Journal of Nanoparticle Research (2007) 9:53–59
DOI 10.1007/s11051-006-9156-8

Special focus: Nanoparticles and Occupational Health

Rationale and principle of an instrument measuring lung deposited nanoparticle surface area

H. Fissan*, S. Neumann, A. Trampe, D.Y.H. Pui and W.G. Shin
*Universität Duisburg-Essen, Ingenieurwissenschaften, Nanostrukturtechnik, Bismarckstr. 81, D-47048, Duisburg, Germany; *Author for correspondence (Tel.: +49-203-3793201; Fax: +49-203-3793268; E-mail: heinz.fissan@uni-due.de)*

Received 27 July 2006; accepted in revised form 2 August 2006

Key words: nanotechnology, nanoparticles, aerosol, health risk, exposure control, exposure measurement, lung deposited surface area, lung simulator, Electrical Aerosol Detector (EAD), Occupational health

Abstract

The risk of nanoparticles by inhalation for human health is still being debated but some evidences of risk on specific properties of particles <100 nm diameter exist. One of the nanoparticle parameters discussed by toxicologists is their surface area concentration as a relevant property for e.g. causing inflammation. Concentrations of these small particles ($\sim <100$ nm) are currently not measured, since the mass concentrations of these small particles are normally low despite large surface area concentrations. Airborne particles will always be polydisperse and show a size distribution. Size is normally described by an equivalent diameter to include deviations in properties from ideal spherical particles. Here only nanoparticles below a certain size to be defined are of interest. Total concentration measures are determined by integration over the size range of interest. The ideal instrument should measure the particles according to the size weighting of the wanted quantity. Besides for the geometric surface area the wanted response function can be derived for the lung deposited surface area in the alveolar region. This can be obtained by weighting the geometric surface area as a function of particle size with the deposition efficiency for the alveolar region for e.g. a reference worker for work place exposure determination. The investigation of the performance of an Electrical Aerosol Detector (EAD) for nearly spherical particles showed that its response function is close to the lung deposited surface areas in different regions of the human respiratory system. By changing the ion trap voltage an even better agreement has been achieved. By determining the size dependent response of the instrument as a function of ion trap voltage the operating parameters can be optimized to give the smallest error possible. Since the concept of the instrument is based on spherical particles and idealized lung deposition curves have been used, in all other cases errors will occur, which still have to be defined. A method is now available which allows in principle the determination of the total deposited surface area in different regions of the lung in real time. It can easily be changed from one deposited region to another by varying the ion trap voltage. It has the potential to become a routine measurement technique for area measurements and personal control in e.g. work place environments.

Introduction

Nanotechnology offers great opportunities for new and improved nanostructured, functionalized materials and devices. Besides thin films the most important building blocks are nanoparticles (Kruis et al., 1998), which can be produced in a solid, liquid or gaseous matrix. Product nanoparticles

are mostly defined to be smaller than 100 nm and down to a few nanometers. The upper size limit is depending on the problem raised and will be defined in this paper for the case of measuring lung deposited nanoparticle surface area. To make use of some of these properties, nanoparticles have to be single isolated particles. In other cases they may consist of aggregated and agglomerated primary nanoparticles.

The mass production of nanoparticles in the gas phase has several advantages, because clean and continuous processing is possible. On the other hand nanoparticles in the gas phase have a high mobility. There are increasing chances for them to escape during gas phase processing, handling and use, than in liquid processes. The particles emitted to work places or more generally into the environment are easily transported with the gas flow to human lungs. They are inhaled and deposited in the nose or mouth and in different parts of the lung. They either may cause negative health effects at the point of deposition or may be transmitted to other end organs (Kreyling et al., 2002; Oberdörster et al., 1995).

The risk of nanoparticle intake is dependent on exposure and hazard. Here we are interested in exposure measurement. For this purpose, monitors for exposure control are needed in the work place, controlling either an area or a person at the point of possible nanoparticle intake. We are introducing a new concept based on an existing instrument for area monitoring, which allows the measurements of the nanoparticle surface area deposited in different parts of the human respiratory system.

Nanoparticle surface area measurement

The measurement objects of current interest are nanoparticles (< 100 nm). Most standards set up by different organizations all over the world for work place measurement thus far are based on mass concentration limits. Mass measurement methods are not sufficiently sensitive for airborne nanoparticles and may not be sensitive toward the specific health relevant properties of nanoparticles. The most sensitive concentration measure in this particle range (< 100 nm diameter) is the number concentration. Unfortunately the number concentration is dominated by very small particles, which are difficult to measure because of increasing line losses and decreasing counting efficiency with decreasing particle size for all counters.

On the other hand the most important question, which has yet to be raised, is whether the number concentration correlates with health effects. This is true for asbestos fibers with a certain probability for each fiber to cause a negative health effect and may be also for nanoparticles in case of clogging after penetrating into the blood. For nanoparticles, toxicologists discuss the particle surface area among others as a relevant measure (Oberdörster, 1996; Donaldson et al., 1998), because most of the processes in the human body environment take place via the particle surface, which is increasing significantly with decreasing particle size in the nanometer size range for the same amount of mass. The health effects after intake are strongly depending also on the deposition regions. Particularly discussed are the deposition in the nose (head), because of possible transfer of nanoparticles to the brain, the tracheobronchial region as well as the alveolar region, because of inefficiency of clearing mechanism and the possible transfer to the blood circulation system with resulting distribution in several end organs (Kreyling et al., 2002).

In Figure 1 the deposition curves for head (H), tracheobronchial (TB) and alveolar (A) deposition are shown. They were obtained using the UK National Radiological Protection Board's (NRPB's) LUDEP Software (James et al., 2000), based on the recommendations of ICRP Publication 66 (ICRP, 1994). Different people performing different activities have different deposition curves. We have chosen a reference worker with the following conditions:

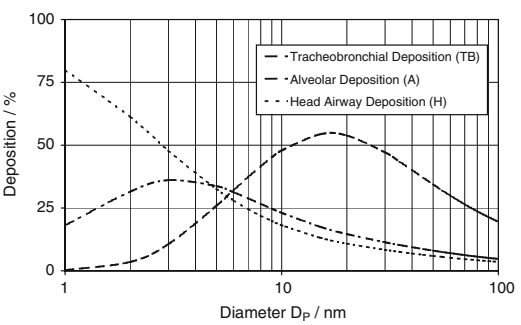

Figure 1. Deposition curves (James et al., 2000).

– Breathing type: nose only
– Functional residual capacity: 3301 cc
– Breathing rate (Breath/min): 20
– Ventilation rate: 1.5 m^3/h
– Activity level: light exercise

From all these considerations it follows that an instrument is needed, which is capable of measuring the total nanoparticle surface area fractions originating from nanoparticle processing, which are deposited in different parts of the human respiratory system.

Needed instrument response

To be able to perform on-line measurements and easy data evaluation the instrument should deliver an electrical signal. If possible, the wanted instrument should have a linear response to particle surface area. Using monodisperse, spherical particles of known size the instrument then can be calibrated by performing parallel number concentration measurements. Knowing number concentration and particle size the surface can easily be calculated. For each size a calibration factor can be determined. Since the calibration is based on electrical mobility diameter of spheres for sizing and the unipolar charging for the generation of the electrical signal, only an equivalent surface concentration based on these processes can be determined in case of agglomerates.

Most emitted particles are distributed as a function of size. If we want to measure the total concentration of a polydisperse aerosol (total number, -surface area, -mass or other -weighted quantities), the instrument has to show a certain size dependent sensitivity depending on the size weighting of the wanted quantity. This sensitivity can be derived by describing the integral over the size distribution by its sum. Each size increment in the sum is proportional to the number concentration times the corresponding diameter weighting, in case of geometric surface area, D_p^2. To normalize the size dependant response with respect to the number concentration, 100 nm particles have been chosen as a reference and their normalized sensitivity has been set to be 1. The needed sensitivities as function of particle size are shown in Figure 2. The surface area shows a D_p^2-dependency and the number is independent of particle size (D_p^0). If we now weight the sensitivities for geometric surface area with the corresponding deposition curves (deposition efficiencies η, see Figure 1), we simulate the deposition in the different regions of the human respiratory system. In Figure 2 the needed response functions for head, tracheobronchial and alveolar depositions are shown. They are nonlinear and less steep compared with the response function for geometric surface area, but further away from the constant curve for number concentration.

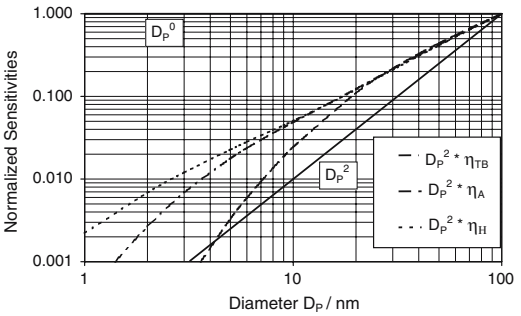

Figure 2. Response function for lung deposited surface area in comparison with response function for number concentration (D_p^0) and geometric surface area (D_p^2).

Instruments based on diffusion charging and their response functions

Diffusion charging is a process which is at least in certain particle size regions proportional to particle surface (Rogak et al., 1993; Jung & Kittelson, 2005). Depending on instrument design the sensitivity as a function of particle size, i.e. the response function, is different because of differences in the charging process and particle losses. Ku and Maynard (2005) have recently shown that the Matter instrument, Switzerland, e.g., the instrument LQ1-DC, does show a D_p^2-dependency in the size range between 30 and 100 nm. Above 100 nm and below 30 nm the sensitivities are smaller then the one needed for a D_p^2-dependency. For these studies monodisperse silver agglomerates were used, synthesized by evaporating silver in a ceramic boat in a furnace. In the cold carrier gas (nitrogen) silver particles were formed, which agglomerated rapidly. In a second oven they were heat treated (Kruis & Fissan, 1999). The polydisperse aerosol was size fractionated using a Differential Mobility Analyzer (DMA). With a second

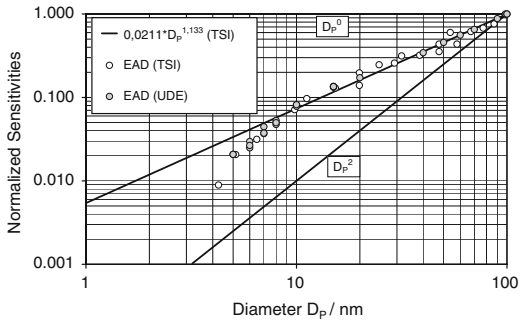

Figure 3. Response function of EAD 3070A.

furnace the particles were sintered at increasing temperature, which did not lead to significant differences in the response function. This demonstrates that the sensitivity is not a strong function of the shape of the particles. They can be assumed to behave like spherical silver particles with the same electrical mobility as the agglomerates.

We performed similar experiments with the Electrical Aerosol Detector (EAD)/TSI 3070A, using unsintered silver agglomerates (see Figure 3). Between 10 nm and 100 nm the normalized sensitivity can be described by the function $0.0211 \cdot D_p^{1.133}$. Below 10 nm the response function drops more sharply compared with the given function. Our data compare well with earlier data given by the manufacturer (Kaufman et al., 2002). If we compare this function with the weighted response functions for lung deposited surface areas (see Figure 2) they match well in the size range 20–100 nm. This brought up the idea to manipulate the EAD response so that it matches better the needed responses for different weightings of lung deposition.

Modification of EAD to measure lung deposited surface area

The EAD consists of a charging chamber where the aerosol is mixed with positively charged ions, which attach to the particles by diffusion. The unipolarly charged aerosol with residual ions is then introduced into an ion trap to which a voltage of 20 V is applied. The highly mobile residual ions are eliminated in the electric field. The charged particles are then collected in a filter downstream of the ion trap which is part of a sensitive electrometer to measure the current caused by the deposited charges. The response function of the instrument changes with the applied voltage to the ion trap, because with increasing voltage particles are also eliminated. The instrument was challenged with differently sized, monodisperse silver nanoparticles in the size range between 10 and 100 nm with an ion trap voltage between 20 and 200 V. The result is shown in Figure 4. The normalized sensitivity is 1.0 for the reference case of 100 nm particles. For all voltages it is decreasing with decreasing particle size, because of a reduction of the average charge level. With decreasing particle size and increasing ion trap voltage the particle losses in the trap also increase causing a further reduction in normalized sensitivity. In Figure 5 the response functions for different ion trap voltages derived from the data in Figure 4 are shown as function of particle size for better comparison with the response functions shown earlier. Especially in the small size range the normalized sensitivity drops more steeply with

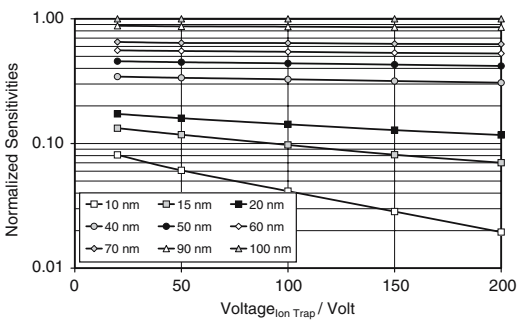

Figure 4. Normalized sensitivities as function of ion trap voltage for different sized particles.

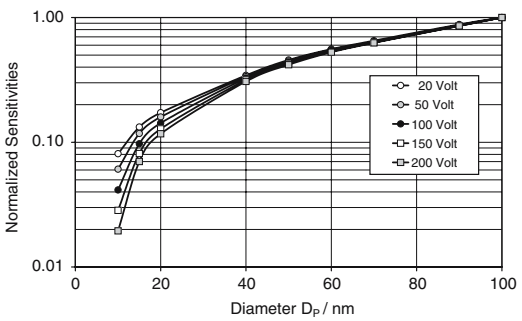

Figure 5. Response functions for different ion trap voltages.

increasing voltage. With increasing voltage larger amounts of small particles are eliminated, causing an increasing drop in normalized sensitivity. Major changes occur only below 40 nm. By eye fitting we have chosen the response function for 100 V ion trap voltage to be a close fit to the needed response function for tracheobronchial deposition. In Figure 6 the measured response function for 100 V ion trap voltage is compared with the response function for tracheobronchial deposition. A deviation occurs only for the very small (<10 nm) particles. For 200 V a good comparison is achieved for the alveolar deposition (Figure 7). The differences between the normalized response functions for alveolar and trachiobronchial deposition are rather small. The main difference is caused by the difference in deposition efficiency at the reference point. This is taken into account through the calibration, which includes the different deposition efficiencies at the reference point of 100 nm particle size. The described procedure for determining the normalized sensitivity as function of particle size allows also the determination of the calibration curves. Multiplying the normalized sensitivities with different number concentrations allows the determination of the lung deposited surface area as function of electrometer current. As long as the response function of the instrument is equal to the needed response function for different particle sizes the data from all measurements can be taken to construct the calibration curve (Figure 8), since they all lead to the same calibration factor. The calibration curves are-linear in the covered concentration range and can be described by the given simple functions. In Figure 9 the calibration factors are plotted as function of particle size. The dotted lines refer to an exceptable error of $\pm 25\%$. In both cases, tracheobronchial and alveolar deposition, the calibration factors are outside of this range only below 10 nm. Fortunately the error contribution to the total surface area of a

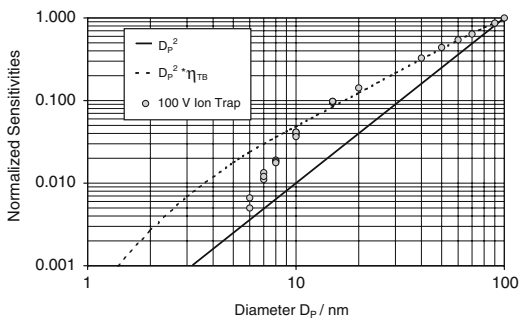

Figure 6. Response function of EAD 3070A – 100 V ion trap.

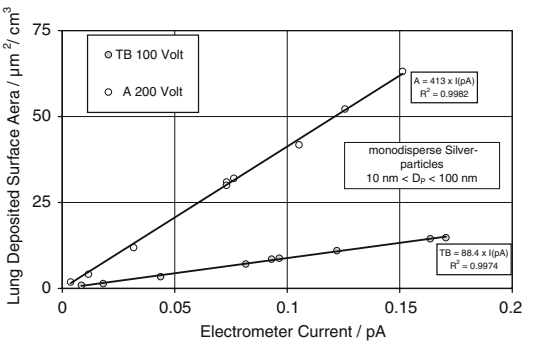

Figure 8. Calibration curve for EAD for tracheobronchial and alveolar lung area (Lung Simulator).

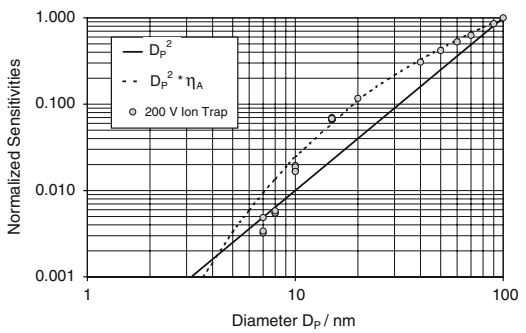

Figure 7. Response function of EAD 3070A – 200 V ion trap.

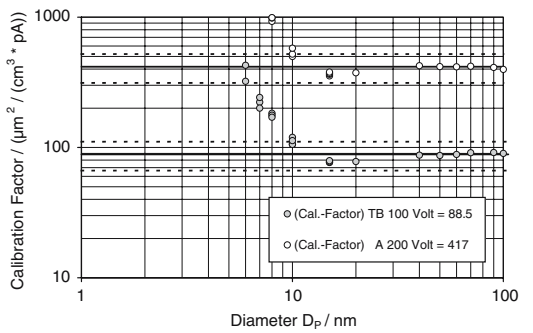

Figure 9. Calibration factor as function of particle size for 100 and 200 V.

polydisperse aerosol by smaller particles is *negligible* because of the D_p^2-dependency. The surface area contribution of a 10 nm particle is only 1% of that of a 100 nm particle.

Up to now we assume that the instrument cuts out all particles larger than 100 nm. This may not be possible, causing large errors. Another upper limit could be the minimum in the deposition curves around 300 nm to include all deposited small particles. Above ~400 nm the deposition curves become density dependent and therefore material dependent.

In any case it still has to be shown that the response function of the instrument in the size range between 100 nm and any larger size follows the needed response function.

Optimal ion-trap voltage

Under certain conditions the available performance data (Figure 4) can be used to choose optimal ion-trap voltages for which the error is minimal. The absolute error in the measured total deposited surface area is depending on the actual size distribution, which we don't know *a priori*. We assume a constant number distribution over the particle size range between 10 and 100 nm. The real size distribution of nanoparticles will normally show smaller number concentrations at both ends of the covered size range between 10 and 100 nm compared with the maximal concentration. This leads to an overestimation of the error at both ends of the size range. The error contribution of the small particles is small, because of the D_p^2 dependency. At the upper end of the size distribution the influence on the sum of errors becomes more important.

We can interpolate or calculate the fitted normalized sensitivities for each ion-trap voltage between 20 V and 200 V for measured particle diameters. The normalized sensitivities for the wanted response function are calculated as described earlier. The squared differences between the calculated normalized sensitivities for a given ion-trap voltage and wanted sensitivity at measured particle diameter are calculated and summed up. Figure 10 shows the results for tracheobronchial, alveolar and head airways deposition. The minimum of these curves of the sum of the errors in case of a constant size distribution within the size range of 10–100 nm represent the optimal ion-trap voltages, where both response functions show the best agreement.

Table 1 shows the optimal voltages and least square sums for the different deposition areas. Also the calibration factor has been derived. For comparison the applied voltages and their corresponding data are also shown. The differences in least square sum as well as in calibration factor are not very large between the different deposition areas. This is due to the fact that the major differences in the response functions occur below

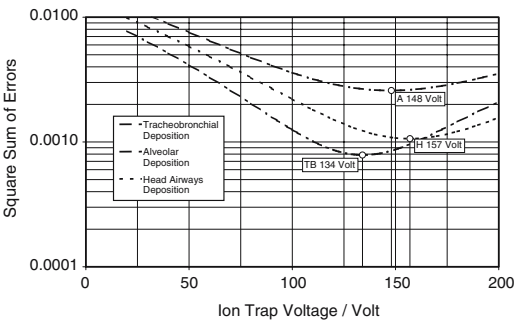

Figure 10. Determination of optimal ion trap voltage.

Table 1. Optimal ion trap voltages

Lung deposition	Measured ion-trap voltage	Optimal ion-trap voltage	Least square sum	Calibration factor
Tracheobronchial deposition	20 V		0.00774	83.3 $\mu m^2/(cm^3 * pA)$
	100 V		0.00125	89.7 $\mu m^2/(cm^3 * pA)$
		134 V	0.00079	92.5 $\mu m^2/(cm^3 * pA)$
Alveolar deposition	20 V		0.01213	347 $\mu m^2/(cm^3 * pA)$
		148 V	0.00259	391 $\mu m^2/(cm^3 * pA)$
	200 V		0.00353	409 $\mu m^2/(cm^3 * pA)$
Head airway deposition	20 V		0.00987	62.4 $\mu m^2/(cm^3 * pA)$
		157 V	0.00106	70.7 $\mu m^2/(cm^3 * pA)$

10 nm, a size range, which does not contribute much to the total surface of a polydisperse aerosol, even if we consider only particles below 100 nm.

Summary

Modifications of the EAD with different ion trap voltages have been tested with the goal of determining the deposited nanoparticle surface area for different regions of the human respiratory system. We have demonstrated that this can be achieved for nanoparticles below 100 nm. The investigation was performed using agglomerated silver nanoparticles. Further studies need to be conducted to investigate what influence different particle shapes and materials may have. Also further studies on the possibilities of modifying the response to get better agreement for different wanted response functions should be investigated. For reference cases additional quantities like dose, dose per lung area or lung mass may easily be derived.

References

Donaldson K., X.Y. Li & W. MacNee, 1998. Ultrafine (nanometer) particle mediated lung injury. J. Aerosol Sci. 29(5–6), 553–560.

ICRP., 1994. International Commission on Radiological Protection Publication 66 Human Respiratory Tract Model for Radiological Protection. Oxford, Pergamon: Elsevier Science Ltd.

James A.C., M.R. Bailey & M-D. Dorrian, 2000. LUDEP Software, Version 2.07: Program for implementing ICRP-66 Respiratory tract model. RPB, Chilton, Didcot, OXON. OX11 ORQ UK.

Jung H. & D. Kittelson, 2005. Measurement of electrical charge on diesel particles. Aerosol Sci. Technol. 39(12), 1129–1135.

Kaufman S.L., A. Medved, A. Pöcher, N. Hill, R. Caldow & F.R. Quant, 2002. An electrical aerosol detector based on the corona-jet charger. AAAR conference (poster).

Kreyling W.G., M. Semmler, F. Erbe, P. Mayer, S. Takenaka, H. Schulz, G. Oberdörster & A. Ziesenis, 2002. Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. J. Toxicol. Environ. Health Pt A 65(20), 1513–1530.

Kruis F.E., H. Fissan & A. Peled, 1998. Synthesis of nanoparticles in the gas phase for electronic, optical and magnetic application – A review. J. Aerosol Sci. 29(5–6), 511–535.

Kruis F.E. & H. Fissan, 1999. Nano-Process Technology for Synthesis and Handling of Nanoparticles. Kona Powder and Particles, No.17, pp. 130–139.

Ku B.K. & A.D. Maynard, 2005. Generation and investigation of airborne Ag nanoparticles with specific size and morphology by homogeneous nucleation, coagulation and sintering. J. Aerosol Sci. 36(9), 1108–1124.

Oberdörster G., R.M. Gelein, J. Ferin & B. Weiss, 1995. Association of particulate air pollution and acute mortality: Involvement of ultrafine particles. Inhal. Toxicol. 7, 111–124.

Oberdörster G., 1996. Significance of particle parameters in the evaluation of exposure-dose–response relationships of inhaled particles. Particul. Sci. Technol. 14(2), 135–151.

Rogak S.N., R.C. Flagan & H.V. Nguyen, 1993. The mobility and structure of aerosol agglomerates. Aerosol Sci. Technol. 18(1), 25–47.