by inertial impaction is most important for larger particles at high velocity close to the surface. Particles come close to the surfaces at high bend angles, which can be found in the head airways and the conducting airways (nasal passages, the larynx, the carnia and further bifurcations).

4.2 Gravitational settling

Settling or sedimentation is driven by the influence of gravity, which makes particles to depart their original air stream. The probability of a particle to deposit due to gravitational settling depends on the ratio of particle settling distance to airway dimensions at an airstream's velocity. The particle settling distance is equal to its terminal settling velocity (Vts) times the residence time in each airway compartment. Vts is given by the gravitational acceleration times the relaxation time (Equation 4-2).

$$V_{ts} = \frac{g\rho_p {d_p}^2 C_c}{18\eta}$$

$g = acceleration\ of\ gravity$
$\rho_p = particle\ density$
$d_p = particle\ diameter$
$C_c = slip\ correction\ factor$
$\eta = air\ viscosity$

Equation 4-2

Equation 4-2 shows that the probability of a particle to deposit due to gravitational settling is directly proportional to its particle size^2 and density. In contrast to inertia it is inversely proportional to the air stream velocity because the residence time decreases at increasing velocity. This mechanism is therefore most important in the smaller airways and in the gas exchange region where the air velocities are low. Sedimentation has its maximum removal effect when airway surfaces approaches horizontal configurations, which is the case in the alveolar region.

4.3 Diffusion

Diffusion is a disperse mass transfer that is caused by random molecular motions also called “Brownian motion”. Small particles displace when they collide with air molecules. This mechanism can be explained by the diffusion coefficient (D) of an aerosol particle which is given in the Stokes-Einstein equation (Equation 4-3).

$$D = \frac{k_B T C_c}{3\pi\eta d_p}$$

$k_B = Boltzmann's\ constant$
$T = Temperature$
$C_c = slip\ correction\ factor$
$\eta = air\ viscosity$
$d_p = particle\ diameter$

Equation 4-3

Equation 4-3 and Table 4-1 shows that, in contrast to settling and impaction, diffusion is inversely proportional to the particle diameter. The probability of a particle to deposit due to diffusion depends on the ratio of the root-mean-square of the displacement during residence ($\sqrt{2Dt}$) to airway dimensions. Similar to gravitational settling, deposition due to diffusion is also increased where airway diameters are small and where residence time is long.

Table 4-1 Properties of standard density spheres with different diameters (Rostami)

Particle Diameter (µm)	Slip correction factor C_c	Relaxation time T (s)	Diffusion coefficient D (m^2/s)
0.00037[a]	-	2.6 x 10-10	1.8 x 10-5
0.01	23.04	7.1 x 10-9	5.5 x 10-8
0.1	2.866	8.8 x 10-8	6.8 x 10-10
1	1.152	3.5 x 10-6	2.7 x 10-11
10	1.015	2.3 x 10-4	2.4 x 10-12

[a] Average diameter of an “air molecule”

4.4 Interception

Interception is the result of physical contact of a particle with the airway surface because of geometrical features. For pure interception is assumed that the particles follow the airstream and thus have negligible inertia, settling and Brownian motion. The particle does not depart its original air streamline but makes contact due to its physical size. Interception depends on the ratio of particle size to airway diameter which means that interception is most important for elongated particles, like fibers, which are long in one dimension but have small enough diameters to reach the small airways.

4.5 Electrostatic attraction

Electrostatic attraction is important for electrically charged particles. These particles can deposit when large numbers of mutual charged particles drive them towards the airway wall. In absence of mutual repulsion, a charged particle can also be attracted to a neutral surface by image forces. An image force is created by the particle itself and is equal but opposite of its own charge. Image forces are weaker than coulombic forces and are only created when the particle is at close range to the surface. Freshly generated particles have higher surface reactivity than aged aerosols. These freshly generated particles may be more charged which results in higher deposition when compared to aged paricles.

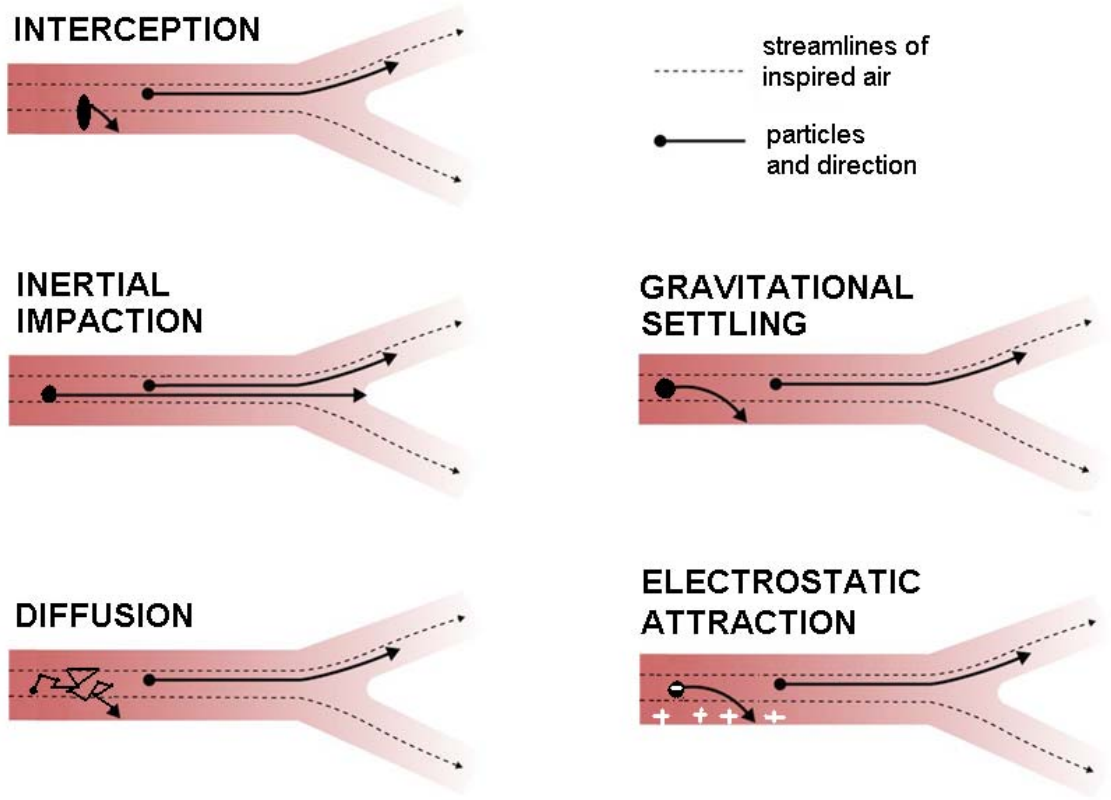

Figure 4-1 Five mechanisms of aerosol particle deposition. Adapted from "Schematic representation of the three mechanisms of aerosol particle deposition" Available at: http://ocw.jhsph.edu. Copyright © Johns Hopkins Bloomberg School of Public Health. Creative Commons BY-NC-SA

5 Particle characteristics

5.1 Particle size

Particle size is the most important physical property that is used to characterize aerodynamic behavior. Particle size is referred to as particle diameter expressed in micrometer (μm) or nanometer (nm). Micron (μ), the older equivalent of micrometer, is no longer accepted as a SI unit. Particle size influences which deposition mechanism is most pronounced under certain conditions (Table 5-1). In the airways, impaction, diffusion and interception are most important (Hinds 1999).

Table 5-1 Relative importance of Impaction, Settling and Diffusion for deposition of 0.1μm, 1μm and 10μm particles of standard density in selected regions of the lung for a steady flow of 3.6 m3/hr [1.0 L/s] (Hinds, 1999)

	Stopping distance[a]/airway diameter (%)			Settling distance[b]/airway diameter (%)			Diffusion length[c]/airway diameter (%)		
	0.1μm	1μm	10μm	0.1μm	1μm	10μm	0.1μm	1μm	10μm
Trachea	0	0.08	6.8	0	0	0.52	0.04	0.01	0
Main bronchus	0	0.13	10.9	0	0	0.41	0.03	0.01	0
Terminal bronchiole	0	0.03	2.8	0	0.18	15.6	1.1	0.22	0.06
Alveolar sac	0	0	0.07	0.12	4.7	410	6.7	1.3	0.4

[a] Stopping distance = particle initial velocity times relaxation time (VpT)
[b] Settling distance = settling velocity times residence time in each airway (Vtst)
[c] Diffusion length = RMS displacement during residence time in each airway (√2Dt)

Ultrafine particles have a higher diffusion coefficient compared to larger particles (Table 4-1). Zhang et al studied the distribution patterns in the upper airways of micro-and nano-sized particles and reported that distribution patterns of particles with a high diffusion coefficient such as NPs are much more uniform compared to particles that deposit due to impaction or sedimentation. The broad deposition area allows more sites to interact with cell membranes (Zhang et al, 2005.).

The probability of a particle to deposit due to diffusion decreases when particle size increases. Impaction and settling become more pronounced for larger particles. At high flow rates, which can be found in the upper airways, the larger particles deposit mostly due to impaction at bend angles and at bifurcations. At low flow rates, which can be found in the gas exchange area, the residence time increases explaining the high deposition due to gravitational settling. Figure 5-1 summarizes the size depended deposition in different regions of the respiratory tract predicted by the ICRP model. It should be noted that deposition in any region depends on deposition in preceding regions. Although the settling distance for 10 μm particles is largest in the alveolar sacs, most of these 10 μm particles do not reach the alveoli because they are already removed by settling and impaction on nasal hairs and at bends in the flow path. Ultrafine particles (<0.1 μm) have an effective deposition in all three regions. The particles <0.001 μm have highest deposition in the head region whereas 0.01μm particles deposit mostly in the alveolar region.

Stuart noted in his review that particle size can be affected by hydroscopicity, which is the chemical property of a particle to ab- or adsorb water molecules from the highly humidified respiratory tract thereby increasing its diameter (Stuart, 1976). Therefore this chemical property also effects total and regional deposition since all mechanisms are size dependent.

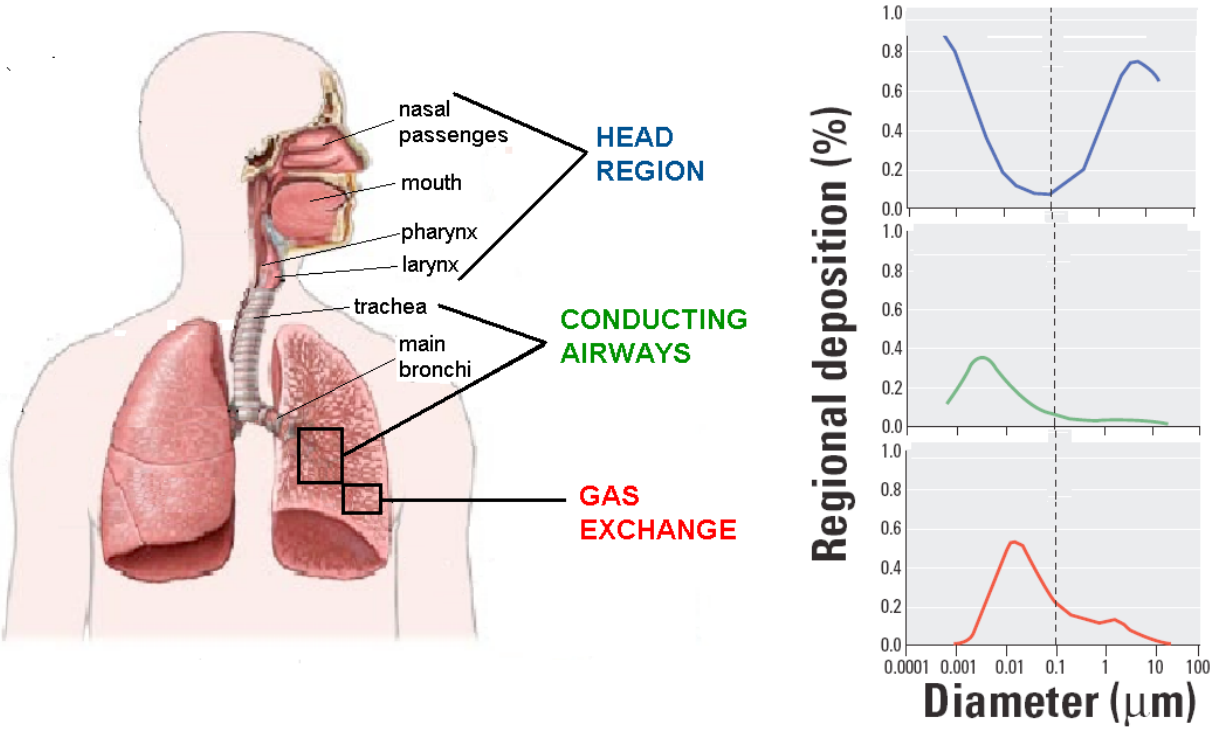

Figure 5-1 Prediction of size dependent particle deposition based on the IRCP model. Adapted from Oberdorster et al., 2005 and Rostami, 2009.

5.2 Particle density

Particle density is usually expressed in kg/m3 and refers to the mass per unit volume of a particle. Chemical composition determines the density of solid particles. Some particles that consist of agglomerates of smaller particles have void space within their structures resulting in a lower density than that of a solid particle of the same material. Equation 4-1 and 4-2 show that particle density is proportional to the probability of a particle to deposit due to impaction and gravitational settling. In aerosol technology, the aerodynamic diameter is often used as an equivalent diameter, which is defined as the diameter of a spherical particle with a density of 1000 kg/m3 that has the same settling velocity as the irregular particle (Figure 5-2).

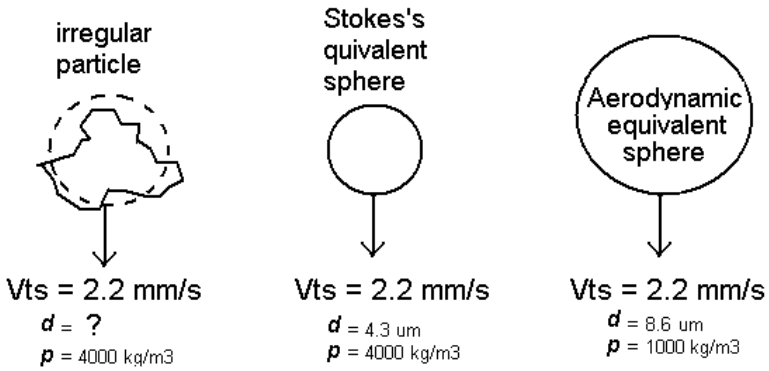

Figure 5-2 An irregular particle and its equivalent spheres. Adapted from Hinds, 1999

5.3 Particle shape

In mathematical models it is usually necessary to assume that particles are spherical. Most particles however are non spherical (Figure 5-3). To overcome this problem, an equivalent spherical diameter or density can be calculated which reflects the particle's physical properties (Hinds, 1999). The Stokes equivalent sphere has the same density as the irregular particle whereas the aerodynamic equivalent sphere gives the diameter of a spherical particle with a density of 1000 kg/m3 (Figure 5-2). Examples of irregular shaped particles that need to be characterized by an equivalent diameter are smoke and fume particles. Particles with extreme shapes such as long thin fibers are even more difficult to treat in equations. Asbestos and carbon nano-tubes are examples of such elongated particles. From 1970 till today several prediction models have been introduced to calculate fibrous deposition by simplifying them as randomly oriented non-spherical shapes. Zhou et al reviewed these theoretical and empirical equations and compared them with experimental data of fiber deposition in realistic human airway replicas using carbon fibers (Zhou, Su, and Cheng, 2007.). There was no consistent agreement found over the Stokes number range of experimental data. For a spherical particle traveling in a tube, the Stokes number is simply a function of particle density, diameter, travel velocity, and the diameter of the tube. However, the Stokes number of a fiber also includes the fiber orientation in the flow. The calculation of the Stokes number for a fiber varies in different theoretical models. Zhou et al showed by experimental evidence that fibers have lower deposition efficiency due to impaction as compared with spherical particles of equivalent Stokes number (Zhou, Su, and Cheng, 2007.). The explanation given in his report for this observation is that fibers tend to align with the airflow, and can therefore penetrate deeper into the airways. Other investigators reported also that fibers follow the air stream and may even reach the small airways and alveoli where they deposit due to interception (Rostami, 2009.;Stuart, 1976).

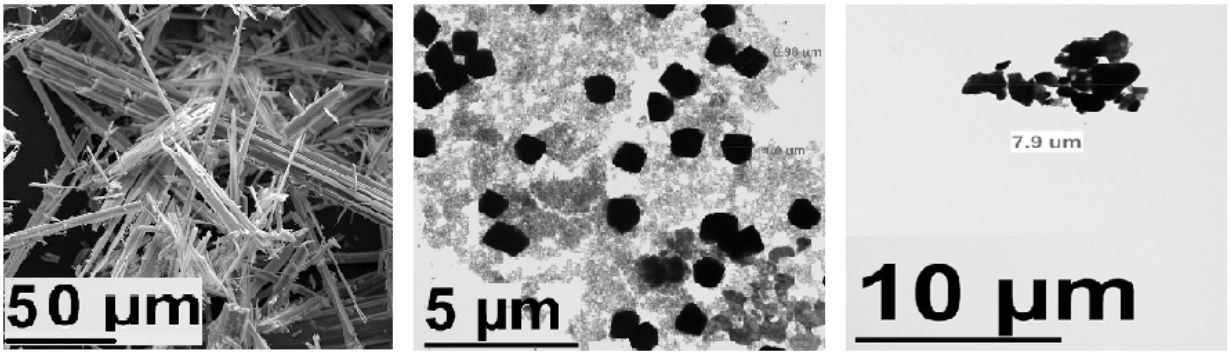

Figure 5-3 Different particle shapes. Left: "Anthophyllite asbestos, Georgia" EM image adapted from USGS Denver Microbeam laboratory; Middle: "Printex 90-Carbon black particles"; Right: "Diesel particles, Baltimore". Middle and right EM images were made in Dr. Oberdorster's laboratory for my research project in Rochester, NY

6 Breathing patterns

Besides the particle characteristics a person's breathing pattern also controls particle deposition. Chapter 4 showed that air velocity is important for the stopping distance of a particle and that particle residence time influences its settling distance and its diffusion length. In a natural situation there is no steady flow rate and the direction of the flow is changing through inhalation and exhalation cycles (Hinds, 1999). A person's breathing pattern can be described by the breathing frequency, the volume of air he or she inhales and the length of pause between inhalation and exhalation (Figure 6-1). These factors determine the flow velocity and particle residence time and thus influence how much and where particles deposit.

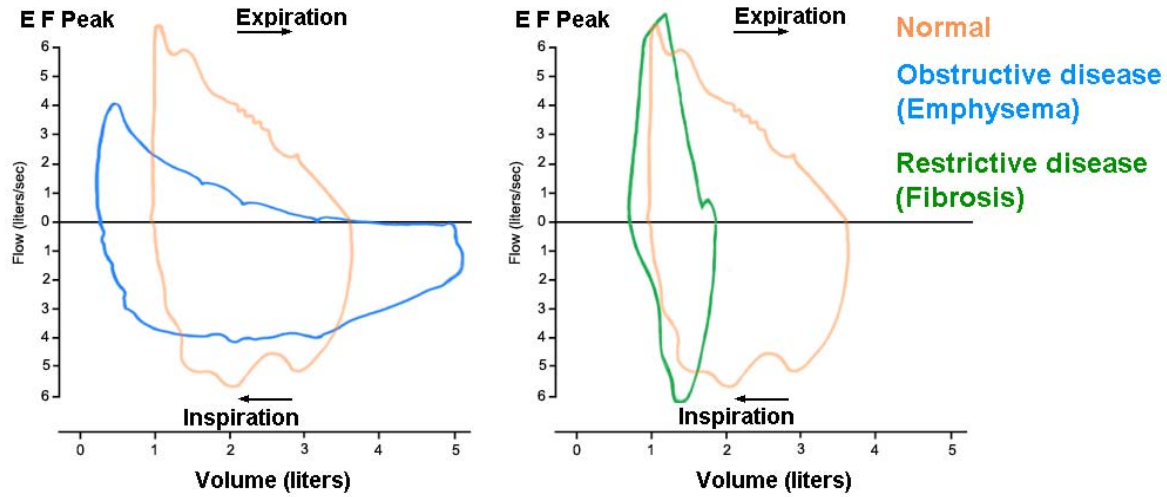

Figure 6-1 Adapted from M. Ludwig: Lecture 8. Lung Dynamics "Flow volumes in the lung in normal and diseased status.
http://www.mmi.mcgill.ca/mmimediasampler2002/images/eidelman-12no3.gif

6.1 Presence of a respiratory disease

Several experimental studies have demonstrated that particle deposition is increased in people with lung diseases compared to healthy subjects (Anderson, Wilson, and Hiller, 1990;Chalupa et al., 2004;Brown, Zeman, and Bennett, 2002). The presence of a respiratory disease significantly affects a persons breathing pattern (Figure 6-1). Anderson et al explained the increase in total respiratory tract deposition of ultrafine particles in subjects with obstructive lung disease by (1) increased residence time of particles, (2) abnormal expiratory collapse of airways due to flow limitation, and (3) disturbed flow as results of airway impairment. (Anderson, Wilson, and Hiller, 1990). In contrast to other investigators, Anderson et al did not report altered deposition in people with restrictive lung diseases. In order to predict regional deposition in patients with COPD, Luo et al used four three-dimensional four-generation lung computer models based on the 23-generation model of Weibel of which three were obstructed in one of the generations. They reported that airway obstruction has a significant influence on the particle deposition downstream of the obstruction (Luo, Liu, and Yang, 2007).

6.2 Physical activity

Breathing patterns are also dependent on a person's physical activity. Flow rate increases at increasing activity. Daigle et al experimentally demonstrated that the total number of deposited particles is more than 4.5-fold higher during exercise than at rest because of the combined increase in deposition fraction and minute ventilation. They used human volunteers and exposed them to ultrafine carbon particles at rest and at exercise. (Chalupa et al., 2004;Daigle et al., 2003) At increasing average flow rate deposition in the head region increases due to increased inertial impaction (Paek and Mccool, 1992).

6.3 Age

Some personal factors such as airway diameter and ventilation rate vary with age (Ginsberg et al., 2008). This can lead to age dependent differences in particle deposition. Children generally inhale more air per body weight and respiratory tract surface area than adults. They have a higher ventilation rate and they breathe more through their mouth than nose (see below). Experimental studies showed that total deposition values, of particles of all sizes, are higher for children than for adults. Deposition decreases as a function of body height and weight. (Schillerscotland, Hlawa, and Gebhart, 1994;Bennett and Zeman, 2004). It should also be noted that (1) children may experience higher exposure levels because they spend more time outdoors and (2) they may be more susceptible to the effects of particulate matter because their lungs and immune system are still developing (Dockery et al., 1994;Foos et al., 2008;Bateson and Schwartz, 2008).

6.4 Mouth versus nose breathing

The ICRP and the MPPD model both allow studying the impact of, breathing pattern, age and the presence of diseases on regional deposition. These whole lung models also correct for nose breathing versus mouth breathing on respiratory deposition. During mouth breathing 20% of 5 μm and 70% of 10 μm particles deposit before air reaches the larynx. In contrast during nose breathing at light exercise; resp. 80% and 95% particles deposit in the head region (Hinds et al., 1999). Due to complex flow patterns during nose breathing, detailed deposition within the nasal area cannot be studied using ICRP and MPPD. The nasal anatomy is complex and there is an enormous variation in shapes and flow patterns under different breathing conditions (laminar versus turbulent). Factors that have been shown to influence deposition are transient breathing, high flow rates, nasal wall motion and nasal valve change during respiratory maneuvers (Xi and Longest, 2008.). Turbulent airflow as a result from high air flow rate inhalations during sniffing has been reported to aid in olfactory detection (Gwinn and Vallyathan, 2006;Zhao et al., 2006). Sniffing might therefore also increase unwanted particle deposition onto the olfactory mucosa. Diseases such as rhinitis and the common cold can influence nasal bio-kinetics (Zhao et al., 2006). Validated local deposition or CFD based models would be useful to study deposition within the nasal cavity.

7 Particle clearance

In the previous chapters I explained the mechanisms that are involved in particle deposition in the respiratory tract. Not all particles that deposit are hazardous. The defence mechanism of the lung is capable to clear most part of the deposited particles from the lung by various pathways. The time between deposition and clearance is called the retention time and is depended on the site of deposition and on particle characteristics (Hinds, 1999). In literature detailed descriptions can be found of the various clearance mechanisms of the lungs. I used Stuarts review, (Stuart, 1984) and chapter two of "respiratiefysiologie" to describe the basic clearance pathways in the various regions of the lung unless noted else wise.

The head airways and conducting airways are covered with a layer of mucus produced by globlet cells, sereus cells and clara cells. Ciliated cells propel the mucus towards the pharynx, where it is swallowed into the gastrointestinal tract. The cilia have been reported to transport the mucus with a rate of 100 to 600 μm/min in the terminal bronchiole up to 5 to 20 mm/min in the trachea. Mucociliary clearance can take place when Insoluble particles that are directly deposited on the mucus layer can be eliminated from the respiratory tract by mucociliary clearance directly or the particles can first be phagocytosed by alveolar macrophages followed by mucociliary clearance. It has been reported that bronchial clearance of insoluble particles varies between 3 to 24 hours. Mucus velocities appear to slow down at increasing age, increasing thereby the retention time of deposited particles. Mucociliary clearance is also slower during sleep, which may explain the increased problems in the mornings that is often experienced by individuals that have asthma or bronchitis.

The gas exchange region and the nasal olfactory region are not covered with ciliated cells and are thus less protected against deposited particles. The alveolar macrophages however are able to eliminate particles from the alveolar region by phagocytosis followed by mobilisation to the airway regions that do contain the mucociliated escalator. This process however is not entirely efficient thus when high exposure occurs, particles do remain in the alveolar region. The large macrophages are also specialised in eliminating other invaders such as bacteria or viruses. The macrophages are found on the alveolar surface and the precursor cells originate from the interstitium or from the bone marrow via blood monocytes. Macrophage clearance depends on site of deposition, the amount of particles that have deposited and on particle characteristics such as size, shape, and surface reactivity. Alveolar macrophages are less efficient to phagocytose ultrafine particles compared to larger particles or fibrous particles such as asbestos compared to spherical particles (Kreyling et al 2002, Karakoti et al 2006, Stanton et al 1977). These ultrafine and fibrous particles retain thus longer in the respiratory tract and can therefore become hazardous, causing lung injury. Clearance by macrophages followed by mucociliary escalator becomes also less efficient when high doses of particles deposit in the respiratory tract. This results in macrophage particle overload (Hinds, 1999). Surface reactivity influences macrophage function due to chemotactic signaling that may facilitate the attraction of the macrophages to the site of deposition (Oberdorster et al 2005). Moreover surface chemistry plays a role in particle agglomeration. When small particles form large aggregates they are more easily phagocytosed by macrophages whereas individual particles can escape macrophage clearance (Karakoti et al, 2006)

Particles that are not removed to the gastrointestinal tract may translocate to other regions including the lung epithelial lining by endocytosis and by caveolae vesicles (Figure 7-1). Epithelial translocation has been shown to be dependent on particle size favoring ultrafine particles (Oberdorster et al, 2005). Surface charge,

which can be expressed by the Zetapotential, influences protein absorption onto the particle surface. These proteins may facilitate epithelial translocation because of interference with the barrier integrity (Karakoti et al, 2006). The particles that have crossed the epithelial cell layer can reach the interstitial space, the lymphatic system and the blood circulation from where they can be distributed to other organs (Figure 7-1). In the gas exchange region the alveolar membrane is very thin which facilitates not only gas exchange but also particle translocation to the capillaries. More recently, particle translocation via sensory nerves that end in the respiratory tract such as the olfactory nerve has been described (Oberdorster et al 2005). Olfactory translocation will be described in detail in the next chapter.

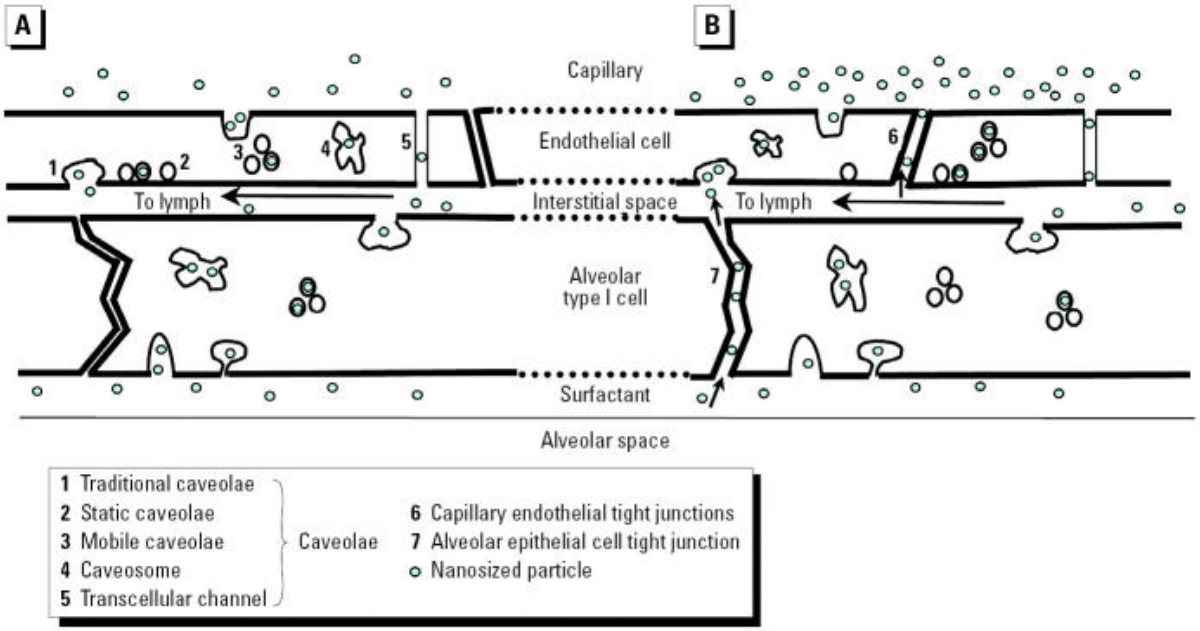

Figure 7-1 different forms of translocation of particles across the lung epithelial barrier. In healthy state (A) particles do not cross cell tight junctions whereas in disease state (B) particles do cross tight junctions. Image source: Oberdorster et al, 2005

Besides the mechanical clearance pathways, particles can also clear via chemical processes. These include loss of elements from the particle (leaching) and dissolution within the mucosal lining fluid (Oberdorster, et al 2005). Particle solubility depends on the particles hydrophilicity and hydrophobicity and on the characteristics of the particles surrounding such as the PH value of intra and extra cellular fluid.

Free radical generation is likely to play a role in particle toxicity. Oxidative stress may be induced directly by the particles surface or by transition metals that are released from the particles surface. Ultrafine particles have a large surface area and may thus generate relatively more free radicals compared to larger particles. Especially irregular particles that are freshly formed during mining and drilling processes form reactive surface species (Fubini et al, 1999). Oxidative stress can also be generated when particles are distributed inside mitochondria. Ultrafine particles have been reported to preferably mobilize to redox active mitochondria (de Lorenzo 1970). Anather way particles can cause oxidative stress is by inducing inflammatory responses that cause oxyradical release by innate immune cells.

8 Health effects

8.1 The lungs

Fine and ultrafine particulate exposure has consistently been related to respiratory effects like asthma and Chronic obstructive pulmonary disease (COPD) (Dockery and Pope, 1994;Peters et al., 1997;Schwartz and Neas, 2000). Aerosol exposure as a result from cigarette smoking is identified as the major cause of COPD (O'Byrne and Postma, 1999). COPD is characterized by increases in alveolar macrophages, CD8+ cells and neutrophilic infiltration (Macnee, 2001). The increase in macrophages indicates that mucociliary clearance mechanisms are not fully efficient resulting in cigarette smoke retention in the lungs. Inflammatory responses cause airway obstruction and damage to the epithelium, which may result in lung emphysema. Asthma pathology involves different immunological processes than the COPD pathology. Often asthma has an allergic background. Cells involved are eosinophils and CD4+ T cells (MacNee, 2001). Antigens such as pollen or house dust mite trigger restriction of the lung and mucus secretion resulting in airflow limitations. Experimental studies showed enhanced sensitization to co-administered antigens in animals following particulate air pollution (Dehaar et al, 2008). However, the decisive characteristics of these particles as well as the mechanisms underlying their so-called adjuvant potential are still not fully understood. Dehaar et al showed that ultrafine particulate exposure cause maturation of dendritic cells. Dendritic cells present antigen to naïve T cells in the lung draining lymphnode, which, in case of asthma, results in an enhanced allergic Th2 response.

Other severe respiratory impairments like pneumoconiosis, asbestosis and silicosis can be a result from specific occupational particle exposures (Mossman and Churg, 1998;Cohen, Patel, and Green, 2008;Wang et al., 1997). Occupational exposure to silica occurs mainly during sandstone or granite mining. But also occupations like foundry work, ceramic industries, construction work and glass manufacturing. Exposure to crystalline silica also named quartz has been associated with various lung diseases first off all silicosis (interstitial lung disease) but also lung cancer and COPD. Free radicals have a potential role in the disease pathology caused by freshly fractured quartz (Vallyathan et al., 1995). Pneumoconiosis can also caused by mixed dust for example in the coal fuel industry where coal workers are exposed to both quartz and coal. Asbestosis is caused by the inhalation of fibrous asbestos. The disease is characterized by the formation of fibrous plaques, pleural effusions and parenchymal interstitial fibrosis. Asbestos exposure has also been linked to lung cancer (Fraser et al 1990 and Parkes 1994).

8.2 Cardio vascular

Cardio vascular mortality and morbidity have also been repeatedly associated with episodes of (ultra)fine particulate air pollution (Seaton et al.;Donaldson et al.;Donaldson et al.;Utell and Frampton;Nemmar et al.;Pope et al.;Schwartz and Morris;Utell and Frampton). Although mechanisms that explain cardio vascular effects are still under investigation it has been suggested that inflammatory responses in the lung but also particle translocation to the bloodstream may induce systemic effects (Utell and Frampton). As described in the previous chapter, particles are known to exit the respiratory tract via the bloodstream (Kreyling WG, Semmler-Behnke M, Moller W). Experimental studies already done in the seventies showed that particles can enter the bloodstream after respiratory exposure within 30 minutes.

The particles were found in platelets of the pulmonary capillaries (Berry et al 1977). Once in the bloodstream particles can be distributed to other organs including the heart. It is still unknown what the direct effects of particles have on the blood or the heart. Figure 7-1 shows varies mechanisms by which nanosized particles reach the capillaries. It also shows that when the lung epithelium is damaged particle translocation is facilitated. This explains why certain lung diseases such as COPD are correlated with cardiovascular diseases. Moreover when the lung is damaged it becomes more difficult for the lung to pump the blood through the pulmonary circulation, which results in right heart hypertrophy. Heart problems themselves may cause pulmonary problems because of pressure build-up in the pulmonary circulation, which results in fluid that gets pushed from the capillaries to the alveoli.

8.3 Central nervous system

More recently has been suggested that the central nervous system (CNS) may be another target for ultrafine particulates (Oberdorster and Utell, 2002). More that 60 years ago neurovirologists Bodian and Howe showed that the virus of poliomyelitis can move along the axons of neurons (Bodian and Howe, 1942). They showed that when the virus is instilled in the nose of monkeys, paralytic poliomyelitis results only when the olfactory connections are intact. This indicates the importance of the olfactory nerve translocation route in the onset of the disease. Other investigators showed that ultra fine particles such as colloid gold and manganese oxide (MnO_2) are also able to translocate via olfactory nerves to the brain (Oberdorster et al., 2005). Olfactory transfer has been demonstrated in rats using model-particles such as colloid gold, Cadmium, manganese oxide and elemental carbon (Dorman et al 2001, Tjalve et al 1996, Oberdorster et al 2004). Elder et al showed that when rats are exposed by whole body inhalation to ultra fine solid Mn particles, while having the right nostril occluded that Mn oxide levels were increased in the left but not in the right olfactory bulb (Elder et al, 2006). Increased particle levels were also found in the striatum, frontal cortex and cerebellum however to a leaser degree. It is suggested that despite the differences between human and rodent olfactory systems, translocation by the olfactory pathway is significant in humans (Oberdorster et al, 2005). Chronic inflammation of the nasal mucosa followed by disruption of the epithelial junction integrity (nose-brain barrier) may facilitate the translocation of particles to the CNS.

As described in the previous paragraph, particles can exit the respiratory tract also via the bloodstream (Oberdorster and utell, 2002). The blood-brain barrier may thus be another route for particles to translocate to the CNS and indeed Lockman et al showed that particle surface charges may alter blood brain barrier integrity and permeability (Lockman et al.,2004). Inflammation of the respiratory tract followed by systemic inflammatory may lead to disruption of the blood-brain barrier and thus facilitate particle translocation to the brain. Circulating cytokines from systemic inflammation can also cross the blood brain barrier and induce additional inflammatory responses and neurodegeneration (Perry, 2004)

Some investigators have already reported that air pollution may play an important role in neurodegenerative diseases like Alzheimer and Parkinson (Oberdorster and Utell, 2002;Calderon-Garciduenas et al. 2002). Only a small percentage of neurodegenerative diseases are thought to have a genetic background, thus environmental factors are likely to contribute to the onset and/or progression of these diseases.

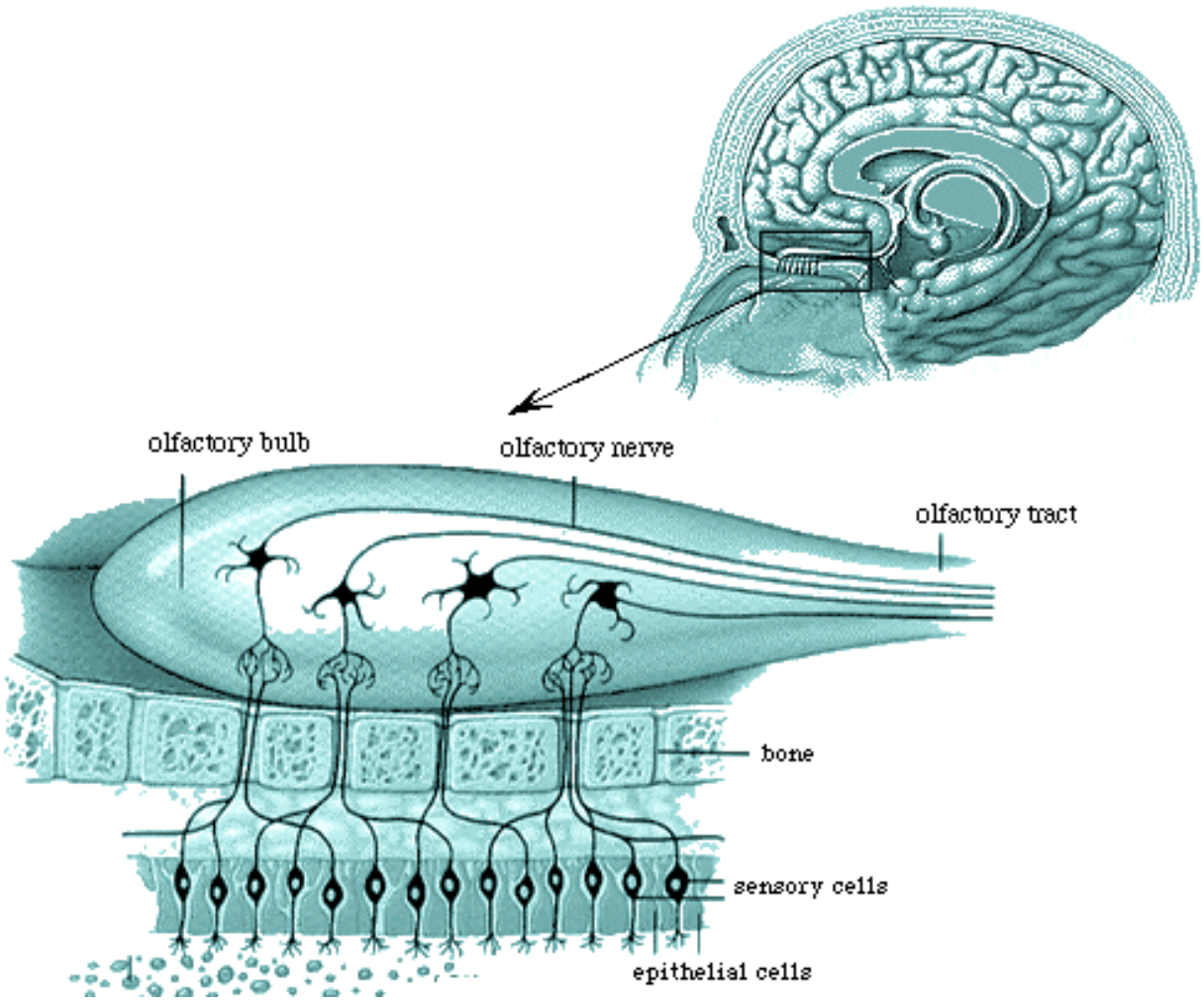

Figure 8-1 Olfactory system, adapted from Collins, advanced science, 1999. The sensory nerves end in the nasal cavity and form a route of exposure of ultrafine particles to the brain.

Braak hypothesised a stage wise progression of the parkinson's disease pathology in the brain starting from the olfactory bulb (Del Tredici et al 2002). Olfactory dysfunction, measured by odor identification, recognition or threshold, has been associated with the risk of future risk of parkinson's disease (Ross et al 2008, Alves et al 2008). Experimental studies done by Calderon-Garciduenas et al showed an association between air pollution and neuro-inflammation in healthy children and dogs. Dogs who lived in a highly polluted region of Mexico City showed damage to the nasal epithelium, pulmonary inflammation, myocardial pathology along with increases of brain inflammation and generation of ROS compared with dogs lived under less polluted conditions. Ultrafine particulate matter has been shown to reach the frontal cortex in these dogs. Healthy children living in the highly-polluted Mexico City have also shown significant damage to the nasal epithelium, pulmonary damage and cytokine imbalance and systemic inflammation. Brain responses in children, studied by MRI, suggested relationships between city of residency and white matter lesions. Mexico-City children also had a significantly lower level of cognitive development.

9 Conclusion

Based on epidemiological and experimental research done over the past 30 years it has become clear that particulate air pollution contributes to the increased incidence of pulmonary and extra-pulmonary diseases. Fine (< 2.5 µm) and especially ultra fines (<0.1 µm) from combustion sources, have a stronger association with adverse health effects than coarse particles. Highest concentrations of primary particles are found close to their emission sources (exhaust gases from highways, occupational exposure to oil smoke and welding fumes, cigarette smoke). The rapid growing field of nanotechnology might also be a source of exposure to nano-sized particulates. There is however still lack of exposure data. Besides exposure data, information about inhalability and regional deposition can also help to predict particle hazards. A large number of particles that are inhaled are also exhaled and are thus not hazardous. Most particles that do deposit in the respiratory tract can be effectively eliminated from the body via the gastrointestinal tract. These particles are not expected to be hazardous, however particles that do retain in the respiratory tract or that translocate to other organs are potentially harmful (

Figure 9-1).

Particle deposition is size, density and shape dependent. Particle size most strongly affects which deposition mechanism is most pronounced. In the airways, impaction, diffusion and interception are most important. I furthermore showed that the site of deposition and particle characteristics such as size, shape, surface chemistry, charge, solubility and surface area are important factors that influence particle clearance pathways. Deposition site and clearance mechanisms together influence subsequent health effects.

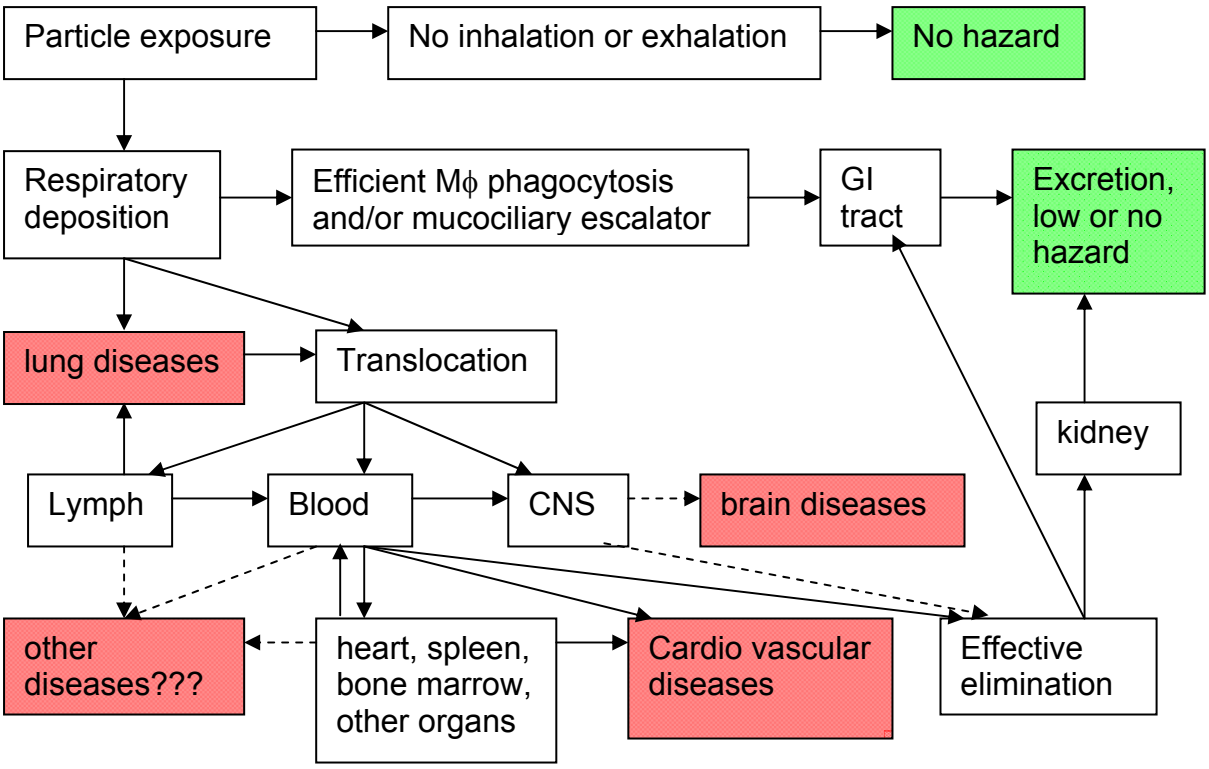

Figure 9-1 Health effects of particle exposure depends on respiratory deposition and subsequent clearance mechanisms. Well studied effects are

lung and cardiovascular diseases. Brain diseases are already hypothesized. Other diseases might also be influenced by particle exposure.

High particle retention time in the lung increases the risk to develop lung diseases such as COPD. Fibrous materials are hazardous because fibers tend to align with the airflow and penetrate deeper into the lungs where they deposit due to interception. Fibers are not efficiently eliminated by alveolar macrophages. I furthermore showed that the risk of ultrafine particles to cause extrapulmonary diseases can be explained by 1) Ultrafine particles are deposited in the alveolar region 2) There is no mucociliary escalator in the alveolar region. 3) Alveolar macrophages are not efficient in clearing ultrafine particles 4) Some ultrafine particles can cross epithelial barriers depending on their surface chemistry thereby reaching the lymphatic system, the bloodstream and the heart. Some of these particles can reach other organs including the brain by crossing the blood-brain barrier. The brain may be extra vulnerable for ultrafine particles because: 1) Ultrafine particles deposit very effectively in the head region due to diffusion 2) the clearance mechanisms of the olfactory region are not efficient due to lack of mucociliary escalator and 3) the olfactory nerves form a direct portal of entry into the brain. The presence of a respiratory disease not only influences particle deposition, it may also facilitate particles to cross epithelial barriers. Oxidative stress is a central factor in the damage caused by pollutants to pulmonary and to extra pulmonary organs. Ultrafine particles have a relative large surface area and may thus generate more radical species.

Environmental particle samples consist of a mixture of different types of particles, which makes it complex to study the effects of individual characteristics of different types of particles. By using engineered particles in experimental studies, the contribution of different physico-chemical characteristics can be analyzed in a reproducible way. For example by using such materials it has become clear, that ultrafine particles elicit a stronger inflammatory reaction in the lungs of animals compared to larger sized particles. Due to the complex mixture of components in APM, it remains however important to study the synergetic effects of complex mixtures. Thus, more research is necessary to get insight in the ensemble of particle characteristics that influence toxicity.

In this thesis I showed how combining knowledge from different disciplines can help to address questions regarding the potential risk of particles that enter the respiratory system. Disciplines that contribute to understanding particle hazards are epidemiology, toxicology, aerosol technology, particle chemistry, diseases pathology and toxico-/ pharmaco-kinetics.

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