Health-related aerosol particle studies, respiratory tract deposition and indoor source identification

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Health-related Aerosol Particle Studies

Respiratory Tract Deposition and Indoor Source Identification

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Licentiate Dissertation
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Department of Nuclear Physics
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HEALTH-RELATED AEROSOL PARTICLE STUDIES
– RESPIRATORY TRACT DEPOSITION AND INDOOR SOURCE IDENTIFICATION

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Preface

Since there is limited possibility for reflection about the world beyond science in a scientific publication, I want to seize the opportunity to add a few comments in this preface.

Science deals with the aspects of the physical world that could be investigated through "unbiased observations and systematic experimentation"[1]. However, anyone who has been dealing with research, or studied philosophy of science, knows that this idealised view is far from the real progress of our organized knowledge. Humans are not objective unprejudiced observers, facts are not simply obtained from experiments because experiments rely on facts and all facts are not explained theories. Furthermore, commonly accepted theories could be contradictory to each other.[2] Science requires a certain amount of belief.

A conviction about the existence of things that are not controllable, repeatable or easily observable is usually referred to religion. From my own experience and from the testimony by others, whom I consider trustworthy, I have come to share the Christian view that there are such things. Moreover, I think that these should not be neglected since they are of vital importance to our lives.

Christianity claims that a man called Jesus, who preached in Palestine during three years almost two millenniums ago, was the Son of God. "For God so loved the world, that he gave his only Son, that whoever believes in him should not perish but have eternal life."[3] If this is true, the passages in the bible that seem obscure to most readers, and maybe also to those who once wrote it, have a meaning which is perfectly clear to God. Where theology is insufficient to clarify the mysteries, maybe science could help. Some texts are of special interest from an aerosol perspective. What is the point of using incense? What kind of signs in the nature could cause anguish and perplexity for the nations?[4] Why should the sky become dark?[5] And is it not fascinating that God often is found in the aerosol? He uses clouds to hide himself, to reveal himself and to show the way forward.[6]

Even if these questions do not constitute a main driving force in my work, they undoubtedly add an extra dimension.

Jakob Löndahl
October 2006, Lund

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[1] Encyclopædia Britannica

[2] Chalmers, A.F., 1999, "Vad är vetenskap egentligen?", Bokförlaget Nya Doxa

[3] John 3:16 (English Standard Version)

[4] Luke 21:25, Matt 24:30

[5] Matt 24:29, Isaiah 13:10, Ezekiel 32:7, Joel 2:10, Rev 6:12 and others

[6] Exod 34:5, Matt 17:5, Rev 14:14, Exod 13:21

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Title and subtitle

Health-related Aerosol Particle Studies
– Respiratory Tract Deposition and Indoor Source Identification

Abstract

Aerosol particles have, since Classical Antiquity, been linked to adverse effects on human health. It is estimated that the particles in urban air pollution causes 100 000 deaths in Europe each year, whereof 5 000 in Sweden. These figures do not include the outcomes of indoor sources or smoking, which shortens the lives of millions of people worldwide. Many studies indicate that fine particles (<2.5 μm) are to be more toxic than larger ones. Especially the ultrafine particles (<0.1 μm), typically originating from combustion sources, have been of much concern. Part of the reason could be their high probability to deposit deep into the lung once inhaled. A novel method has been developed for determination of fine and ultrafine particle deposition in the respiratory tract. It is designed to be used on larger groups of human subjects in exposure studies and in typical ambient and indoor environments. The method is demonstrated to have a precision in the determined deposition fraction (DF) of 0.02–0.08 and to be sensitive enough to quantify differences between breathing patterns and between hygroscopic and hydrophobic aerosols. The results for hydrophobic particles are in agreement with the well-established ICRP 66 model. The developed instrument was used to investigate the influence of hygroscopicity (the ability to grow by uptake of water), exercise level, gender and intersubject variability on size-dependent deposition of fine and ultrafine particles (12-320 nm) during spontaneous breathing. DF was measured for 29 healthy adults (20 men, 9 women) in four exposure situations; rest and light exercise with both hydrophobic (Di-Ethyl-Hexyl-Sebacate) and hygroscopic (NaCl) particles. DF was 2-4 times higher for the hydrophobic ultrafine particles than for the hygroscopic. DF of hygroscopic ultrafine particles could be estimated by calculating their equilibrium size at 99.5% relative humidity. The differences in average DF due to exercise level and gender were essentially insignificant, but the minute ventilation was 4-fold higher during exercise and 18%-46% higher for the males. Consequently the deposited dose of particles was 4-fold higher during exercise and considerably increased for the male subjects. Some individuals generally had a high DF in all four sessions.

To assist the work for healthy indoor environments, a methodology for identifying sources to particles larger than 0.5 μm was designed and applied in a study of three houses in southern Sweden. The methodology includes (1) visual inspection in order to identify deposited particles and potential sources, (2) measurement of airborne particles at different positions in a building with simultaneous logging of activities and (3) isolation of potential sources in a test chamber for controlled characterizations of the generated particles. The results show that source identification is facilitated by knowledge of concentration variations between different rooms, real-time measurements together with activity reports and information on particle characteristics that are comparable with results from laboratory simulations. Major particle emissions from textile handling, likely due to detergent zeolite residues, were found in the studied houses.

Key words

aerosol particle, health, respiratory tract, deposition, ultrafine particles, nanoparticle

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Papers

This dissertation is based on the following papers, which are appended at the end. In the text, they are referred to by their Roman numerals.

I *A Set-up for Field Studies of Respiratory Deposition in Humans*
Löndahl, J., Pagels, J., Swietlicki, E., Zhou, J., Ketzel, M., Massling, A. and Bohgard, M.
Journal of Aerosol Science. 37:1152-1163 (2006)

II *Size-Resolved Respiratory Tract Deposition of Fine and Ultrafine Hydrophobic and Hygroscopic Particles during Rest and Exercise*
Löndahl, J., Massling, A., Pagels, J., Swietlicki, E., Vaclavik, E. and Loft, S.
Accepted for publication in Inhalation Toxicology 15 Sep 2006.

III *Methodology for identifying particle sources in indoor environments*
Gudmundsson, A., Löndahl, J., Bohgard, M.
To be submitted to Journal of Environmental Monitoring

The Authors Contribution to the Papers

Paper I
I evaluated a predecessor to RESPI, initially constructed by Dr. Joakim Pagels. From the experiences, after a literature review and after discussions with Dr. Pagels, Prof. Erik Swietlicki and Dr. Jingchuan Zhou, I developed the RESPI set-up. I performed the experiments, made the data analysis and wrote a main part of the paper.

Paper II
I made most of the work, from planning and performing of the experiments to data analysis and writing of the paper.

Paper III
I participated in the field measurements, made a considerable part of the data analysis and wrote an initial version of the paper as an abstract to the European Aerosol Conference 2004. I have also joined in the exchange of ideas about the described methodology and in the continued work with the text.

Related publications

Other publications by Jakob Löndahl not included in this dissertation.

Abstracts at conferences and meetings

Boman, C., Pagels, J., Löndahl, J., Massling, A., Rissler, J., Swietlicki, E., Bohgard, M., Nordin, A., Blomberg, A., Sandström, T. "A new chamber set-up for studies of health effects, respiratory deposition and characteristics of biomass combustion aerosols", Conference proceedings, NOSA 2005, 8-10 November, Helsinki, Finland

Löndahl, J., Massling, A., Pagels, J., Swietlicki, E., Vaclavik, E. and Loft, S. "Respiratory tract deposition of fine and ultrafine hydrophobic and hygroscopic aerosol particles during rest and exercise", Conference proceedings, NOSA 2005, 8-10 November, Helsinki, Finland

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Massling, A., Löndahl, J., Swietlicki, E., Ketzel, M., Jensen, M., Wahlin, P., Bilde, M., Kristensson, A., Hansson, H.-C., Ströhm, J., Jonsson, A., Hallquist, M., Lunder, C. "DMPS/SMPS intercomparison in terms of particle sizing", Proceedings of 3rd Joint BACCI meeting, 15-17 May, Hyytiälä, Finland.

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Abbreviations and Symbols

η	viscosity of the gas
ϱ_g	density of the gas
ϱ_p	average density of the particle
ϱ_w	density of water
σ_g	geometric standard deviation
σ_{sol}	surface tension of a solution
Φ	resistance to gas flow
χ	particle shape factor
a_w	water activity (RH at the surface of the particle)
C_{mm}	Cunningham factor for a specific d_{mm}
C_{ve}	Cunningham factor for a specific d_{ve}
C_{ex}	exhaled number concentration
C_{in}	inhaled number concentration
C_k	Kelvin curvature correction factor
d_d	droplet diameter
D	diameter of tube
DF	fraction of particles deposited in the respiratory tract
DF_{eq}	fraction of particles deposited in the instrument
d_{em}	electrical mobility diameter of the dry particle
d_{mm}	mechanical mobility diameter of the dry particle
d_p	diameter of the dry particle
d_{ve}	volume equivalent diameter of the dry particle
e	elementary charge
Gf	hygroscopic diameter growth factor
GMD	number geometric mean mobility diameter
i	van't Hoff factor, ~number of soluble ions per molecule
L	length of the DMA cylinder
M_p	average mole weight of the particle
M_w	mole weight of water
n	number of elementary charges
PM	particulate matter
$PM_{2.5/10}$	mass of PM with aerodynamic diameter <2.5 μm respectively <10 μm
Q_a	DMA aerosol flow
Q_{sh}	DMA sheath air flow
R	ideal gas constant
r	radius of tube
r_1, r_2	inner respectively outer radii of the DMA volume
RH	relative humidity
RV_{box}	plethysmographic functional residual capacity
SD	standard deviation
T	temperature
UFP	ultrafine particles
v	gas velocity
V_T	tidal volume
V	voltage of DMA electrode
Z_p	Electrical mobility of the par*ticle*
ΔZ_p	Full width at half height of the DMA transfer function

Contents

Introduction

Less than a century ago huge chimneys emitting thick black plumes was a sign of success. Thus, a fourth smokestack was built on the showpiece Titanic to make it look more impressive. But, analogous to the sudden end of Titanic when it met an iceberg on its first overconfident journey, our admiration of industrial emissions faded as soon as we began to understand the downsides of air pollution. Nature limits our progress and it is not always we discover it in time.

First to be noticed among the consequences of air pollution was the effects on human health, which, although known since the Classical Antiquity, attracted serious attention after an episode in London in the early fifties. Since then there have been regular reports about the negative outcomes of our emissions into the atmosphere. They damage ecosystems and harvests, reduce visibility in heavily populated areas, destroy historical heritage and lead to millions of premature deaths every year. Most serious is the influence on global climate. Nevertheless climate change has not been given the medial attention it deserves, probably because it is a complex, slow and uncertain process with consequences not yet dramatic enough to visualise (Jagers and Thorsell 2003). Often the poor, who contribute least to the pollution, are the most affected from both a health and a climate perspective.

Aerosol science, which is the area of research where this dissertation belongs, is engaged in all the problems mentioned above. An aerosol is a suspension of solid or liquid particles in a mixture of gases. Both the particles and the gas, which most often is air, are included by the concept. Particle sizes range from about 0.002 μm, a gathering of molecules, to more than 100 μm, which is clearly visible and where forces exerted by the gas no longer are able counteract the gravitation and keep the particles in the air more than a few minutes. The atmosphere is an aerosol as well as wind blown dust from a sand storm, sea spray or the local smoke from a cigarette. Because of the wide variety of circumstances involving aerosols, the research area stretches from applied chemistry and physics to medicine and meteorology. The present work is concerned with some aspects of the impact of aerosol particles on human health.

The first objective of this dissertation is to develop and apply a method to determine the deposition of fine (< 2.5 μm) and ultrafine (< 0.1 μm) environmental aerosol particles in the respiratory tract. The second objective is to develop and apply a methodology for source determination of particles in indoor environments.

Background

Health Effects of Aerosols

Pollution episodes in Meuse Valley, Belgium, in 1930, Donora, Pensylvania, 1948 and in London 1952 provided early evidence that extremely high levels of airborne particulate matter had negative effects on public health. However, during the last decades a number of epidemiological studies has shown that also low concentrations of particulate matter, as in most of the populated areas, have an impact on the mortality (Abbey et al. 1999;Dockery et al. 1993;Pope et al. 1995). Together these studies estimated a relative risk (the probability of an effect for the exposed group compared to the unexposed) of premature death to be about 1.06 ± 0.03 per $10\,\mu g/m^3$ increase of $PM_{2.5}$. The relationship between concentration and response seem to be linear and no threshold has been found below which the pollution could be considered harmless (Samoli et al. 2005). It has been estimated that urban particulate matter (PM_{10}) causes 800 000 premature deaths annually in the world, whereof 100 000 in Europe and 5 000 in Sweden (Ezzati et al. 2002;Forsberg et al. 2005;World Health Organization 2002). These figures do not include indoor smoke from solid fuels, which is reckoned to lead to another 1.6 million deaths, or tobacco smoke, which is guilty of shortening 4.9 million lives. It is thus vital to seek an understanding of the relationship between the pollutants in the air and their effects on human health.

A substantial number of outcomes have been linked to PM exposure, whereof most are cardiovascular and respiratory diseases. Other responses, as for example damages on the central nervous system, has also been suggested (Oberdorster et al. 2004). Susceptible subgroups have been identified that are more vulnerable to PM exposure than the average population. Among these are people with pre-existing heart and lung diseases, elderly, children and possibly infants (Air Quality Criteria for Particulate Matter 2004). Other factors that probably contribute are genetic predisposition, socioeconomic status and possibly also diabetes, medication use, gender, health care availability, educational attainment, housing characteristics and amount of outdoor activity (Pope and Dockery 2006).

Inhaled particles interact with the body in a variety of different ways. They trigger inflammation in the lungs by production of reactive oxygen species (Nel 2005). This could in turn worsen asthma, chronic bronchitis, airway obstruction,

decrease gas exchange or lead to damages of proteins, membranes and DNA. The pathways leading to severe cardiac effects are not fully understood. Part of the cause could be due to ultrafine particles (UFPs), which have been shown to be able to pass rapidly into the blood circulation and brain (Nemmar et al. 2002;Oberdorster et al. 2004). However, not all studies confirm these results (Brown et al. 2002).

It has not been possible to identify a single characteristic of particles that accounts for the toxicity. Air quality guidelines have so far focused relatively rough measures as PM_{10} or $PM_{2.5}$. Nevertheless, PM is dominated by the larger particles and both epidemiological and toxicological studies indicate that small particles are more closely linked with adverse health outcomes than larger ones (Schlesinger et al. 2006). Many toxicological studies show a better fit of the dose-response relationships if the dose is expressed as surface area of the particles rather than mass (Brown et al. 2001;Donaldson and Tran 2002;Nygaard et al. 2004;Stoeger et al. 2006;Tran et al. 2000). But also other parameters are of importance for the toxicity such as biopersistence (the durability in the lungs), shape (especially for fibres, [Lippmann 1990]) and chemical composition (carbon compounds, secondary inorganic material, sulphates, nitrates or metals).

Parts of the work in this dissertation deal with UFPs, which have been of much concern in recent years. UFPs typically originate from combustion processes or condensation of gases with low volatility and appear in high number concentrations in many environments. Several epidemiological studies show an association between UFPs and adverse health effects (Peters et al. 1997;Wichmann and Peters 2000;von Klot et al. 2005), but not all agree (Pekkanen et al. 1997;Tiittanen et al. 1999). The mechanisms of interaction between UFPs and the human body are not fully understood. A number of reasons have been suggested for a higher toxicity of UFPs compared to corresponding masses of fine particles. For example their high probability to deposit deep in the respiratory tract, their large surface area, oxidative capacity and their ability to form radical species is thought to induce inflammatory effects, cause cellular DNA damage or inhibit macrophage phagocytosis (Kreyling et al. 2004).

There has often been scepticism about the results from the health assessments of particle exposure, especially about those from the epidemiological studies. It has been argued that, since the effects usually are small they are likely to be due to confounding factors not controlled by the investigators. One such factor, was an error in S-Plus, a common program for statistical evaluation, which led to a re-analysis of many of the studies (Knight 2002). Another factor was a publication bias noticed for time-series studies, but after correction the associations were still positive (Anderson et al. 2005). An additional problem with the epidemiological studies is the exposure assessment. A majority of the studies rely on ambient

monitoring data and not on personal exposure measurements. This is misleading considering that people spend most of their time indoors (Jenkins et al. 1992;Leech et al. 2002) where the exposure is uncertain. Moreover there are often large local differences in the concentration of pollutants. The estimates of PM mortality tend to be higher when the exposure is calculated with more focused spatial resolution or when local sources, such as traffic, are accounted for (Pope and Dockery 2006). For example the relative risk of mortality has been estimated to 1.17-1.41 for people living near major roads (Finkelstein et al. 2004;Hoek et al. 2002). Previously it was a question mark that no known mechanisms could explain how exposure to very low concentrations of particles could cause an effect as serious as death (Vedal 1997). But as our knowledge improves, the connection between air pollution and health is becoming clearer.

It is not certain that inhalation of ambient aerosol is solely damaging. For instance, it has been shown that farmer's children, exposed to high amounts of bacterial components and endotoxins from the animals, suffer less from allergy, hay fever and allergic sensitization (Braun-Fahrlander et al. 1999;Riedler et al. 2000). It has been discussed if the exposure could be an explanation (von Mutius et al. 2000). Furthermore, antioxidants have been found in wood smoke (Kjallstrand and Petersson 2001). These reduce oxygen radicals and are suggested to counteract other negative effects of the emissions.

Respiratory Tract Deposition

A key parameter to understand the health effects of aerosol particles is their probability to deposit in the respiratory tract. A recent review states that "ultimately, it is the deposited dose that determines any response" but "such characterization is rarely performed in contemporary toxicological evaluations" (Schlesinger et al. 2006). The deposited dose of the inhaled particles depends on a number of factors, including exposure concentration, exposure duration, ventilation parameters, respiratory tract anatomy and particle characteristics. Most important of the particle characteristics regarding deposition are the size and the ability to grow by absorption of water vapour. It is complex to model the dose and it necessarily involve simplifications. Therefore, to validate the models and increase our comprehension there is a need to measure the deposition of inhaled particles from different sources for different people (Air Quality Criteria for Particulate Matter 2004).

The respiratory tract

The respiratory system can be divided into three regions – the head airways, the lung airways and the alveolar region as shown in Figure 1 and Table 1 (Hinds 1999; Seeley et al. 2003).

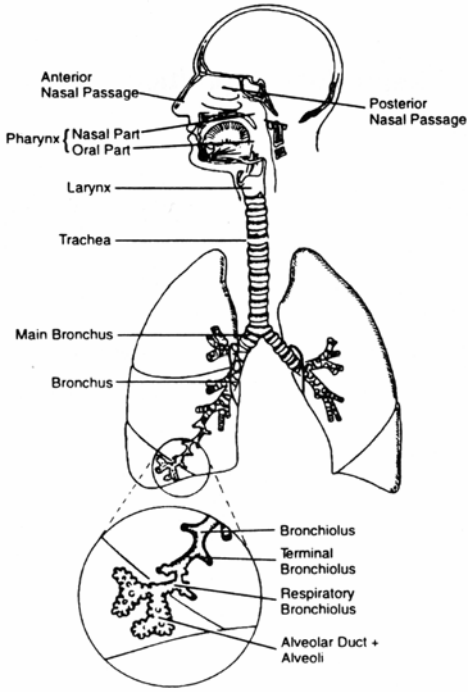


Figure 1 The respiratory tract (Hinds, 1999)

Region	*Function*	*Anatomy*	*Surface (m^2)*
Head airways Extra thoracic	Air conditioning; temperature and humidity,	Nose Mouth Pharynx Larynx	4.5×10^{-3}
Lung airways Tracheo-bronchial	air conducting, cleaning	Trachea	2.9×10^{-2}
		Main Bronchi Bronchi	
		Bronchioles Terminal Bronchioles	2.4×10^{-1}
Alveolar	Air conduction, gas exchange, slow particle clearance	Respiratory Bronchioles	7.5
	Gas exchange, very slow particle clearance	Alveolar Ducts Alveolar Sacs	140

Table 1 Function of the respiratory system[1]

The head airways or extrathoracic region includes nose, mouth, pharynx and larynx. In this region the incoming air is heated, moistened and cleaned from most of the coarse particles before moving further down into the trachea and the lungs. Nasal breathing heats, humidifies and cleans the air more efficiently than oral breathing. Though pure oral breathing almost only occurs when the nose is blocked, as during a cold. For nasal breathing removal of particles begins by inertial impaction and diffusion in the nostrils and continues with filtration of large particles as the air passes the hairs in the vestibule behind the nostrils. The nasal septum, the partition dividing the nasal cavity into right and left parts, and the nasal conchae, three bony ridges on the side of the cavity, increases the surface area and make the airflow more turbulent, which leads to a more efficient absorption of particles (Seeley et al. 2003).

The pharynx is connecting the nasal and oral cavity with the digestive system and the lungs. The larynx, which contains the vocal cords, follows after the pharynx. The deposition due to inertial impaction is high just before entering the

[1] From (Annals of the ICRP 1994) and (Hinds 1999)

larynx, because of the sharp change in direction of the stream, and in the area around the vocal cords where the passage is narrower.

The lung airways or tracheobronchial region is branching like a tree turned upside down in about sixteen generations and it encompasses the parts from the trachea to the terminal bronchioles. This region can also be called the conducting zone since it functions as a passageway for air movement. It begins with the trachea, a tube approximately 12 mm in diameter and a decimetre long stretching from the larynx down to the carina where it divides into the main bronchus. The main, or primary, bronchi branch off to form five secondary bronchi that in turn split up into smaller bronchi and so forth down to the terminal bronchioles with a diameter around 1 mm. All these tubes are surrounded by muscles, that contracts when air is exhaled.

The tube walls in the tracheobronchial region are lined with ciliated epithelium, which catch debris and remove it in a mucus escalator. The rate of removal is 4-6 mm/min in the trachea and much slower further down, probably between 1-100 μm/min in the terminal bronchioles (Air Quality Criteria for Particulate Matter 2004; Morrow et al. 1967; Yeates et al. 1975). As a scientific curiosity can be mentioned that if all the 6 μm long ciliated cells, which are waving back and forth with 13 beats per second, were moving simultaneously the mucus would not be transferred anywhere. Instead they move individually so that adjacent cells differ slightly in phase not unlike the legs of a running centipede. How this is coordinated is still not known since there is no links between the cells. Each of them seems to be working by itself. Possibly they can feel positions of their neighbours through the mucus (Wentzel 2003).

Finally the air reaches the parts where gas exchange takes place – the alveolar region. This is the respiratory zone with about seven generations of branching. It begins with respiratory bronchioles, followed by alveolar ducts and finally comes the alveolar sacs. Alveoli are attached to all parts of the region. There are around 300 million alveoli in the lungs, each with a diameter of approximately 50 – 250 μm (Jonson et al. 1998; Seeley et al. 2003) and together these constitute the main part of the total lung volume. The area of the alveoli is roughly corresponding to half the size of a tennis court.

The tissue surrounding the alveoli contains elastic fibres allowing expansion and contraction during breathing. The epithelium of the alveolar region is not ciliated as the lung airways region is, but particles can be cleared out by macrophages. The alveolar cells can be activated to function as macrophages. The macrophages do not accumulate, but move either to the terminal bronchioles where they are trapped by the mucus or into the lymphatic vessels.

Clearance of deposited particles depends on region in the respiratory tract, but also on particle properties (Oberdorster et al. 2005). Solid particles are either

removed by physical translocation or chemical clearance processes. The physical translocation mechanisms are mucociliary movement, macrophage phagocytosis, epithelial endocytosis, interstitial translocation, lymphatic drainage, penetration into the blood circulation or by sensory neurons. The chemical processes are dissolution, leaching and protein binding. There are still gaps in the knowledge of how these mechanisms are affected by particle size. Especially for UFPs the clearance, translocation and retention is not fully understood (Kreyling et al. 2002; Kreyling et al. 2006; Semmler et al. 2004).

The ventilation cycle is driven by both active muscle labour and of passive forces. During inspiration the lung volume is increased by contraction of the diaphragm and by muscles elevating the ribs. Expiration normally consists of relaxation of the muscles, which lead to a passive decrease in volume. If the breathing is laboured muscles of expiration depress the ribs. When the lung volume decreases there are two forces leading to contraction of the alveoli. Firstly elastic fibres, as mentioned above, surround the alveoli and make them recoil. Secondly a thin layer of water lines the walls of the alveoli and the surface tension arising draw the alveoli together. But if this surface tension where acting alone it would be far too strong and lead to collapse of the lungs (Seeley et al. 2003). For this reason a mixture of lipoprotein molecules, so-called surfactant, is produced that reduce the surface tension.

The surfactant is a mixture of phospholipids, proteins and ions. It spreads uniformly over the surface of the alveoli because one part of each molecule is hydrophilic and dissolves in the water whereas the other part is hydrophobic giving a hydrophobic surface exposed to air (Guyton and Hall 2000). The purpose of the surfactant is not only to decrease the surface tension. It is also important in preventing hydrophilic molecules to dissolve and reach the blood.

Spirometry

The lung volumes and respiratory capacities are studied with spirometry. During the 19th century it was discovered that these volumes changed in connection with certain lung diseases and spirometry is now an established method in making diagnoses. Below is a short summary of the respiratory volumes (ICRP Publication 66 1995; Stocks and Quanjer 1995; Roca et al. 1998).

There are four pulmonary volumes and four pulmonary capacities, which are the sum of two or more volumes (Figure 2):

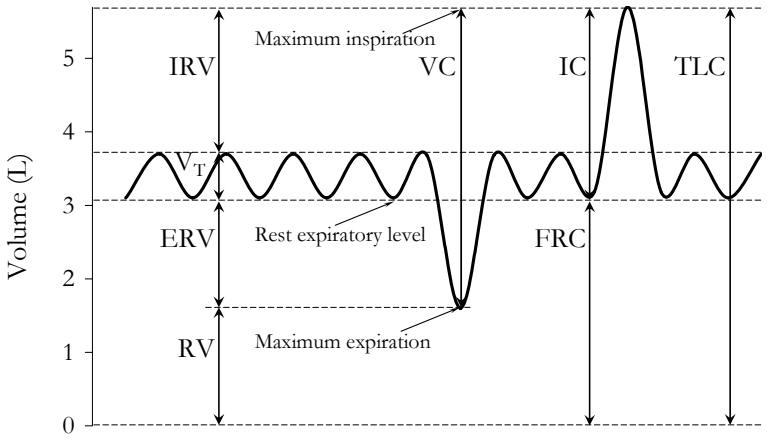


Figure 2 Respiratory volumes

Respiratory volumes		**Average adult value (L)**
V_T	Tidal volume, volume inspired or expired during normal breathing	0.6
IRV	Inspiratory reserve volume, volume that can be inspired after V_T	2
ERV	Expiratory reserve volume, volume that can be expired after V_T	1.5
RV	Residual volume, volume remaining after maximum expiration	1.6
VC	Vital capacity, volume between full inspiration and maximum expiration	4.3
IC	Inspiratory capacity, (IRV + V_T)	2.6
FRC	Functional residual capacity, (ERV + RV)	3
	ITGV or TGV, intra thoracic gas volume, if measured with plethysmography	
TLC	Total lung capacity, TLC, sum of all the volumes	5.8

Other common pulmonary tests are:

Respiratory airflows		**Average adult value**
PEF	Peak expiratory flow, maximum exhaled flow rate	10 L/s
FEV_1	Forced expiratory volume in one second	4 L
MMEF	Maximum midexpiratory flow	
FVC	Forced vital capacity, maximum forcefully expired volume	
IVC	Inhaled vital capacity, maximum inhaled volume	
EVC	Exhaled vital capacity, maximum exhaled volume	
FEF	Forced expiratory flow	
FIF	Forced inspiratory flow	
FET	Forced expiratory time, the length of expiration in seconds	

It should also be noted that according to international conventions the spirometric volumes should be given at "body temperature and pressure, saturated", BTPS, which is 37 ºC and 100 % humidity (Jonson et al. 1998). Values measured at ambient conditions, ATPS, must be converted to BTPS.

Factors influencing the deposition

The most important mechanisms for deposition within the respiratory system are inertial impaction, diffusion and gravitational settling (Brain and Valberg 1979).

Coarse particles mainly deposit by impaction. Impaction occurs when the air changes direction and is therefore highest at the dividing point of the tracheal bifurcation and in the tracheobronchial region where the streamlines bend sharply at every branching. Settling is most efficient in the narrow, horizontally oriented, airways further down in the lungs. Deposition by diffusion is the principal mechanism for particles with a diameter below 0.5 μm and it takes primarily place in small airways where residence time is long. Diffusion, in contrast to the mechanisms important for larger particles, decreases with particle diameter and is less dependent of particle density and flow rate. Deposition by interception is only of interest for fibers, which have a small aerodynamic diameter if they are oriented axial to the airflow but a large extension. If the particles are highly charged it is worth considering electrostatic attraction, but otherwise this mechanism is of minor importance since the surfaces inside the lung can be regarded as conducting since they contain ions. However, measurements with a hollow-cast model shows that it could be of significance for UFPs (Cohen et al. 1998).

The probability of an inhaled particle to deposit is dependent on its size, hygroscopicity, shape, density, breathing pattern, airway geometry and on the density and viscosity of carrier gas. The size dependent total and regional deposited number fraction (DF) according to the ICRP model is illustrated in Figure 3 (ICRP Publication 66 1995).

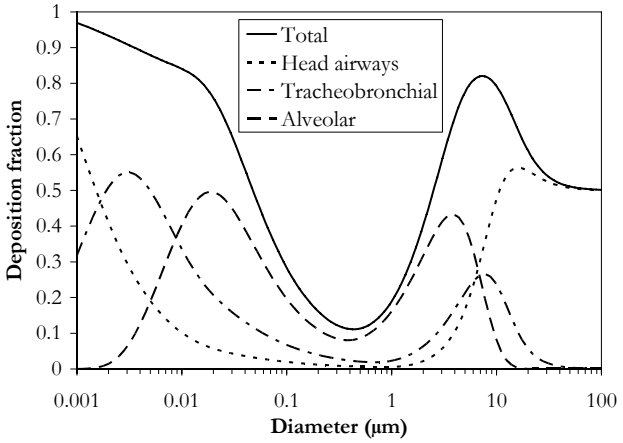


Figure 3 Total and regional respiratory tract deposition of unit density spheres for a sitting male adult according to the ICRP model. Mouth breathing, tidal volume 0.75 L/min and frequency 12 breaths/min.

The diameter of the particles in the respiratory tract is highly influenced by their ability to alter size due to hygroscopic growth via uptake of water vapour. The relative humidity (RH) in the lungs is close to 99.5% (Anselm et al. 1990; Ferron et

al. 1988a). Therefore an inhaled hygroscopic particle will grow by condensation of water vapour to a diameter up to six times the original size. Calculated estimations of the change in respiratory tract deposition for hygroscopic compared to hydrophobic particles is shown in Figure 4 (Asgharian 2004;Ferron et al. 1988b).

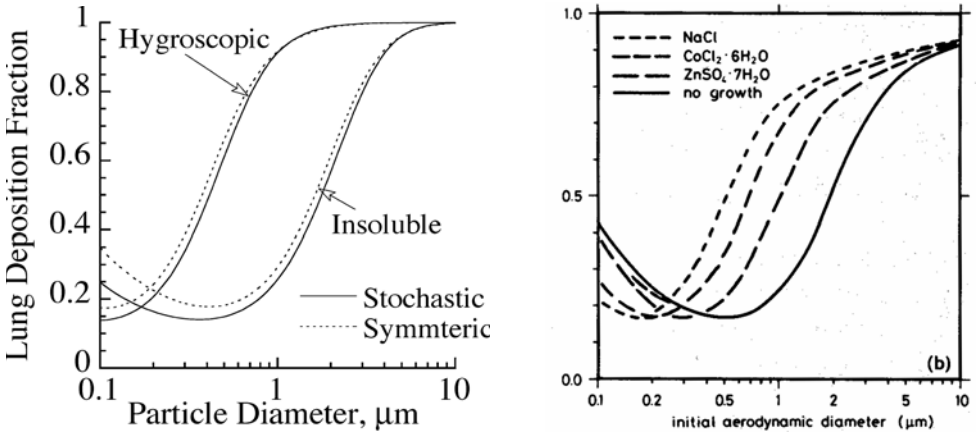


Figure 4 Modelled respiratory tract deposition of hydrophobic and hygroscopic particles. Left (Asgharian 2004) and right (Ferron et al. 1988b).

A detailed description of the theory and the calculations of hygroscopic growth could be found in a recent thesis by (Rissler 2005). The growth factor (*Gf*) is the size of the diameter of the droplet (d_d) compared to the diameter of the dry particle (d_p):

$$Gf = \frac{d_d}{d_p}$$

Below are given three basic equations to estimate *Gf* with reasonable precision at high RH:

$$Gf = \left[1 + \frac{i\varrho_p}{\varrho_w} \cdot \frac{M_w}{M_p} \cdot \left(\frac{a_w}{1-a_w}\right)\right]^{\frac{1}{3}}$$

$$a_w = \frac{RH}{C_k}$$

$$C_k = \exp\left(\frac{4M_w\sigma_{sol}}{RT\varrho_w d_d}\right)$$

Here i is the van't Hoff factor (in a first approximation the number of soluble ions per molecule), M_p and ϱ_p are the average mole weight and density of the particle, M_w and ϱ_w the mole weight and density of water, a_w, the water activity (RH at the surface of the particle), C_k, the Kelvin curvature correction factor, σ_{sol}, the surface tension of the solution, R, the ideal gas constant and T, the temperature.

Deposition fraction is partly determined by the breathing pattern. Important parameters are tidal volume (V_T), breathing frequency and flow rate. A large V_T increases deposition. A high breathing frequency increases the efficiency of impaction and thus the deposition of particles larger than 1 µm, while the

deposition of smaller particles is favoured by a low frequency (Kim and Jaques 2004). A pause between inspiration and expiration increases deposition. A main part of the deposition studies for submicrometer particles uses a square wave breathing pattern; equal flow rate at inspiration and expiration without pause in between. Nevertheless, spontaneous breathing is much more complex which alters the deposition. This is illustrated in Figure 5 where DF is calculated with the ICRP model. In both cases breathing frequency, V_T and minute volume flow are equal, but for "spontaneous breathing" the flow rate during expiration is 30% lower than during inspiration and a pause of 0.3 s is added between inspiration and expiration. Most likely this explains the difference between model and measurement in Paper II, Figure 6.

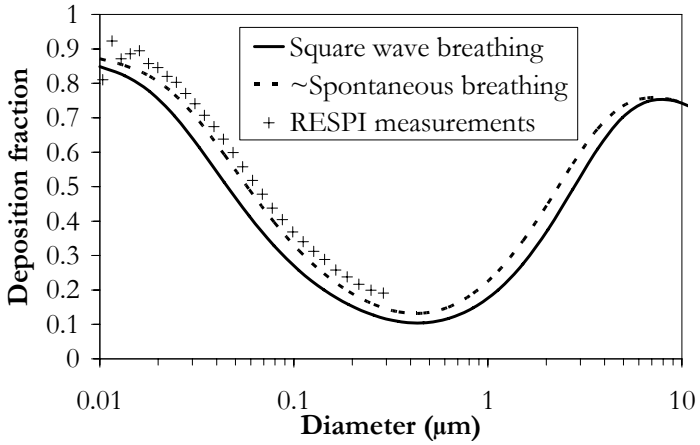


Figure 5 Deposition fraction with similar breathing frequency (12.9 breaths/min**)**, total breathing flow (9 L/min) and tidal volume (0.7 L), but different flow rate at inhalation and exhalation calculated with the ICRP model. Mean values from measurement with RESPI inserted for comparison (frequency 12.3 breaths/min, flow 7.9 L/min and V_T 0.73 L).

The shape of the particles is of significance especially for deposition of fibres (Lippmann 1990). The deposition by interception increases when the fibre deviates from axial alignment. The alignment is altered at each bifurcation in the respiratory tract, which leads to an enhanced deposition. The shape is also of relevance for agglomerated particles, which are far from spherical. The deposited mass can be estimated if the effective density and mobility size are known.

Density influences the deposition by inertial impaction and gravitational settling. Hence, it is the particles above ~0.5 µm that are affected. A particle with a high density will have a longer stopping distance and higher settling velocity than a particle with similar geometric diameter but a lower density. Consequently the probability of deposition will increase. However, two particles with similar aerodynamic diameter, which is a more common diameter in many applications, have the same stopping distance and settling velocity. The aerodynamic diameter is defined as the diameter of a sphere with standard density (1000 kg/m^3) and the same settling velocity. It is used as the density is often unknown, while the settling velocity can be measured.

Airway geometry differs between individuals and in particular for those with a diseased lung the DF may be altered. DF has been shown to be higher for asthmatics (Chalupa et al. 2004;Kim and Kang 1997;Svartengren et al. 1990), for patients with airway obstructions (Anderson et al. 1990;Bennett et al. 1997;Kim et al. 1989;Segal et al. 2002) and for smokers (Kim and Kang 1997). It has been suggested that DF measurements could be used to identify lung abnormality (Kim et al. 1988). In Paper II intersubject variability is measured for healthy subjects. It is likely that the variability is explained partly by respiratory tract morphological factors such as dimension and structure of the airways (Heyder et al. 1982;Hofmann et al. 2002).

The deposition is furthermore dependent on whether the airflow is turbulent or laminar. Turbulence in a tube arises when the Reynolds number, *Re*, exceed 1800. Reynolds number is the ratio between the inertia and the frictional forces, and is given by

$$Re = \frac{\varrho_g v D}{\eta}$$

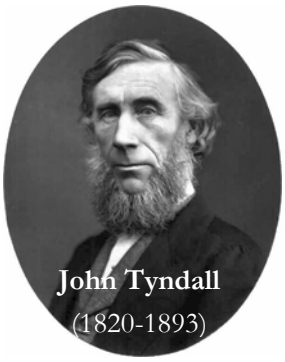
where ϱ_g the density of the gas, v is the gas velocity, D the diameter of the tube and η the viscosity of the fluid. A comparison of deposition when particles were inhaled with air respectively a helium/oxygen mixture, which have a three times lower *Re*, indicated that turbulence was important, especially in constricted airways (Svartengren et al. 1989). It is noteworthy that a minor airway constriction could cause a significant resistance in the gas flow. According to Poiseuille's equation the resistance (Φ), is inversely proportional to the fourth power of the radius (r):

$$\Phi \propto \frac{\eta}{r^4}$$

Finally, volatile components on the particles may evaporate because of the heating when they are inhaled, if it is colder than 37 °C outside. Because of the rapid diffusion of gaseous molecules they are likely to hit the airway surface and maybe also deposit.

Measurements of respiratory tract deposition

John Tyndall was the first to study respiratory tract deposition of aerosol particles (Thomas 2005). He observed light scattering of his own breathing and reported that it was astonishingly free of floating matter – in particular at the end of the expiration. Inspired by Lister, a contemporary researcher, he considered the discovery as an argument that diseases could spread through microorganisms in the air. This conclusion was controversial at the time and when he



John Tyndall
(1820-1893)

presented his results to the Royal Institution 1870 he became much criticised by physicians who thought that a physicist needed more knowledge about disease before investigating it.

The particle detection in the appended papers of this dissertation are, as Tyndall's, based on light scattering, although the performance of the instruments have been developed since 1870 and a size classifier has been added. A main part of the previous studies of DF have been made with monodisperse aerosols, where the inspired and expired concentrations are compared. These results are reviewed by, among others, the International Commission on Radiological Protection (ICRP Publication 66 1995). In Paper I a novel instrument is described, where the deposition of polydisperse aerosol is measured. Previous deposition studies with polydisperse aerosols are summarized further down.

Respiratory tract deposition of aerosol particles can be studied with a number of different techniques apart from light scattering (Bailey 2006;Brain and Valberg 1979). Radioactive tracers can be used, as in SPECT (single photon emission computed tomography), PET (positron emission tomography) and autoradiography. With SPECT a cross-sectional view of the lung, free of overlying tissue, is obtained. Furthermore, it could provide a 3D image of the clearance rate. PET is useful for studying the gas exchange and metabolism in the lungs. Methods based on magnetic fields can contribute with additional structural information. Most common are MRI (magnetic resonance imaging), MRS (magnetic resonance spectroscopy; a combination of MRI and NMR [nuclear magnetic imaging]) and MEG (magneto-encephalography). Structural information could also be provided with CT (X-ray computed tomography). However CT is most suitable for dense tissue, while for non-calcified tissue, MRI is preferable. EIT (electrical impedance tomography) can provide 3D information of the ventilation. Dissection of animals exposed to aerosol particles has answered questions about the spatial distribution of the deposition. Electron microscopy is used to achieve information about the deposition with a high precision, for instance to examine if the particles have been ingested by macrophages (Karlsson et al. 2005). Finally the deposition can be estimated from model calculations, but these need to be verified by experiments.

Polydisperse measurements

It is laborious to cover a large size range when measuring respiratory tract deposition with monodisperse particles and especially for ambient particles long sessions would be needed to achieve good statistics. To improve time resolution and counting statistics, polydisperse methods can be used. The deposited fraction is then determined for each size channel by comparing complete size distributions of the inhaled and exhaled aerosol. Thereby the DF can be determined on a time-scale of minutes.

Respiratory tract deposition experiments with polydisperse aerosols have been made in a few previous studies. It was first suggested by Hiller et al. (1980; 1982), who described an inhalation system with sampling from bags. Using this system Wilson et al. (1985) were probably the first to measure DF from polydisperse aerosols. In their pioneer work they studied DF with an Electrical Aerosol Analyzer in the range 20-400 nm for five male subjects inhaling hydrophobic aerosol. The time for each breathing session was less than two minutes. The results for DF were in accordance with theoretical predictions at the time, but considerably higher than estimations by today's models and experiments, including the measurements in Paper I and II. Anderson et al. (1990) later used this system to compare deposition for five subjects with obstructive or restrictive lung disease with ten normal subjects. They found that ultrafine hydrophobic particles were deposited to a higher extent in the subjects with diseased lungs, but also got a higher DF than more recent estimations.

Morawska et al. (1999) studied respiratory deposition of Environmental Tobacco Smoke (ETS) in 12 individuals and found that the average DF was ~0.56 which is much higher than predicted (~0.17) when taking the breathing parameters for each subject into account (Hofmann et al. 2001). Subjects inhaled aerosol with a silicon mask connected to a large chamber. Exhaled aerosol was directed into a smaller (9 dm^3) chamber. Particle size distributions were measured with a scanning mobility particle sizer (SMPS, 90 s total scan time, see Methods section, (Baron and Willeke 2005) from both chambers. In addition this group reported a higher deposition fraction than theoretically predicted in measurements of aerosols from diesel and petrol engines (Hofmann et al. 2003; Morawska et al. 2005). The sampling procedure is not entirely clear from the publications and errors caused by size shifts are not taken into account (see Method section).

Rosati et al. (2002) presented a method where inhaled and exhaled aerosol samples are collected in 25 dm^3 latex bags. The exhaled bag was heated to 38 °C to avoid condensation. The aerosol was passed through a diffusion drier and sampled with an SMPS system for 15-700 nm particles and an aerodynamic particle sizer (APS, see Methods section) for particles > 500 nm. Internal losses in the system were on the order of a few percent for 300 nm particles. Later Rosati et al. (2003) used the system to determine particle deposition in a packed bed filter and found good agreement between DF determined from discrete sections of polydisperse aerosol and monodisperse particles for sizes larger than 300 nm. No studies involving human subjects have been reported with this set-up.

Daigle et al. (2003) determined respiratory deposition of artificially generated spark discharged soot particles (geometric mean mobility diameter, GMD 26 nm) at high particle concentrations (~$2 \cdot 10^6$ cm^{-3}) in groups of 12 and 7 healthy subjects at rest and exercise, respectively. At rest the mean deposition (0.66) was in

agreement with modelled data, while the deposition at exercise (0.80) was significantly higher than modelled data. They used a flow-through system (Chalupa et al. 2002) with short residence time and only electrically conducting parts. An SMPS system with a scan time of 10 minutes was used in the size-range 7.5-75 nm to measure the particle size distribution in inhaled and exhaled air and the mass was determined with a TEOM (tapered element oscillating microbalance). The system was also used in a study of deposition of UFPs in asthmatics (Chalupa et al. 2004). The impact of agglomeration of the particles is not discussed.

Montoya et al. (2004) studied respiratory deposition of ambient particles for six subjects. They found reasonable agreement with the ICRP model for particles smaller than 400 nm for the mean values of the group. However the deposition minimum was shifted towards smaller particles. They attributed this to hygroscopic growth involving ammonium sulphate in ambient particles. Particle concentrations in dried samples of ambient and exhaled air were measured with an SMPS system and an API Aerosizer in the size range 40-1800 nm. They used a flow-through method, which involved dilution of the exhaled sample with filtered air.

Apart from the above described polydisperse measurements with electrical or aerodynamic size spectrometers, experiments have been made with laser diffraction. Invernizzi et al. (2006) used this technique to determine deposition of tobacco smoke in a single breath for ten healthy volunteers.

Methods

Aerosol measurement

A huge variety of instrumental techniques have been used in aerosol studies since the research field has applications in a wide range of sciences (Baron and Willeke 2005). Apart from the TEOM (tapered element oscillating microbalance), all the instruments mentioned in Papers I-III detect the particles with light scattering, sometimes combined with different methods for size classification.

SMPS – Scanning Mobility Particle Sizer

A scanning mobility particle sizer (SMPS) is the primary instrument for studying size distributions of particles below 0.5 μm in diameter. It is a combination of a differential mobility analyzer (DMA) and a condensation particle counter (CPC). Particles of a specific electrical mobility are selected with the DMA and thereafter counted with the CPC. The DMA (Figure 6) consists of a high voltage electrode contained in the middle of a cylinder. The aerosol enters the cylinder in a thin slot along the inner walls and between the aerosol and the electrode there is a sheath flow of particle free air. When a voltage is applied to the electrode, particles will be attracted or repelled depending on their charge and move in the electrical field as they follow the air flow. Only particles of a specific electrical mobility, Z_p, will penetrate the outlet connected to the particle counter.

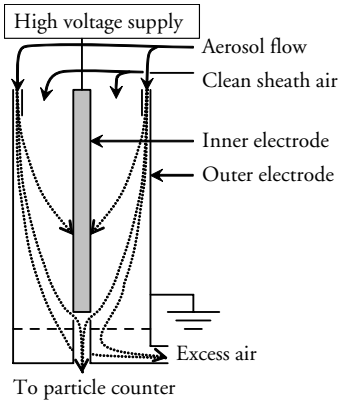


Figure 6 Differential mobility analyser (DMA)

The size of the particles selected by the DMA is obtained from the transfer function. The transfer function is determined by the voltage of the electrode, V,

the sheath flow rate, Q_{sh}, and the dimensions of the DMA (inner radii, r_1, outer radii, r_2, length, L) and it is centred at:

$$Z_p = \frac{Q_{sh} \ln\left(r_1 / r_2\right)}{2\pi\, LV}$$

It has a triangular shape with a full width at half maximum depending on sheath to aerosol flow ratio:

$$\Delta Z_p = Z_p \frac{Q_a}{Q_{sh}}$$

The penetrating particles have a similar electrical mobility diameter, d_{em}. The mechanical mobility diameter, d_{mm}, of the selected particles can be calculated if charge distribution is known:

$$d_{mm} = \frac{neC_{mm}}{3\pi\eta Z_p}$$

where n is the number of elementary charges, e, and C_{mm} is the Cunningham factor. The mechanical mobility diameter is most important for the deposition of particles smaller than 0.5 μm since it is related to the diffusion velocity. In some applications it is of interest to know the volume equivalent diameter, d_{ve}, as for example when the hygroscopic growth should be calculated. The growth depends on the number of soluble ions and hence the volume. The volume equivalent diameter can be derived from the mobility diameter if the shape factor, χ, is known (C_{ve} is the Cunningham factor for particles with diameter d_{ve}):

$$d_{ve} = \frac{d_{mm}}{\chi} \cdot \frac{C_{ve}}{C_{mm}}$$

Originally the DMA was stepped (Fissan et al. 1983), but to reduce measurement time a scanning instrument was later developed (Wang and Flagan 1990;Zhou 2001). As is illustrated in Figure 7, the transfer function is not perfectly triangular at short scan times and there is a discrepancy between up and down scan (Collins et al. 2004). Furthermore, at short scan times, the CPC signal is smeared because of mixing of particles with different mobility in its inner volume (Collins et al. 2002). By correcting for these biases, we have been able to decrease the scan time to around 30 seconds (Paper I), which enhances the performance of the respiratory tract deposition measurements substantially.

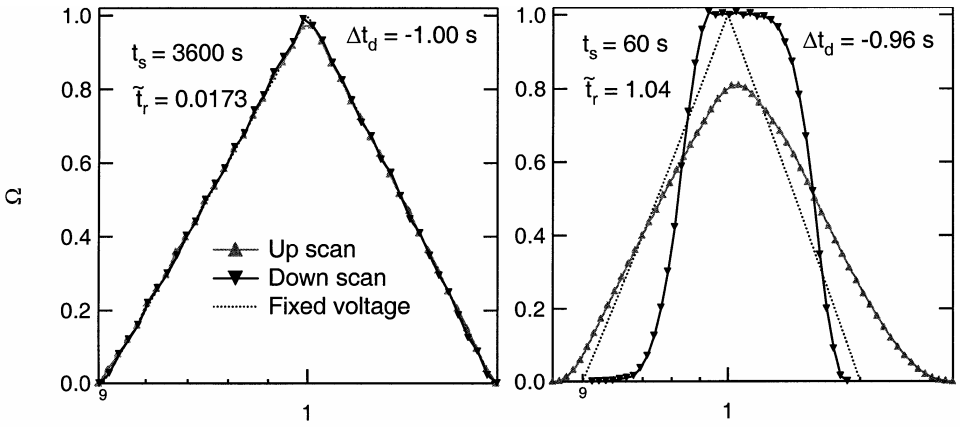


Figure 7 DMA transfer function at long scan time (left) and short scan time (right) from Collins et al. (2004).

As a quality control the SMPS used in Paper I and II has been tested in a Nordic intercomparison of SMPS/DMPS systems (Massling et al. 2006).

APS – Aerodynamic Particle Sizer

An APS (aerodynamic particle sizer, TSI Inc., USA), used in Paper III, is a the time of flight instrument measuring the time it takes for the particles to pass between two parallel laser beams in an accelerating flow field (Agarwal et al. 1982). The particles are detected from the scattered light. The time between the two signals is related to the aerodynamic diameter. Thereby the size distribution in the interval 0.5-20 μm can be determined with high resolution. Because the passage time is not exclusively dependent on aerodynamic diameter a correction has to be made for density and shape for particles larger than 1 μm (Cheng et al. 1993;Chen et al. 1990).

TEOM – Tapered Element Oscillating Microbalance

A TEOM (tempered element oscillating microbalance, Thermo, USA) is a filter based system for real-time determination of PM (Patashnick and Rupprecht 1991). The particles are collected on a vibrating filter and the mass is calculated from the frequency change when the load increases. An inlet could be used to separate the measurements into different size fractions. The main uncertainty with the method is to correct for the rate of evaporation from the filter, which otherwise lead to an underestimation of the mass. To deal with this, a separate FDMS (filter dynamics measurement system) unit can be added to quantify the volatile fraction. However, this unit is not incorporated in the TEOM used in Paper III.

RESPI – respiratory particle deposition instrument

Set-up

RESPI is a novel instrument developed at Lund University. It is described in detail in Paper I and more generally in Paper II. Since the original set-up the system has been improved with a number of flow and pressure sensors as a quality control of the data (Figure 8).

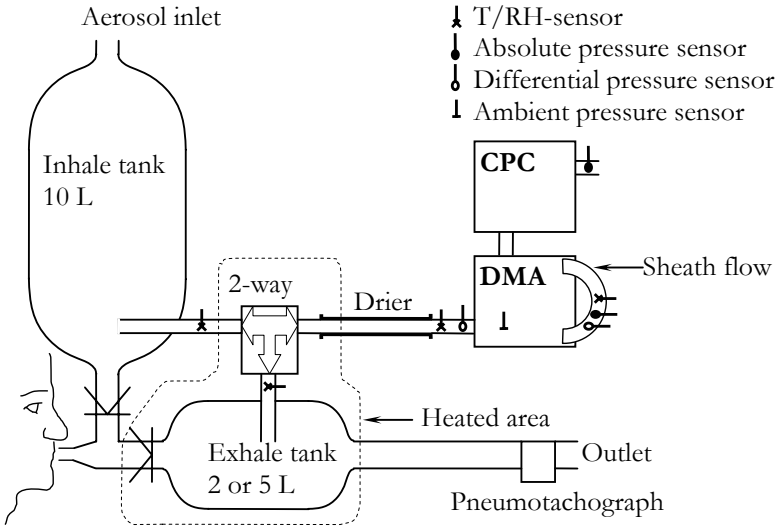


Figure 8 RESPI, schematic picture of the set-up.

Methodological difficulties and solutions

Several potential artefacts may seriously affect the results if not accounted for. These have been considered to a varying degree in the previous polydisperse respiratory tract deposition measurements. The following difficulties have been identified in a review of the literature and during our own experiments:

- The polydisperse techniques is sensitive to small size shifts of the dried diameter between the inhaled and exhaled sample (Pagels et al. 2003).
  RESPI: This main difficulty is discussed extensively in the next section. In Paper I and II aerosols were used for which the size shifts could be expected to be minor. Although size shifts may cause substantial errors, it has been neglected in previous studies.

- Losses (e.g. electrostatic) in the measurement equipment may be interpreted as an increased deposition. This is especially tricky for bag-systems since the losses depend on the volume in the bags.
  RESPI: All parts are conductive; valves are covered with gold and reservoirs are made of stainless steel. Furthermore the residence time of the aerosol in the system is only a few seconds, compared to bag systems where it usually is

several minutes. The small, but remaining, losses left are well-characterised and easily corrected for.

- Pressure variations caused by the breathing distort the aerosol flow in the DMA and may give errors in the particle sizing.
  RESPI: The system is open to atmosphere, which minimizes pressure variations.

- An error may arise if the scan time is long and the inhaled concentration varying because the size distribution could change too much between the scans.
  RESPI: Recent improvement of the SMPS inversion (previous section) has made it possible to reduce scan time a factor four, when compared to previous systems.

- Temperature and RH is higher in exhaled than inhaled air.
  RESPI: The reservoir for exhaled air is heated to 37°C to prevent condensation and additional losses. The aerosol is dried below 20% RH before entering the DMA.

- The air trapped in the dead space in the mouthpiece after exhalation is inhaled again. Thereby the inhaled concentration is lower than measured, which cause an underestimation of DF.
  RESPI: Gebhart et al. (1989) described a correction that has been neglected in most experiments. Thereby a majority of the DF measurements in literature present values that are 1-5% too low. The dead volume in RESPI is relatively small. The correction has been used in Paper II, but was not considered in Paper I was written.

- Smearing of the output signal in the SMPS mainly caused by the finite CPC response time introduces cross sensitivity in the size-classification (Wang et al. 2002).
  RESPI: A CPC de-smearing routine is added in the SMPS inversion.

- None of the cited studies have presented a lowest acceptable concentration limit due to counting statistics or an upper concentration limit, e.g. due to particle coagulation.
  RESPI: The measurable concentration range is 600-500 000 cm^{-3}. A number of studies use concentrations far above the upper limit determined for RESPI.

The size shift problem

The single most difficult problem with polydisperse respiratory tract deposition measurements is that the particles could change mobility size between the inhaled and exhaled sample. Depending on size distribution and deposition curve, a diameter change as minor as 1% could cause a substantial error if it is not

accounted for (Figure 9, see also paper I). An unwanted shift in size may occur if the particles coagulate, evaporate, restructure or absorb gaseous material. Coagulation could be avoided by keeping the concentration low and if the aerosol is well characterised, non-volatile and has a stable shape it is possible to deal also with the other three processes. However, for an ambient aerosol it is in most cases unachievable to fulfil these criteria. Therefore, to be able to use RESPI with more complex aerosols than those produced in the laboratory, it is necessary to find a solution to the size shift problem.

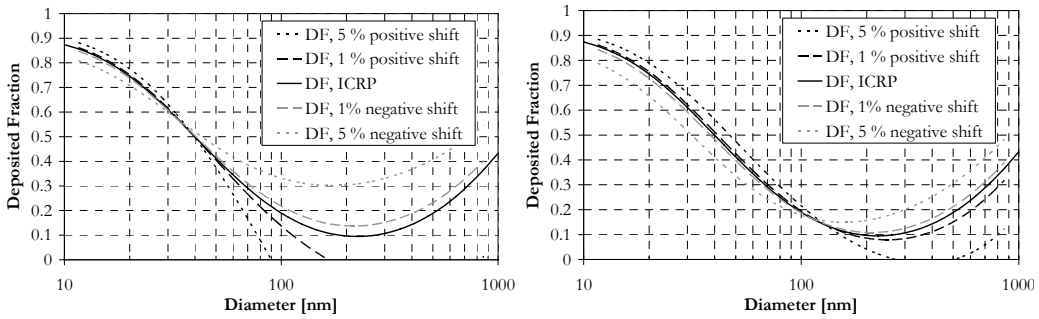


Figure 9 The error caused by a 1% respectively 5% diameter change between the inhaled and exhaled sample for a size distribution with σ_g 1.6 and GMD 30 nm (left, as used by Daigle et al. [2003]) and for the size distribution of DEHS in Paper II (right).

There are basically two approaches to handle size shifts; to make sure that the particles preserve their size after inhalation or to measure the shift with very high accuracy and correct for it afterwards. Apart from these there is the alternative to do monodisperse measurements instead, i.e. select one size at a time with a DMA and count the inhaled and exhaled concentration with a CPC. Some of the advantages with RESPI are lost when using this approach, as for example its simplicity and its high size and time resolution. But it is valuable as a verification of the accuracy of the results if the multiply charged particles, with a larger size but same mobility as the singly charged, are corrected for appropriately. A number of suggested means to deal with the size shift problem in RESPI are discussed below.

Pre-processing the particles before inhalation to avoid a size shift

The particles could be pre-processed to prevent a mobility change after inhalation. The main disadvantage is that DF is not measured for the original aerosol. In addition, it does not work if the particles contain too much volatile material since the evaporation will continue with increasing speed the smaller the particles become. Three ways of pre-processing have been discussed:

- To heat the aerosol enough to evaporate volatile material and preclude agglomerate restructuring by humidifying it to at least 99.5% RH, the same as in the lungs. However, it is technically difficult to humidify a big constantly

changing volume of aerosol to high RH without a large pressure drop in the system.

- To inhale the aerosol before inhaling it a second time in RESPI and thereby both heat and humidify it to the right temperature and RH. This is both complicated and has the shortcomings that only the particles reaching the lungs will be humidified to 99.5% and that a large part of the particles will be lost, especially those with highest probability to deposit.
- To humidify the aerosol to 80% RH, which could be done without pressure drop, then cool it to reach super saturation and finally heat to evaporate volatile components. This approach has shown to be the most promising, but since heat transport is slower than water transport it is not certain that the particles will become supersaturated – the condensation could take place on the walls of the cooler instead.

The method of pre-processing is usable when only a fraction of the material on particles is volatile and when they the shape of the processed particle does not differ too much from the real exposure.

Measurement of the size shift and correction afterwards

Particles of a well defined size could be selected with a DMA, inhaled and thereafter size classified with an SMPS system. Alternatively a TDMA set-up could be used. The problem is the high accuracy needed. The size shift could vary with time and breathing parameters. In practice this method is only valid for a well defined aerosol with a relatively small size shift. It has its main usefulness to check that the diameter change is within acceptable limits. If the shift could be modelled and explained by a theoretical model it is an advantage, as in the case of the DEHS particles in Paper II.

Processing the inhaled aerosol sample

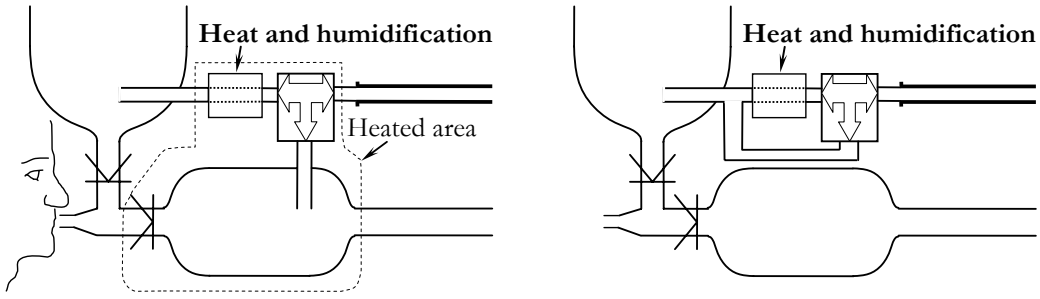


Figure 10 Processing of the inhaled sample; to the left during exposure and to the right the switch-over to measure losses and transformation in the processing unit.

By processing only the particles *sampled* by the instrument from the inhaled air the two size distributions could be compared with a minor error because of size shift (Figure 10). The measured sample of inhaled particles is exposed to the same

humidity as in the respiratory tract and a heating that leads to a corresponding evaporation. Since the particle losses during this processing can be determined with high (± 1%) accuracy, the respiratory tract deposited fraction can be calculated as

$$DF = 1 - \frac{C_{ex}\left(1 - DF_{losses\ proc.}\right)}{C_{in}\left(1 - DF_{losses\ instr.}\right)}$$

where C_{ex} is the number concentration of the exhaled particles, C_{in} the number concentration of the inhaled particles after the processing, $DF_{losses\ proc.}$ the deposited fraction during the processing of the inhaled sample and $DF_{losses\ instr.}$ the deposited fraction in the instrument between the inhaled and exhaled air.

The processing of the particles is made by leading them through a 10 cm long Gore-Tex tube in a bottle of hot water. The humidity becomes close to, or just above, saturation when the aerosol is cooled in the tubing before it enters the valve that switches between inhaled and exhaled sample. A temperature sensor in the water, a temperature/RH-sensor before the valve and slight condensation in the tubing confirms the high RH. The losses in this processing are about 10% for 20 nm particles and 1-2% for particles above 100 nm (measured for traffic aerosols in Copenhagen).

The approach to process only the sample of the inhaled aerosol has several advantages. Firstly the subject inhales the unprocessed aerosol. Secondly it is technically easier to process a steady airflow of about 1 L/min than processing all inhaled air. Thirdly the problem of size shifts by evaporation is dealt with in a better way since the inhaled and exhaled sample could be adjusted to evaporate approximately the same amount. The size distribution of particles before the shift can be obtained either by measuring the shifts with a TDMA or by running RESPI between the processing line and an equally long line without processing. In this case it is not critical to know the shift with less than 1% uncertainty.

Some potential errors may occur also for this method. It assumes that a particle that is deposited before its dry mobility diameter is shifted is deposited with approximately the same probability as if the size shift had taken place. This approximation is in most cases good. Furthermore it is difficult to achieve an RH of 99.5% in the processing line. If the sample becomes supersaturated the diameter change might be altered. However, these shortcomings are probably minor compared to those for the other methods.

Results and Discussion

Reliability of the measurements with RESPI

As shown in the Method section, all identified technical difficulties identified are encountered for in RESPI. A systematic experimental validation is given in Paper I. As illustrated in Figure 11 the results from RESPI agrees well with the only two previous publications with hygroscopic UFPs and with the ICRP model if the deposition curve is shifted for the growth of NaCl at 99.5% RH. However, the resolution is higher and the time to perform a measurement lower.

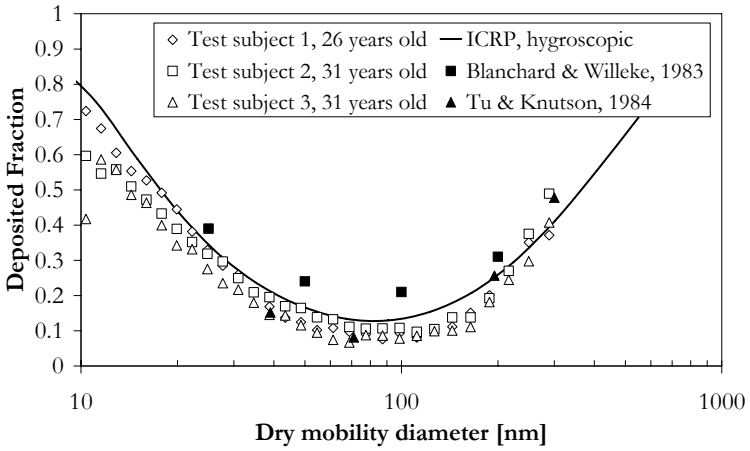


Figure 11 RESPI measurements compared to the only two previous measurements of hygroscopic UFPs (Blanchard and Willeke 1984;Tu and Knutson 1984).

Because the values obtained in some measurements seemed to be higher than expected from the ICRP model (Paper II, Figure 6), additional tests have been made. It was hypothesised that the loss correction was inadequate since the sinus breath pump, used to simulate breathing without deposition, was not connected to the mouthpiece (Paper I, Figure 3). However, as illustrated in Figure 12, the control measurements of the losses were insignificantly different from the original.

There is reason to believe that the slightly higher DF measured with RESPI compared to ICRP estimates is reliable. One probable explanation is that our subjects were breathing spontaneously (see Figure 5). But it is not unlikely that the model underestimates the DF. It seems the hydrophobic aerosols used in some experimental studies contain soluble ions, as for example when the oil particles are generated with a NaCl core (Kim and Jaques 2005). One group employ kerosene particles, which could be somewhat hygroscopic and furthermore restructure because of their agglomerated shape (Tu and Knutson 1984). This would lower the

deposition for the UFP:s. There are also studies where monodisperse particles are selected with a DMA and as Blanchard and Willeke (1984) points out a fraction of multiply charged particles with another mobility equivalent diameter will alter the measured DF. As mentioned previously most studies do not take the dead space in the mouthpiece into account which would increase the DF.

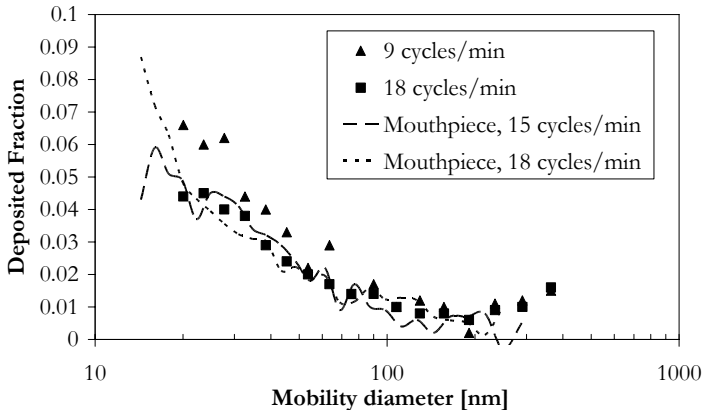


Figure 12 Previous measurements (triangles, squares) where the breath simulator was connected to the inhalation tank (from Paper I, Figure 3) and more recent (lines) where it was connected to the mouthpiece instead. It is more than one and a half year between the measurements, which show that the system is stable over time.

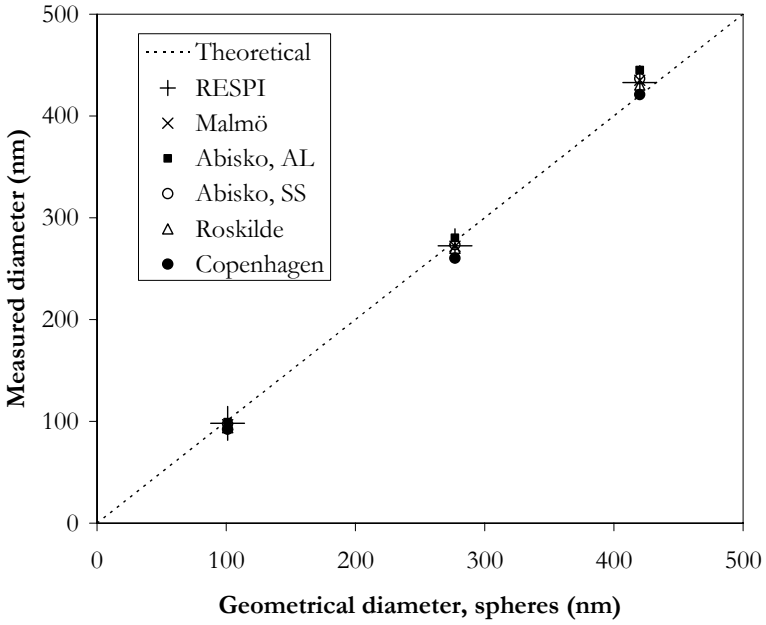


Figure 13 Intercomparison of Nordic SMPS/DMPS systems.

In the ongoing intercomparison of Nordic SMPS/DMPS systems it is demonstrated that RESPI measures the size of the particles with high accuracy (Figure 13). All systems, including RESPI, overestimated the diameter of the 420 nm spheres with 14 ± 8 nm (3.2% ± 2%). No satisfactory explanation for this has been found, but in a next step the size could be measured with electron microscopy.

Respiratory tract deposition measurements

RESPI was built for studies of respiratory tract deposition of ambient aerosols on field campaigns. DF of particles from biomass combustion and an urban street canyon has been measured, though not yet published in peer-reviewed papers (Löndahl et al. 2006a; Löndahl et al. 2006b). Although, in the first project DF of salt and oil particles were investigated (Paper II).

Figure 14 shows DF of hydrophobic and hygroscopic aerosol particles during both rest and exercise, measured for a group of 29 healthy volunteers. For most sizes there is no significant difference between rest and exercise, despite the volume breathing flow is about four times higher in the latter case. The subjects were breathing spontaneously and an explanation of the similarities in DF can be that the increase in tidal volume was compensated by the breathing frequency to maintain the DF on a constant level. A higher tidal volume increases deposition while a higher breathing frequency decreases it. No gender differences in DF were observed, but the intersubject variability was substantial (more than a factor two).

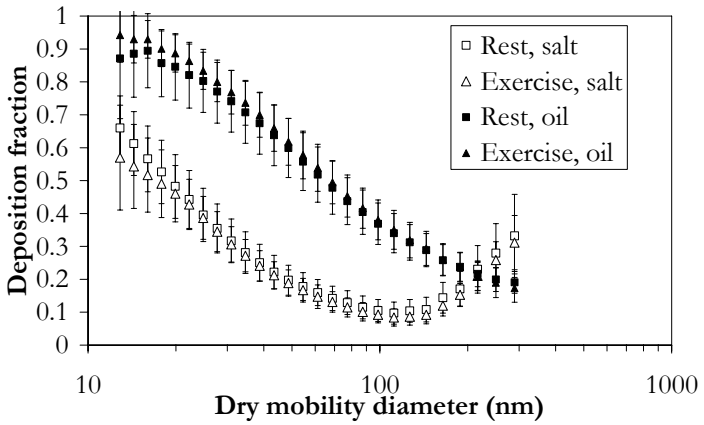


Figure 14 Deposition of hydrophobic and hygroscopic particles during rest and exercise.

Aerosol particles from different kinds of combustion of woody biomass showed a low respiratory tract deposition compared to the hydrophobic reference aerosol particles (Figure 15). According to the preliminary analysis, the total number of deposited particles was 0.21 and 0.24 for the efficient and low-temperature combustion particles respectively. This can be due to their size-dependent hygroscopic properties. However, the DF of traffic particles was high, more than twice as much as for the biomass particles. This was due to the small size of the traffic particles, which increase the deposition by diffusion and that they were almost hydrophobic. These two studies clearly demonstrate that the deposited dose of some aerosols can be considerably higher than for others during the same exposure conditions. It could be concluded that twice as high emissions should be allowed for particles from biomass combustion compared to traffic, at least for the number concentration.

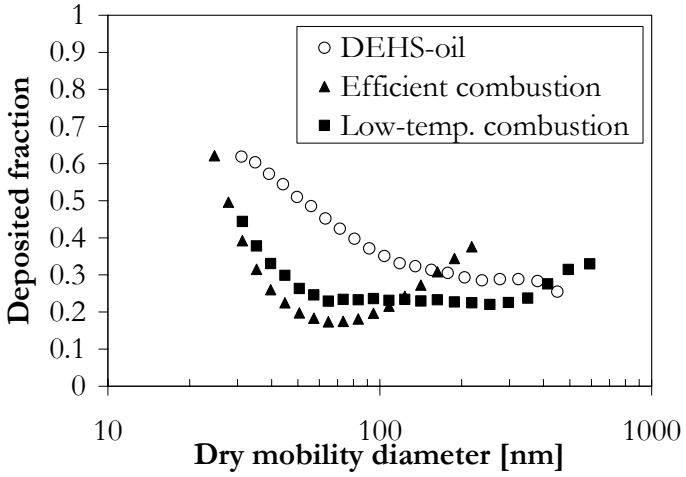


Figure 15 Deposition Fraction (DF) of biomass particles compared to a hydrophobic reference.

Methodology for source determination indoors

Paper III describes a methodology for identification of sources to aerosol particles indoors, but furthermore a hygiene problem is implied. In this small study it was found that particles from laundry detergents can be a major source of airborne particles indoors (Löndahl et al. 2004). Since introduced 1976 in phosphate free detergents, the market for zeolites has grown rapidly. Year 2000 the consumption was 650 000 tons in Europe (HERA, Zeolite A 2004).

There are several reasons for concern about health effects from zeolites. The mean size of zeolite particles is 3.5 μm (Zeolites for detergents 2000). This means that a large part of the particles belong to the respirable fraction and are able to penetrate to the alveolar region. Exposure studies have been done (HERA, Zeolite A 2004;Gloxhuber et al. 1983), but these are not conclusive, especially with respect to the character and suspected extent of the emissions. First of all, they estimate the exposure concentration only from the filling of the washing machine where an amount of 0.1 μg per cup is supposed to mix with the air. The water insoluble particles attached to the textiles and are not considered. We found peak concentrations corresponding to mass concentrations above 1000 $\mu g/m^3$ during laundry in the houses with zeolite detergents, i.e. more than 10,000 times higher than could be expected from the previous studies. Secondly, it is difficult to extrapolate the effects found on about 100 rats and hamsters and six monkeys to the whole European population. Even a minor relative risk could mean thousands of respiratory diseased when millions of people are exposed, as is the case for ambient air pollution. Thirdly, negative effects were found in some of the studies reported (HERA, Zeolite A 2004), as bronchiolitis and alveolitis in one of the

monkeys. Two of the four described studies were terminated because of sudden incidences of deaths among the animals, in both the exposed and control groups.

There are detergents free from both phosphates and zeolites on the market, but considering the results of Paper III it is noteworthy that several countries and, judging from the election promises, soon also Sweden, have legislated against detergents containing phosphate without a more substantial risk evaluation of those with zeolites, which is the most common alternative. Epidemiological studies are needed as well as new, well-documented, toxicological ones.

Conclusion and Outlook

Paper I-III cover different aspects of inhalable particles; measurement (I), deposition (II) and identification (III). It has been shown experimentally and argued theoretically that the respiratory tract deposition of aerosols could vary substantially depending on source, exposure conditions and individual. Nevertheless, dose estimates in toxicological studies are often limited to calculating the exposure concentration multiplied by the exposure duration. This is relevant when relating the effects to levels measured at ambient monitoring stations, but insufficient when trying to understand the mechanisms behind the effects.

A number of ongoing and future projects are planned related to respiratory tract deposition. Diesel particles will be studied in Umeå. Particle concentrations are measured since 2000 at a rural background station (Vavihill, Söderåsen) and at urban roof top level (Rådhuset, Malmö). These data could be used to estimate a dose for the population. Further, it would be of interest to measure deposition at different inhalation temperatures. If cold inhaled air becomes supersaturated, as calculations indicate (Ferron et al. 1984;Ferron and Hornik 1984), the deposition would be completely altered. This has not been verified experimentally. There is also a lack of data for several susceptible subgroups, especially for children and elderly. With a sufficient amount of data it would be possible to look for predictors of deposition, such as gender, smoking status, BMI, age etc. It has been discussed to add an APS to RESPI to be able to measure DF in a larger size range.

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Paper I

A Set-up for Field Studies of Respiratory Deposition in Humans

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Massling, A. and Bohgard, M.

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Paper II

Size-Resolved Respiratory Tract Deposition of Fine and Ultrafine Hydrophobic and Hygroscopic Particles during Rest and Exercise

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