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SOURCE SPECIFIC RISK ASSESSMENT OF INDOOR AEROSOL PARTICLES

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Academic dissertation

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Antti Joonas Koivisto
University of Helsinki, 2013

Abstract

In the urban environment, atmospheric aerosols consist mainly of pollutants from anthropogenic sources. The majority of these originate from traffic and other combustion processes. A fraction of these pollutants will penetrate indoors via ventilation. However, indoor air concentrations are usually predominated by indoor sources due to the small amount of dilution air. In modern societies, people spend most of their time indoors. Thus, their exposure is controlled mainly by indoor concentrations from indoor sources.

During the last decades, engineering of nanosized structures has created a new field of material science. Some of these materials have been shown to be potentially toxic to human health. The greatest potential for exposure to engineered nanomaterials (ENMs) occurs in the workplace during production and handling of ENMs. In an exposure assessment, both gaseous and particulate matter pollutants need to be considered. The toxicities of the particles usually depend on the source and age. With time, particle morphology and composition changes due to their tendency to undergo coagulation, condensation and evaporation. The PM exposure risk is related to source specific emissions, and thus, in risk assessment one needs to define source specific exposures.

This thesis describes methods for source specific risk assessment of airborne particulate matter. It consists of studies related to workers' ENM exposures during the synthesis of nanoparticles, packing of agglomerated TiO_2 nanoparticles, and handling of nanodiamonds. Background particles were distinguished from the ENM concentrations by using different measurement techniques and indoor aerosol modelings. Risk characterization was performed by using a source specific exposure and calculated dose levels in units of particle number and mass. The exposure risk was estimated by using non-health based occupational exposure limits for ENMs. For the nanosized TiO_2, the risk was also assessed from dose-biological responses which had been extrapolated from inhalation studies conducted in mice. The ENM exposure levels were compared with background particle concentrations in order to determine the relevant ENM exposure metrics and exposure scenarios.

Keywords: aerosol, exposure, dose, risk, nanomaterial

Contents

List of publications

This thesis consists of an introductory review, followed by four peer-reviewed research articles. In the introductory part, these papers are cited according to their roman numerals. The articles are reproduced with the kind permission of the journals concerned.

I Koivisto, A.J., Hussein, T., Niemelä, R., Tuomi, T., Hämeri, K. (2010). Impact of particle emissions of new laser printers on modeled office room. *Atmos. Environ.* 44:2140–2146.

II Koivisto, A.J., Mäkinen, M., Rossi, E.M., Lindberg, H.K., Miettinen, M., Falck, G.C.-M., Norppa, H., Alenius, H., Korpi, A., Riikonen, J., Vanhala, E., Vippola, M., Pasanen, P., Lehto, V.-P., Savolainen, K., Jokiniemi, J., Hämeri, K. (2011). Aerosol characterization and lung deposition of synthesized TiO_2 nanoparticles for murine inhalation studies. *J. Nanopart. Res.* 13:2949–2961.

III Koivisto, A.J., Aromaa, M., Mäkelä, J.M., Pasanen, P., Hussein, T., Hämeri, K., (2012). Concept to estimate regional inhalation dose of industrially synthesized nanoparticles. *ACS Nano* 6:1195–1203.

IV Koivisto, A.J., Lyyränen, J., Auvinen, A., Vanhala, E., Hämeri, K., Tuomi, T., Jokiniemi, J. (2012) Industrial worker exposure to airborne particles during the packing of pigment and nanoscale titanium dioxide. *Inhal. Toxicol.* 24:839–849.

1 Introduction

The air that we breathe contains both gaseous and particulate matter (PM) pollutants. These originate mainly from natural sources but the fraction of anthropogenic pollutants has been growing since the industrial revolution in the 18th century, mostly due to fossil fuel combustion (Lefohn et al., 1999; Streets et al., 2009). Urban air pollution is recognized as a major contributor to the global burden of disease (Ezzati et al., 2002; Brunekreef and Holgate, 2002). Increases in atmospheric particulate matter <10 μm [PM_{10}] are associated with morbidity and mortality due to pulmonary and cardiovascular diseases (Pope, 2000; Anderson, 2009; Franchini and Mannucci, 2012; Kelly and Fusell, 2012), central nervous system disease (Block and Calderon-Garciduenas, 2009), and different adverse pregnancy outcomes (Dadvand et al., 2013).

According to epidemiological data, an increase of 10 μg m^{-3} in urban aerosol PM_{10} concentration increases cardiovascular mortality by nearly 1 % (Anderson, 2009). For example, in 2005, an estimated 5 million years of life were lost due to fine particulate matter <2.5 μm [$PM_{2.5}$] pollution in Europe (EEA, 2010), which originates mainly from anthropogenic sources, such as traffic and local combustion sources (Almeida et al., 2005). Recently, ultrafine particulate matter <0.1 μm [$PM_{0.1}$] has been assessed as being the most harmful fraction with respect to pulmonary uptake (Seaton, 1995; Peters et al., 1997; Donaldson et al., 2001; Oberdörster et al., 2001, 2002; Nel, 2005; Politis et al., 2008). This is because ultrafine particles are efficiently deposited in all regions of the respiratory tract in the human lung, they evade specific defence mechanisms, and they can translocate out of the respiratory tract via a variety of pathways and mechanisms (Oberdörster et al, 2005; Oberdörster, 2010; Geiser and Kreyling, 2010).

At the end of 20th century, a new field of technology called nanotechnology was discovered (Siegel et al., 1999; Roco, 2011). Nanotechnology refers to the engineering of functional systems at the molecular scale. One common property for engineered nanomaterials (ENMs), such as nanoparticles (NPs), nano-objects, nano-fibers, and nanoplates, is that they have at least one dimension less than 100 nm (ISO, 2008; Kreyling et al., 2010). These ENMs are used in a huge range of applications for example energy, electronics, paper, cosmetics, textiles, nutrition, and medical drugs. Nanotechnology is one of the fastest growing and most promising technologies in advanced societies (OECD, 2009a; Roco, 2011). For example, the European Union has identified nanotechnology as one of the Key Enabling Technologies, and it is believed

that it will employ 400 000 persons in Europe by 2015 (EC, 2012). Nanotechnology endows technological benefits, but on the other hand, ENMs have been claimed to pose new challenges in safety issues. This is because the potential toxicities of ENMs are far from clear (see for example reviews by Borm et al., 2006; Nel, 2006; Xia et al., 2009; Savolainen et al., 2010; Yokel and MacPhail, 2011).

Some nanomaterials have been produced since the 1980s, such as TiO_2 and SiO_2 NPs, but since the year 2000, production and use of many new ENMs has increased spectacularly (Piccinno et al., 2012). These new materials have given birth to a new field of toxicology, called nanotoxicology that examines the toxicity associated with particles with physical structures in the size range of 1 to 100 nm (Donaldson et al., 2004; Oberdörster et al, 2005). However, because "nano" is not well defined, Maynard et al. (2011) proposed that a better term would be the toxicology of sophisticated materials that would include also some particles with a dimension over 100 nm. This has spurred a demand for a source specific inhalation exposure assessment where exposure to urban PM and local indoor sources are examined separately.

The highest potential risk for human exposure to ENMs occurs in the workplace, in both the manufacturing industry and research laboratories (Balas et al., 2010; Brouwer, 2010). Currently, there are very few ENM exposure studies. There are no quantitative exposure levels for ENMs and differences in the format of reporting data compile the comparison of different studies. This is because the fraction of background particles associated with the ENM concentration is usually not well-known (Brouwer, 2010; Kuhlbusch et al., 2011). It is also unclear which metrics should be used to describe the ENM exposure and which parameters are best associated with the biological response (i.e. toxicity). In the ENM exposure assessment, the measurement metric should be sensitive to the ENM concentrations but not to the background particles that are assumed to be less dangerous to human health. On the other hand, the metric should correlate with the biological response so that the health effects can be estimated directly. Some studies have indicated that the particle surface area is associated with the biological response (Maynard and Kuempel, 2005; Oberdörster et al., 2000). However, the surface area alone may not provide a sufficient indicator of the biological response (Warheit et al., 2006) and thus there is no agreement about appropriate measurement metrics (Maynard et al., 2011). In an ENM exposure assessment, Maynard and Aitken (2007) proposed that investigators should measure the main concentrations, namely particle number [cm^{-3}], surface area [μm^2 cm^{-3}], and mass concentration [μg m^{-3}].

Currently, there are only recommended occupational exposure limits (OELs) for ENMs (see IFA (2010) with the limits for ENMs given in units of particle number concentration, NIOSH (2009) for TiO_2 NPs, and NIOSH (2010) and IFA (2010) for CNTs). van Broekhuizen et al. (2012) has supported the usefulness of the proposed OELs in different exposure scenarios. Official OELs are lacking because the relevant exposure scenarios are not well known, measurement metrics are unclear, and epidemiological studies are incomplete (Schulte et al., 2010; van Broekhuizen et al., 2012).

The first epidemiological studies have not shown any human illnesses to be related to ENM exposure (Schulte et al., 2009; Liou et al., 2012). However, exposure risks have been estimated using the dose-response model devised by Hill for workers using TiO_2 NPs (Liao et al., 2008, 2009; Ling et al., 2011) and workers in carbon black production (Ling et al., 2011). These studies detected an excess in health risks but they were criticized mainly for their inappropriate dose response assessment and exposure data (Tomenson and morfeld, 2010a,b; Morfeld et al., 2012).

Recently, improved exposure and risk assessment tools have been developed with which to estimate the potential ENM exposure and risk in different work scenarios (for example Stoffenmanager and NanoSafer exposure modules; the model is described by Shneider et al., 2011). However, these tools have not been validated and tested due to the lack of quantitative and representative ENM exposure and release measurements (Clark et al., 2012).

In summary, the quantitative ENM exposure levels are key factors if one wishes:

- to identify relevant ENM exposure scenarios (Brouwer, 2010)
- to define ENM exposure metrics in different exposure scenarios (Maynard and Aitken, 2007; Brouwer et al., 2009)
- to estimate the regional dose to provide a basis for defining metrics of the dose-biological response (Maynard and Aitken, 2007)
- to define OELs (van Broekhuizen et al., 2012)
- to conduct epidemiological studies (Liou et al., 2012)
- to undertake risk assessment modelings (Ling et al., 2011)
- to validate risk assessment tools (Clark et al., 2012)

In order to obtain high quality and comparable exposure data, several guidelines and harmonized measurement strategies have been developed for ENM exposure analysis (e.g. ISO, 2007; Brouwer et al., 2009; Methner et al., 2010; Kuhlbusch et al., 2011; OECD, 2009b; NIOSH, 2009; ECHA, 2012a). All of these strategies emphasize that it is difficult to discriminate background particles from their ENM counterparts (see different discrimination methods from Kuhlbusch et al., 2011). The background particles are classified as particles originating from natural sources and incidental anthropogenic sources. The personal exposure to ENMs occurs mainly in the indoor environment where the air quality depends on the penetration of pollutants originating from both outdoor and indoor sources.

Several studies have shown that the indoor sources govern the indoor concentrations irrespective of the type of the built-up environment (see e.g. concentration studies for homes: Hussein et al. (2005a,b); Afshari et al. (2005); Géhin et al. (2008); Bhangar et al. (2011), offices: Koponen et al. (2001); He et al. (2007); McGarry et al. (2011); **Paper I**, and industry: Hämeri et al. (2003, 2009); Elihn and Berg (2009); Heitbrink et al. (2009); Brouwer (2010); Buonanno et al. (2011); Koponen et al. (2011); Vosburgh et al. (2011); **Papers III, IV**). The exposure to background particles should be considered also when a worker's risk is being estimated. In some cases, background particles may be even potentially more hazardous for human health than manufactured or used ENMs (**Paper IV**).

This thesis describes how to assess source specific exposure and dose (**Papers I, III, IV**). It can be used in the assessment of risks from specific emission source if one knows the biological responses evoked by the emitted particles. An exposure protocol was introduced to estimate the biological response of synthesized NPs from murine inhalation studies (**Paper II**). The source specific risk assessment provide causality information for use in epidemiological studies and to enable targeted risk control measures. This thesis provides quantitative exposure data for the open questions listed above. It is shown how to exploit indoor aerosol modelings to characterize particle emitters and estimate their influence on indoor concentrations (**Paper I**). This is beneficial in predictive source specific exposure and risk assessment which can be used to design building environments with better air quality. This thesis describes the methods that are essential for conducting source specific risk assessment of inhaled particles.

2 Methods

The work included measurements in the laboratory and in workplaces. Both physical and chemical properties of aerosol particles were analyzed with electron microscopy. Indoor aerosol modelings were used to resolve particle emission rates and to estimate source influence on the indoor particle concentrations. This section provides a theoretical background for the methods used in this thesis.

2.1 Measurement techniques

Airborne particle concentrations were measured with on-line methods and particles were collected from the workstations air. Particle samples were analyzed in an electron microscope. Time resolved particle concentration measurements may be generally divided into two types; size integrated and size-resolved (Kuhlbusch et al., 2011). In this work, the most important quantity is particle size-resolved concentration which was used to characterize particle emission sources, to assess source-specific exposure, and to calculate the deposited dose of inhaled particles.

2.1.1 Measurement principles of size-resolving instruments

The definition of the particle size is not self-evident because it depends for example on particle morphology and dielectric properties (see e.g. Seinfeld and Pandis, 1997; Sorensen, 2000). Thus, especially for non-uniform atmospheric aerosol, the size of the particle will depend on the detection technique (Zhang et al., 2008). In this work, particles were size classified according to their diffusity (mobility diameter), inertia (aerodynamic diameter), and optical properties (light scattering).

Mobility sizing

The mobility of a particle is defined as the speed at which it moves in response to a steady force. The mobility is one of the most fundamental of the aerosol properties because it determines the particle diffusivity and coagulation kinetics. In an electric field, a charged particle moving at constant velocity experiences an electrostatic force

which is exactly equal and opposite of the aerodynamic drag force. The electrical mobility of a singly charged particle may be expressed as

$$Z = \frac{eC(Kn)}{3\pi\eta D_b} \tag{1}$$

where e [C] is elementary charge, $C(Kn)$ is the Cunningham slip correction factor as a function of Knudsen number Kn (Kn defined as $2\lambda/D_p$, where λ [m] is the mean free path of the carrier gas), D_b [m] is the particle's mobility diameter, λ [m] is the mean free path of the carrier gas, and η [kg m^{-1}s^{-1}] is the viscosity of the gas (Baron and Willeke, 2001a). In this work, particle number mobility size distributions were measured with a mobility spectrometer, also known as a scanning electrical mobility spectrometer (SMPS). For example, the SMPS has been described by Wang and Flagan (1990).

Inertial classification

Aerosol particles may be classified according to their inertia. This quantity is called an aerodynamic diameter which is defined, for a particular particle, as the diameter of the spherical particle having unit density (1 g cm^{-3}) that has the same settling velocity as the true particle (Seinfeld and Pandis, 1997). In this work, particle aerodynamic size distributions were measured with an electrical low pressure impactor (ELPI) where aerosol particles are charged with a unipolar diffusion charger after which the particles enter the cascade low pressure impactor, and subsequently the current carried by the particles is measured (Keskinen et al., 1992). Response functions of the ELPI impactor are described in detail by Marjamäki et al. (2005).

Optical sizing

In optical sizing, single particle scatters light which is collected and measured with a photomultiplier tube. The pulse height (or area) depends strongly on particle size, shape, and refractive index (Sorensen, 2000). Optical particle sizer response functions for two light scattering geometries are described by Pinnick et al. (2000). It is usual in particle optical size measurements, the measured particles are assumed to have the same shape and refractive index as the particles used in the instrument calibration.

Particle sizing uncertainties are also increased by resonances in Mie scattering, where particles of different sizes may give the same response.

2.1.2 Metrics of size integrating instruments

Total particle number (N, [cm^{-3}]), active surface area (S, [μm^2 m^{-3}]), and mass (M, [μg m^{-3}]) concentrations were measured respectively with condensation particle counter (CPC, see for example McMurry, 2000), diffusion charger (DC, Baron and Willeke, 2001b; Asbach et al., 2012), and tapered element oscillating microbalance (TEOM, Patashnick and Rupprecht, 1991). These instrument responses depend mainly on concentration and particle size. In the particle number count, the measurement signal weight is the same for each particle ($N \propto D_p^0$), while in the active surface area the measurement signal is proportional to D_p^2 in the free molecular regime ($Kn \gg 1$) and to D_p^1 when $Kn \ll 1$ (Maynard and Kuempel, 2005; Heitbrink et al., 2009), and in mass measurement, signal is proportional to the particle volume ($M \propto D_p^3$). Thus, large particles make a significant contribution to the mass concentration. For example, one 10 μm water droplet contains the same amount of mass as 10^9 water droplets whose diameter is 10 nm. On the other hand, if the mass concentration is 100 μg m^{-3}, it requires 190 cm^{-3} water droplets having a diameter of 10 μm, or 190×10^9 cm^{-3} whose diameter is 10 nm. This indicates that large particles do not affect significantly the total particle number concentration, and on the other hand, NP's contribution to the mass concentration is insignificant.

2.1.3 Metric conversions from the mobility diameter

The size-fractional number concentrations may be converted to size-fractional active surface area and mass concentrations. This can be used to estimate the regional deposition for different metrics which may be relevant information when biological effects are considered.

Active surface area

The active surface area of a particle may be described as the area that interacts with air molecules and ions. This comprises a fraction from geometrical surface area (Pandis

et al., 1991; Rogak et al., 1991; Baron and Willeke, 2001b; Keller et al., 2001; Ku and Maynard, 2005; Heitbrink et al., 2009). The particle mobility is defined by the aerodynamic drag force which is governed by particle-molecule collisions. Similarly, ion attachment (or mass transfer) rate in diffusion charging is based on ion diffusivity and coagulation with aerosol particles. In the charging calculations, hydrated protons are often used as representatives of positive ions (Biskos et al., 2004; Ramachandran et al., 2005). Thus, it is theoretically possible to use either quantity to measure active surface area (Keller et al., 2001; Ku and Maynard, 2005). However, it is best to keep in mind that the area of active surface area depends on the nature of the interacting molecules. For example, mass transfer of hydrated lead molecules measured by the Epiphaniometer (Gäggeler et al., 1989; Pandis et al., 1991; Rogak et al., 1991; Shi et al., 2001) gives a different active surface area than that measured by the diffusion charger due to differences in ions/molecules diffusivity and coagulation kinetics (see Biskos et al. (2004) for hydrated protons and Su et al. (1988, 1990) for lead molecules).

It has been shown experimentally that the product of active surface area and particle mobility is constant up to 750 nm (Rogak et al., 1993; Keller et al., 2001). Thus, as described by Heitbrink et al. (2009), the active surface area s [m^2] of the particle may be calculated from the mobility diameter as

$$s = \frac{3\pi\lambda D_b}{C(Kn)\delta}\,, \tag{2}$$

where λ is the mean free path for air 0.066 μm, and the scattering parameter δ for air is 0.905 (de la Mora et al., 1998).

Mass

As the diameter of an agglomerate is not self-evident neither is the density of an agglomerate. The characterization and the definitions for the particle densities have been described by DeCarlo et al. (2004). In this study, mass m [g] of the particle was calculated from the particle mobility diameter D_b [m] and effective density ρ_{eff} [g cm^{-3}] (DeCarlo et al., 2004; Ristimäki and Keskinen, 2006; Rostedt et al., 2009):

$$m = \rho_{\text{eff}}\frac{\pi}{6}D_b^3\,. \tag{3}$$

Here, the effective density ρ_{eff} was defined from the differences between particle electrical mobility diameter and aerodynamic diameter which reflect the particle shape factor and Cunningham slip correction factor. In this work, the effective density was assumed to be constant for the whole particle population. However, for an agglomerate, the effective density usually decreases while particle size increases because the porosity of the particles tend to increase in relation with increasing particle size (McMurry et al., 2002; Khlystov et al., 2004). The effective density links the mobility diameter and aerodynamic diameter as described by Kelly and McMurray (1992):

$$D_a = D_b \sqrt{\frac{C(Kn, D_b)}{C(Kn, D_a)} \frac{\rho_{\text{eff}}}{\rho_0}}, \tag{4}$$

where C_c is the slip correction factor for the corresponding aerodynamic or mobility particle size Baron and Willeke (2001c) and ρ_0 is unit density (1 g cm^{-3}).

2.1.4 Electron microscopy

The electron microscope can be used to characterize the particle projected surface area, primary particle size, composition, and crystalline structure. The diameter of the particle can depend upon the definition. For example, the projected area equivalent diameter is defined as the diameter of a circle that has the same area as the projected area of a particle seen under the microscope (Baron and Willeke, 2001c). Samples for the electron microscope were collected directly on a copper grid or with an electrostatic sampler (Dixkens and Fissan, 1999).

2.2 Calculation of inhaled dose

The regional dose of the particles during inspiration and expiration can be calculated by multiplying particle aerodynamic size concentrations by the International Commission on Radiological Protection human respiratory tract model deposition fractions (ICRP, 1994), respiratory minute volume, and exposure time. However, the exposure time can be left as an open parameter in order to obtain the regional dose rate (or minute dose) $\dot{n}(t) = dn(t)/dt$ [min^{-1}] which is a more useful quantity for risk assessment modeling.

The mathematical expression of the regional dose rate is:

$$\dot{n}(t) = \sum_{i=1}^{n} \begin{bmatrix} DF_{\mathrm{HA}} \\ DF_{\mathrm{TB}} \\ DF_{\mathrm{Alv}} \\ DF_{\mathrm{total}} \end{bmatrix} \times \frac{dN_i(t)}{d\log(D_{p,i})} \times d\log(D_{p,i}) \times RMV \times \epsilon\,, \tag{5}$$

where the deposition fractions in head-airways DF_{HA}, trachea bronchi DF_{TB}, alveolar region DF_{Alv}, and total deposition DF_{total} were calculated by using simplified equations for the ICRP model as described by Hinds (1999) which are shown in Figure 1, $N_i(t)$ [cm^{-1}] is the particle number concentration at size-section i, $d\log(D_{p,i})$ is logarithmic width of the size bin i, RMV [min^{-1}] is the respiratory minute volume, and ϵ is the respirator particle penetration factor (ϵ =(protection factor)$^{-1} \leqslant 1$, see AIHA (2002) for definition of protection factor). In this work, the particles were assumed to preserve their size during inspiration. However, it has been shown that the particles may grow in the high relative humidity of the lungs which can influence the deposition region and probability (Anselm et al., 1990; Schum and Phalen, 1997; Löndahl et al., 2007, 2009; Keskinen et al., 2011).

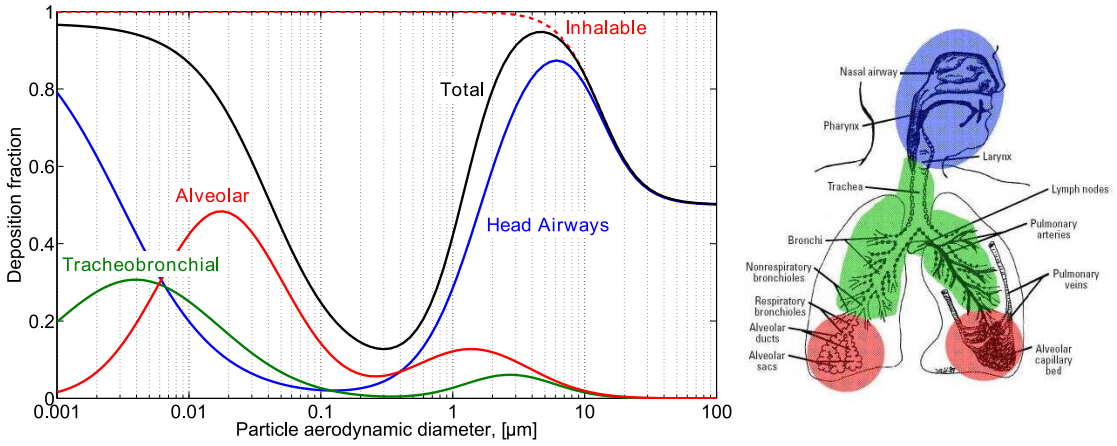

Figure 1: Predicted total and regional deposition probabilities for light exercise (nose breathing) according to Hinds (1999) simplified equations for the ICRP deposition model. (Reprinted with permission and adapted from Oberdörster et al (2005). Copyright Environmental Health Perspectives).

2.3 Indoor aerosol modelings

The dynamics of indoor aerosol particles were described with a general dynamic equation of aerosol particles (Hussein and Kulmala, 2008). The model is based on a mass balance of aerosol particles which in this work incorporated ventilation, deposition, coagulation and particle sources as follows (Nazaroff, 2004; Hussein et al., 2005a):

$$\frac{dN_i(t)}{dt} = N_{out,i}(t)\lambda_v P_i - (\lambda_v + \lambda_{d,i})N_i(t) + S_i(t) + \left.\frac{dN_i(t)}{dt}\right|_{coagulation} \quad (6)$$

where $N_i(t)$ and $N_{out,i}(t)$ [cm^{-1}] are the particle number concentrations indoors and outdoors, λ_v [h^{-1}] is the ventilation rate, P_i is the penetration factor of outdoor particles to indoors, $\lambda_{d,i}$ [h^{-1}] is the deposition rate of aerosol particles onto indoor surfaces (Lai and Nazaroff, 2000), the coagulation process is implemented from the UHMA aerosol model (Korhonen et al., 2004), and the subscript i refers to certain size-sections. In this simplified model, particles are treated as primary particles and it does not take into account gas-particle interactions.

3 Risk assessment of airborne particles

In toxicology, risk is defined as the probability that exposure to a hazard will damage human health. Figure 2 displays schematic for risk assessment of airborne particles. It is divided into five sections where the first step is hazard identification (Figure 2A). Emission sources include penetration of outdoor pollutants to indoors and emissions from incidental sources and processes. Emission sources may be characterized with chamber measurements and indoor aerosol modelings (**Paper I**). The indoor environment characterization includes parameters that can influence indoor concentrations, such as ventilation and spatial properties. The workers' activity includes information about the use of emission sources and personal protection.

Source specific exposure and dose (Figure 2B) are defined by linking work activity with size-resolved concentrations measured both from the work station and representative background concentration, such as the incoming ventilation air, far from the workstation, or outdoors. The emission rates from different processes may be resolved from measured concentrations with the indoor aerosol modelings, in units of cm^{-3} s^{-1} or s^{-1}, depending on the knowledge of spatial distribution of the concentrations (Hussein et al., 2005a; Koivisto et al., 2012). The emission rates may be utilized in exposure analysis, risk control measures, and in the exposure modelings (**Paper I**, Koivisto et al., 2012). The regional inhalation dose can be calculated from the size-resolved concentrations by using the ICRP respiratory tract model (e.g. **Paper III**).

Risk may be characterized (Figure 2D) from the exposure concentrations and by using occupational exposure limits (OELs). However, if there are no OELs available, the risk may be estimated with a dose-response model (Liao et al., 2009; Ling et al., 2011). This requires information about dose-response profiles in the sources, which can be defined with toxicological studies, or from epidemiological data (Figure 2C). **Paper II** shows an exposure protocol that was used to study synthesized TiO_2 NPs pulmonary inflammation (Rossi et al., 2010) and the genotoxic response in mice (Lindberg et al., 2011).

In risk control measures (Figure 2E), source emission rates and their toxicities provide valuable data to estimate the best method with which to decrease the risk. The priority is to reduce exposure concentrations and then to increase personal protection. Concentrations may be reduced by changing process methods, altering material usage in the sources, or they may be achieved via structural changes.

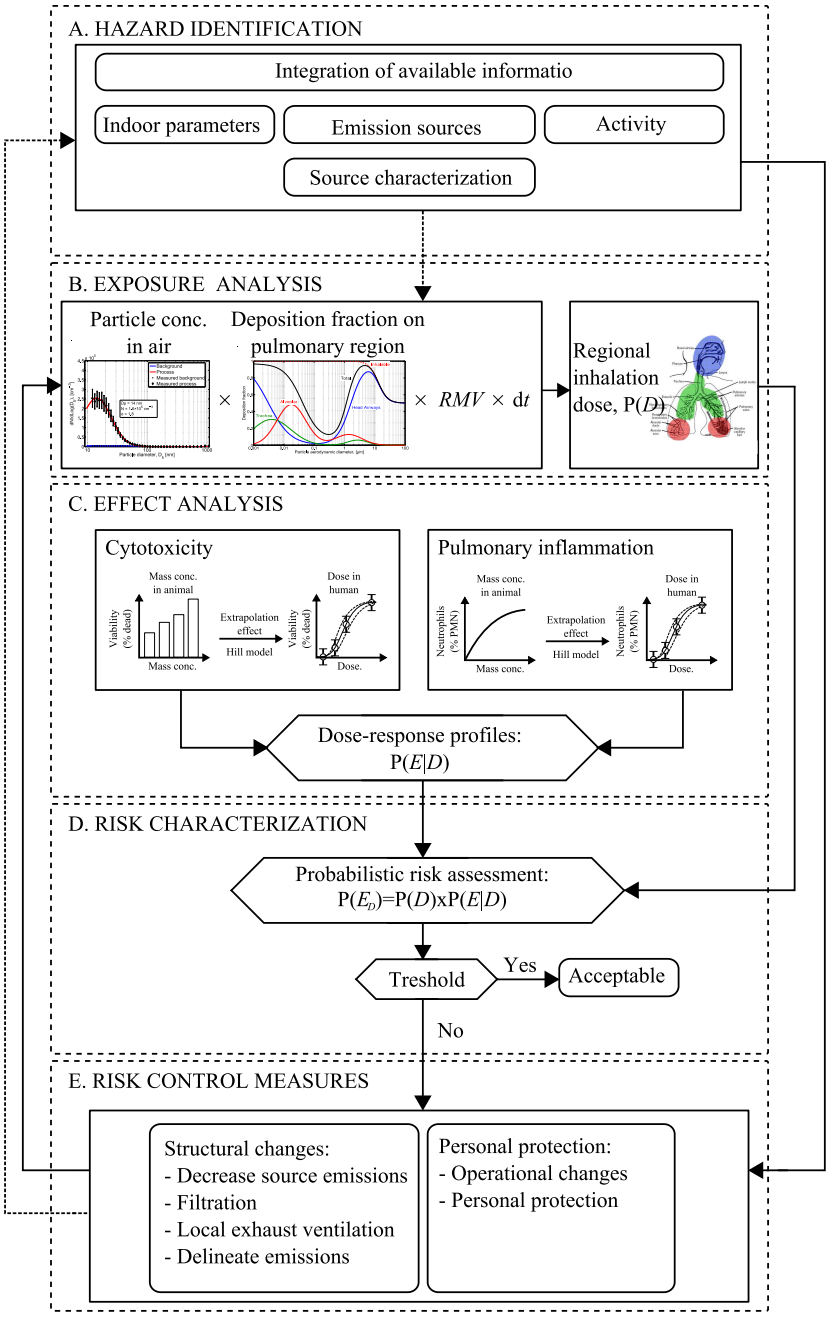

Figure 2: Schematic for risk assessment of airborne particles (modified from Ling et al., 2011). Solid arrows shows how the risk assessment proceeds and dashed arrows shows where indoor aerosol modelings may be used for predictive risk assessment.

4 Exposure scenarios

This section shows how workers' ENM inhalation exposures and doses were assessed in three different workplaces: NP synthesis (**Paper III**), packing of pigment and nano-sized titanium dioxide (**Paper IV**), and handling of nanodiamonds (to be published). The ENM concentrations were discriminated from background particles which were used to assess the risk of ENM exposure. The exposure scenarios were be compared with an average exposure to urban background particles defined by Hussein et al. (2013).

4.1 Nanoparticle synthesis

The NPs were synthesized with a liquid flame spray process (Tikkanen et al., 1997; Mäkelä et al., 2004). Synthesized NPs were either collected in a ventilated chamber (see photo in Figure 3) or directly deposited on components over the flame. Figure 3 shows a layout of the work environment with information on the workers' positions during the synthesis and the locations of instruments.

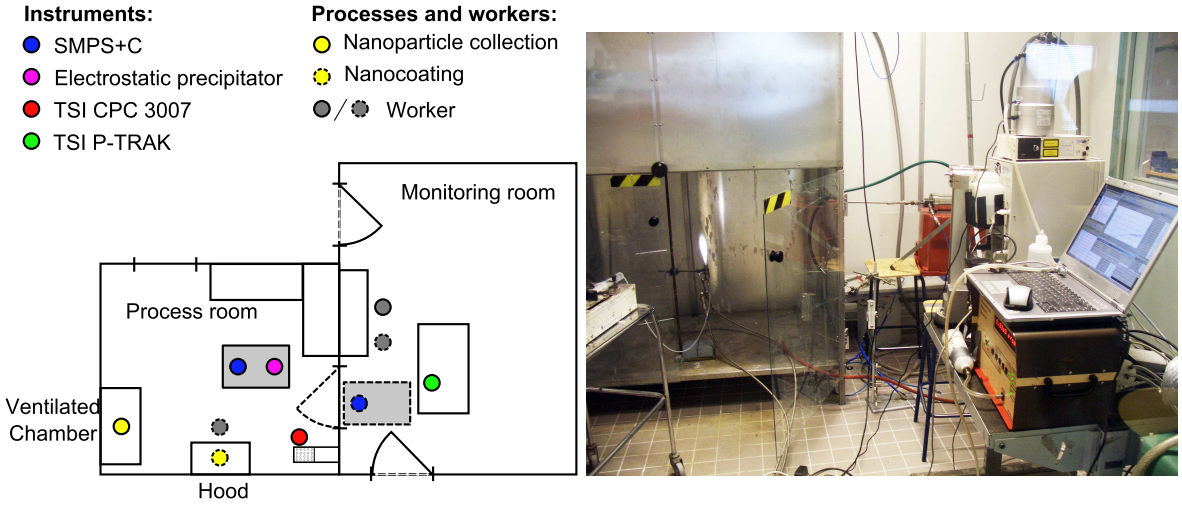

Figure 3: Process environment where solid lines refer to NP collection and dashed lines refer to nanocoating. The photo shows the aerosol instrumentation and the TiO_2 NP synthesis in the ventilated chamber.

Figure 4a shows that in the time between the processes of synthesis, the background particle concentration varied from 2000 up to 100 000 cm^{-3} which were mainly smaller

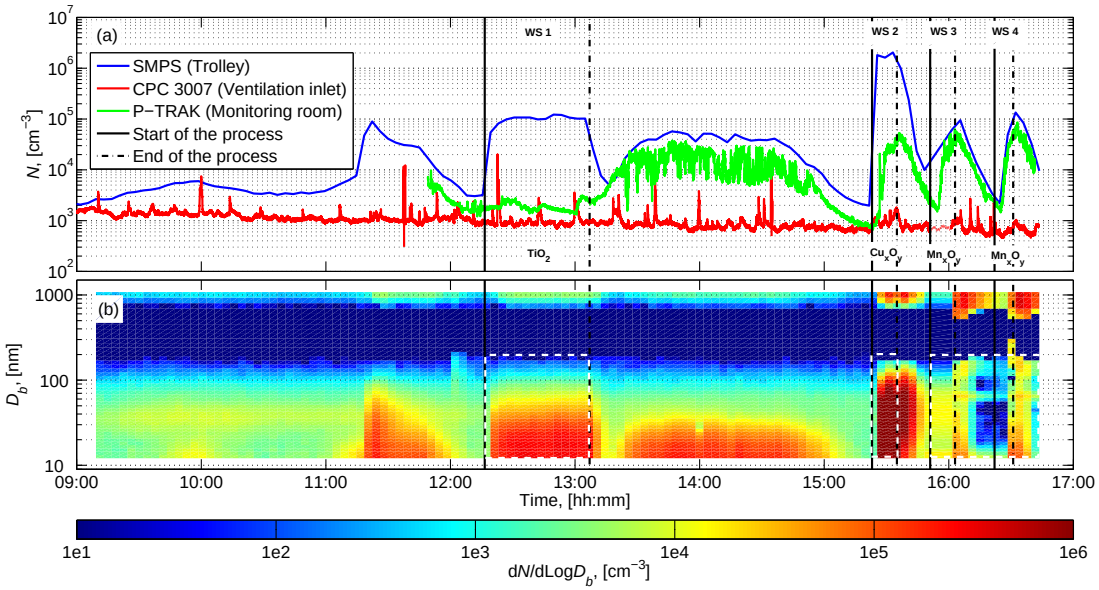

Figure 4: Time series of (a) particle concentrations and (b) particle mobility size distributions. Beginning and end of the processes are marked with vertical lines and (b) white dashed rectangles show the exposure concentrations of NPs.

than 100 nm (Figure 4b). These background particles originated mainly from the main building because the incoming ventilation air concentration was around 1000 cm^{-3} and the background particles were seen both in the process room and monitoring room (Figure 4a). The process under the hood, produced background particles over 500 nm in diameter (Figure 4b; WS2, WS3, and WS4). These were most likely semivolatile side product combustion particles from the process. The white rectangles in Figure 4b show the ENP concentrations to which the workers were being exposed. Tables 1 and 2 show the workers' exposure and dose rate of synthesized TiO_2 particles (Figure 9a) during the work session between 12:15 and 13:10.

4.2 Packing of pigment and nanoscale TiO_2 particles

Industry workers' exposure to airborne particles were defined during packing of pigment TiO_2 ($pTiO_2$, primary particle size ~200 nm, Figure 9d) and nanoscale TiO_2 ($nTiO_2$, primary particle size ~50 nm, Figure 9b). The $nTiO_2$ and $pTiO_2$ packing areas were located in separate factory buildings. Both factories were large, over 2000 m^2 and contained four to five floors. The packing areas had open pathways to other parts of the factories.

Packing of $pTiO_2$ material

Diesel powered forklifts were used to transport the $pTiO_2$ sacks (500 or 800 kg) to a storing room. Figure 5a shows that the forklifts increased the particle concentrations up to 3.0×10^5 cm^{-3} which was mainly attributable to combustion particles below 30 nm in diameter (diesel particulate matter (DPM), Figure 9d, and Figure 5b and 5c distributions at 10:44 and 10:46). Figure 5c background particle size distributions measured at 12:00 and 15:47 total number concentrations were respectively 10×10^3 cm^{-3} and 20×10^3 cm^{-3}. It was assumed that these were mainly secondary particles formed from sulphuric acid originating from the TiO_2 extraction process. $pTiO_2$ agglomerates were larger than approximately 500 nm. They were emitted into workstation air during the bagging process and re-suspended in pressurized air cleaning and during forklift activity. Table 3 shows the worker exposure and dose rate averaged over the time period described in Figure 5. The average exposure concentration consists of $\sim 15 \times 10^3$ cm^{-3} secondary sulphuric acid particles, $\sim 25 \times 10^3$ cm^{-3} combustion particles, and ~ 290 cm^{-3} $pTiO_2$ particles.

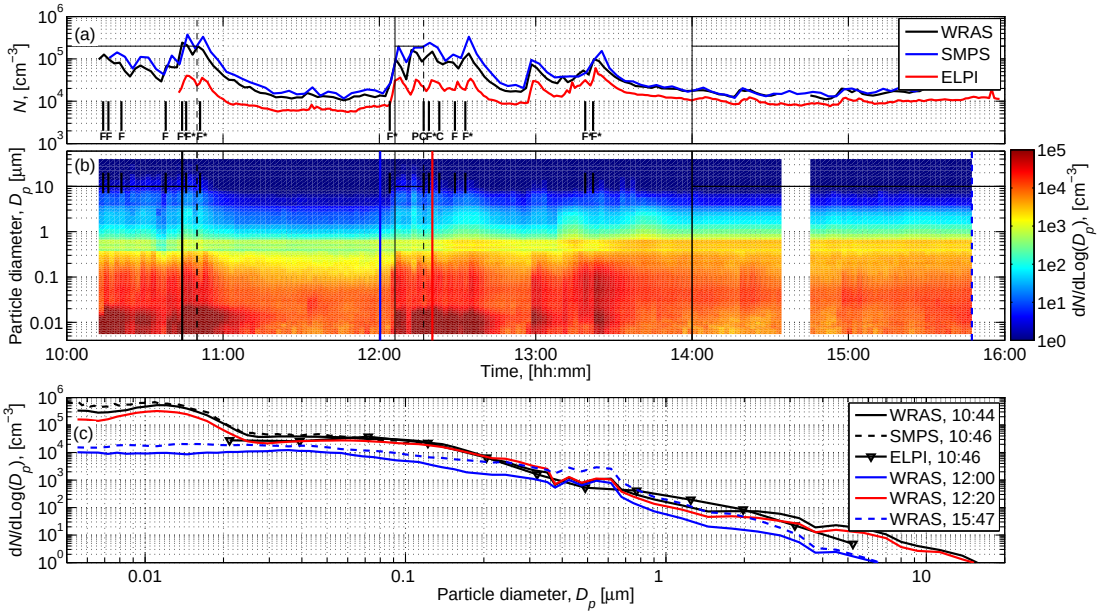

Figure 5: $pTiO_2$ packing area: (a) particle concentration time series where **F** is forklift, **F*** is forklift and change of a large bag, **PC** is pressurized air cleaning and **C** is the cleaning vehicle, (b) particle size distribution time series, and (c) shows the selected particle size distributions which are plotted with the respective line color and style in (b).

Packing of $nTiO_2$ material

$nTiO_2$ material was bagged into 25 kg sacks and stored with an automatized system. The first phase conducted in the factory hall was a jet milling process, after which there was a 20 minute break, and then the packing started (Figure 6a). The background particle size distribution was defined as the average of the before packing and the after packing distributions as shown in Figure 6c. The packing process itself did not increase significantly the particle concentrations (compare Figure 6c blue and black lines). However, three events were identified where a sack was poured into a silo by a worker (red lines in Figure 6b and c). These pouring events particularly increased over 200 nm particle concentrations which were identified in the electron micrographs to be $nTiO_2$ agglomerates (Figure 9b). The $nTiO_2$ concentrations were defined by omitting the average of the background particle size distributions from the pouring event distributions. These concentrations were used to estimate the workers' exposure and dose of $nTiO_2$ agglomerates (Tables 1 and 2).

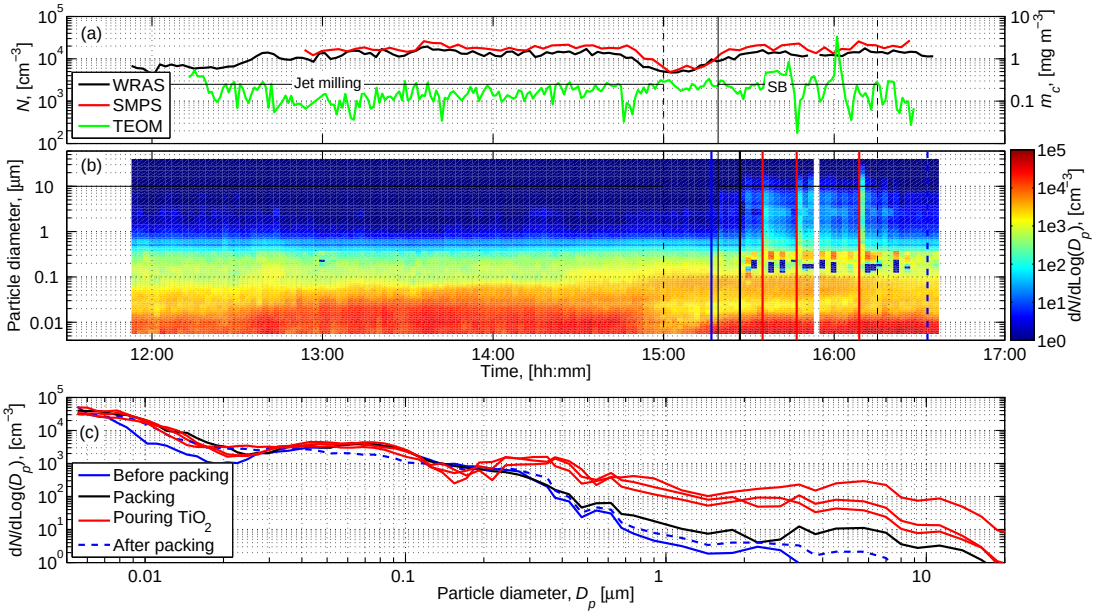

Figure 6: $nTiO_2$ packing area: (a) shows the particle and mass concentration (TEOM) time series, (b) shows the particle size distribution time series, and (c) shows the selected particle size distributions which are plotted with the respective line color and style in (b).

4.3 Handling of nanodiamonds

Nanodiamonds (NDs, crystal size 4-6 nm, Figure 9c) were handled in a glove box and percolated with a shaker that was located either in a laminar flow cabinet or a room (Figure 7). In cleaning work, the components were washed in a ventilated washing chamber (Figure 7). The room was a part of a modern office building. The room ventilation rate was approximately 2 h^{-1} and it was maintained at 5 Pa under-pressure compared to the corridor.

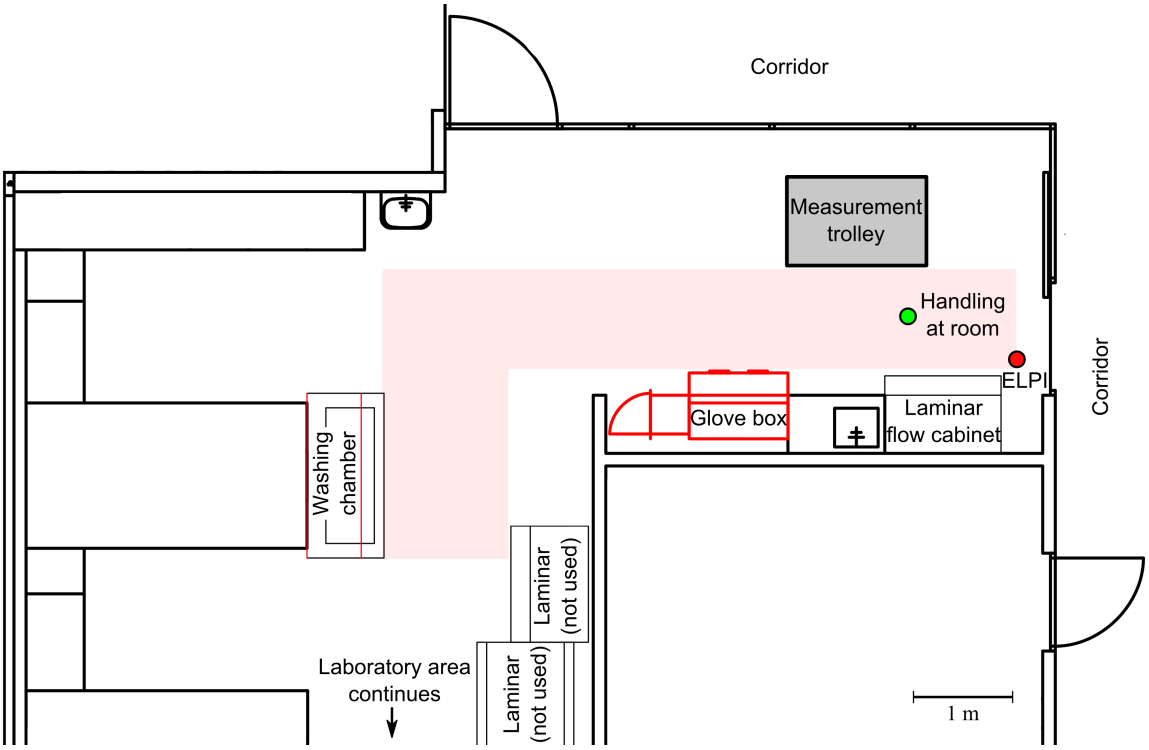

Figure 7: Layout of the work area. ND handling and cleaning areas are shown with light red.

The particle number size distributions were measured with a 3-way valve alternately from the incoming ventilation air or at a work station. During the workday, work station particle number concentrations were almost the same as those measured from the incoming ventilation air (Figure 8a). Thus, the incoming ventilation air determined the work station total particle number concentration. During ND handling in a laminar flow cabinet and glove box, there were a few peaks in the mass concentration measured by the DustMonitor (Figure 8a). ND handling in the room and also the cleaning operations clearly increased the mass concentration (Figure 8a) and this was caused

by particles roughly over 1 μm in diameter (Figure 8b). This increased also personal particle exposure as measured by the diffusion charger (MiniDisk). Figure 8c shows the background particle number and mass distributions measured before the work activity and during a spill of NDs that occurred during the ND handling. During the spill event, the workers' ND exposure and dose were estimated (Tables 1 and 2).

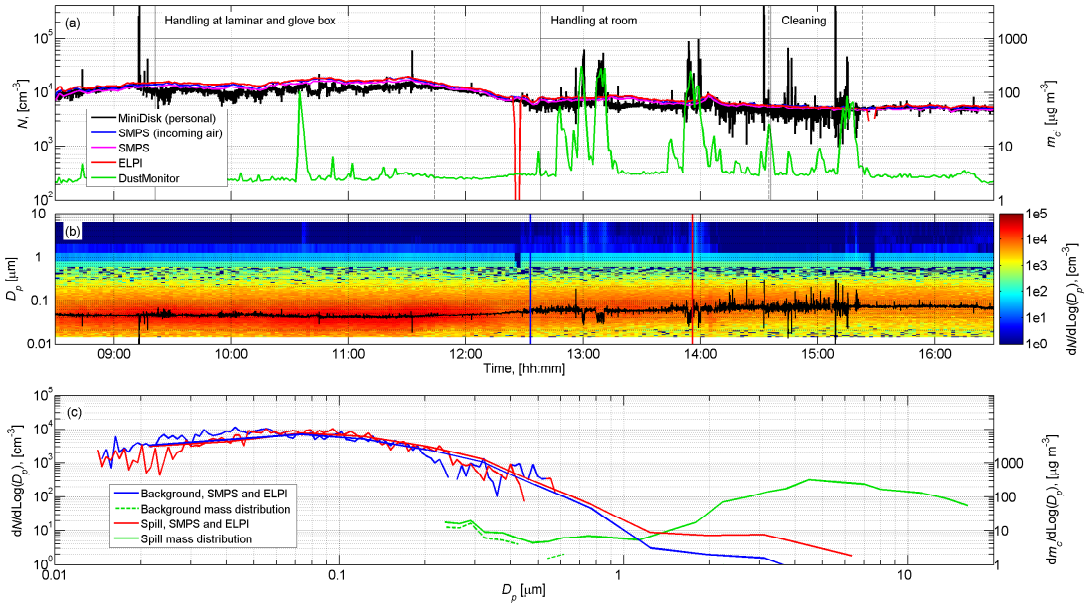

Figure 8: Particle concentrations during handling of NDs: (a) shows the particle number and mass concentration (DustMonitor) time series, (b) shows the particle number size distribution time series, and (c) shows the selected number particle size distributions which are plotted with the respective line color and style in (b), and mass size distributions measured by the DustMonitor from corresponding events with dashed and solid green lines.

4.4 Average exposure to urban background particles

The urban background (UBG) in Table 3 shows an average exposure and dose rate modeled for an office worker to urban outdoor particles during a 24-hour exposure (Hussein et al., 2013). The work day included activities such as working in indoors, transit between locations, outdoor activity and rest at home (Hussein et al., 2012). The UBG takes into account penetration of outdoor particles into the indoors. Thus, the average exposure concentration is lower than the average urban outdoor particle

concentration. The UBG values can be used as a baseline for PM exposure and to define dose levels for adults living and working in an urban area where the exposure to local sources is excluded.

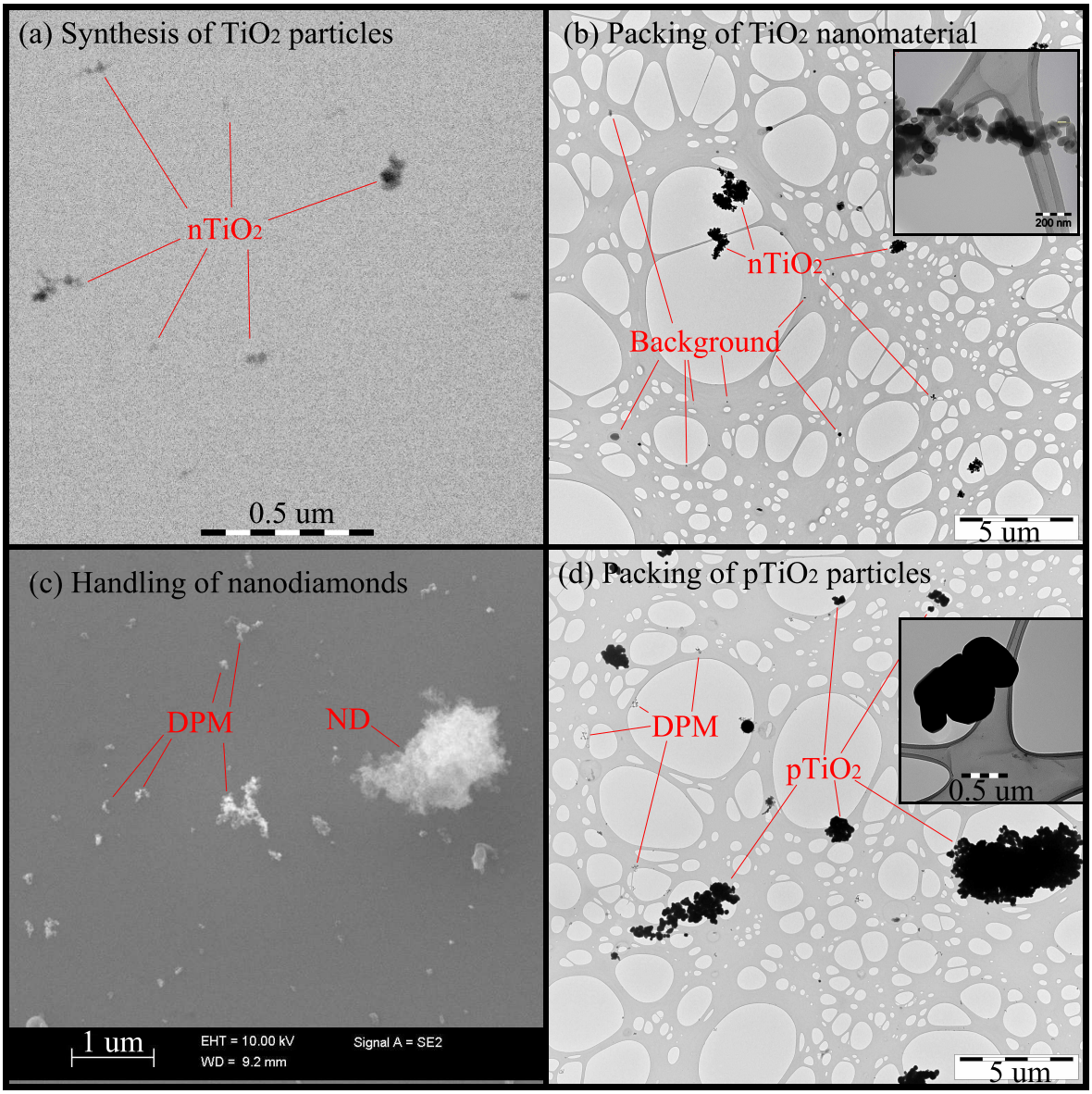

Figure 9: Micrograph of the process particles sampled from (a) synthesis of TiO_2 particles, (b) packing of $nTiO_2$ particles, (c) handling of NDs, and (d) packing of $pTiO_2$ particles.

Table 1: Workers' background particles and ENM exposures and calculated dose rates in units of particle number (N and $\dot{n}$) and mass (M and $\dot{m}$). Respirators' protection factors were not taken into account in the exposure and dose rate calculations. Workstation concentrations were assumed to be equivalent to the exposure concentrations.

	Synthesis		**$nTiO_2$ Packing**		**ND handling**	
	Background	Synthesis	Background	Pouring	Background	Spill
Composition	–	TiO_2	–	TiO_2	–	ND
Size	–	< 200 nm	–	$\gtrsim 200$ nm	–	$\gtrsim 100$
N, [cm^{-3}]	17800	1.0×10^5	10500	450	7000	–
M, [$\mu g\ m^{-3}$]	0.15[a,b]	0.0018[a,b]	160[c]	1500[a,d]	3[e]	162[e]
$\dot{n}$, $\times10^6$ [min^{-1}]	260	1460	208	3.6	67	–
$\dot{m}$, [$\mu g\ min^{-1}$]	2.2	0.017	3.0	31	0.005	3.12

[a]Calculated mass from mobility diameter and effective density.
[b]$\rho_{\text{eff}} = 1.7$ g cm^{-3} (Keskinen et al., 2007).
[c]Measured by the TEOM.
[d]Optical and mobility diameter are assumed to be equivalent and $\rho_{\text{eff}} = 0.1$ g cm^{-3}.
[e]Spherical particles with density of 2.6 g cm^{-3} (instrument default setting).

Table 2: Inhalation exposures and dose rates of ENMs when workers' use of respiratory protection factors of 50 in synthesis and 200 in ND handling were taken into account, and regional distribution of deposited particles in percentages to the head airways (H-A), the trachea bronchi (TB), and the alveolar region. Approximate exposure times were 10 min in synthesis, 10 min in pouring, and 1 min during the ND spill event.

	Synthesis		**$nTiO_2$ packing**		**ND handling**
Exposure	2000 cm^{-3}	0.036 ng m^{-3}	450 cm^{-3}	1500 $\mu g\ m^{-3}$	0.81 $\mu g\ m^{-3}$
Dose rate	29×10^6 min^{-1}	0.34 ng min^{-1}	3.6×10^6 min^{-1}	31 $\mu g\ min^{-1}$	15.6 ng min^{-1}
H-A, [%]	11	10	71	86	90
TB, [%]	19	17	5	5	4
Alveolar, [%]	70	73	24	9	6

Table 3: Inhalation exposures, dose rates, and regional distribution of deposited particles in percentages to the head airways (H-A), the trachea bronchi (TB), and the alveolar region for $pTiO_2$ packing area and urban background (UBG). $pTiO_2$ packing area concentrations consist mainly of diesel particulate matter (DPM) ($\sim 25 \times 10^3$ cm^{-3}), sulphuric acid background particles ($\sim 15 \times 10^3$ cm^{-3}), and $pTiO_2$ particles.

	$pTiO_2$ packing area	**Urban background**[a]	
Exposure	40100 cm^{-3}	3600 cm^{-3}	4.3 μg m^{-3}
Dose rate	680×10^6 min^{-1}	39×10^6 min^{-1}	0.027 μg min^{-1}
H-A, [%]	21	12.5	43
TB, [%]	26	20	9
Alveolar, [%]	53	67.5	48

[a]For 18 - 63 years old males; size range approximately from 4 to 950 nm; Spherical particles with density of 1.0 g cm^{-3}.

5 Discussion

The main points raised in this section are the definitions of the exposure metrics, risk assessment of exposure to ENMs, and comparison of ENM exposures and dose rates with background PM. The analysis was limited to particle number and mass concentrations.

ENM exposure metrics

Table 1 shows that the ENM number concentration was high during synthesis (100 000 cm^{-3}) as compared to packing (450 cm^{-3}) and handling (value not defined). Nonetheless, ENM mass concentrations were 1.8 ng m^{-3} in synthesis, 1.5 mg m^{-3} in pouring, and during the ND spill event 162 μg m^{-3} (Table 1). The differences in ENM concentrations are explained by the size of the particles (Figures 4b, 5c, 8c, and 9). In the exposure analysis of ENMs, it is recommended that one should measure particle number concentration in synthesis, and mass concentration in packing and handling, in order to minimize the contribution of background particles to the ENM concentration (Table 1). This is consistent with dustiness tests which revealed that handling of ENMs produces large agglomerates which are sized in a range of hundreds of nanometers to tens of micrometers (e.g. Evans et al., 2013).

Risk assessment of ENM exposure

Our murine inhalation studies have shown that synthesized nTiO_2 particles do not evoke any signs of pulmonary inflammation at a retained dose of 12.6 μg in mouse lung (Rossi et al., 2010). In fact, they seem to reduce allergic pulmonary inflammation in a murine inhalation model (Rossi et al., 2010). In addition, they do not induce any genotoxic effects at a retained dose of 84 μg in mice lungs (Lindberg et al., 2011). However, there are other studies showing that nTiO_2 may induce pulmonary inflammation (e.g. Chen et al., 2012) or genotoxicicity (e.g. Falck et al., 2009). Furthermore, the International Agency for Research on Cancer (IARC) has classified TiO_2 particles as "possibly carcinogenic to humans" (Group 2B, IARC, 2010). Toxicity may also depend on crystalline structure and structural modifications. For example, Rossi et al. (2010)

showed that silica coated $nTiO_2$ particles were able to induce pulmonary neutrophilia in mice.

The human equivalent dose can be estimated by using simplified extrapolation methods (see for example Reigner and Blesch, 2002; Reagan-Shaw et al., 2008; ECHA, 2012b). By applying the dose translation method described by (Reagan-Shaw et al., 2008), the human equivalent dose for 12.5 μg of $nTiO_2$ would be 3.0 mg in human lungs, when using conversion factors of 37 for an adult (body mass 60 kg) and 3 for a mouse (body mass 0.02 kg). The respective human equivalent dose of 84 μg would be 20 mg in the human lung. During the packing of $nTiO_2$ particles, over a 10 minute period, the worker's dose of $nTiO_2$ particles was 310 μg. By assuming that the biokinetics of mice and humans would be similar, then the $nTiO_2$ packing worker's risk to suffer inflammatory or genotoxic effects should be negligible. The risk is even lower if one can assume that only the alveolar dose is hazardous. This would reduce the risk by a factor of 10, because only 9 % of the $nTiO_2$ dose would be deposited in the alveolar region.

Table 2 shows that in synthesis and ND handling, the proposed OELs in Table 4 were not exceeded due to the use of respirators. The exposure during pouring of $nTiO_2$ material was momentarily higher than the numerical value of the proposed OEL. However, because the activity continued for only tens of minutes and the proposed value applies for time-weighted average concentrations for up to 10 h per day during a 40-h workweek, the proposed OEL was not exceeded. It has to be noted that the monthly average exposure may deviate significantly from the single day concentration measurements. The exposure data reliability may be improved by measuring longer periods as this would be one way to reduce statistical uncertainties.

Comparison of ENM exposures with background PM exposures

The ENM exposures and dose rates were compared with: (a) urban background (UBG) exposure in the Helsinki area outdoor aerosol particles (Table 3), (b) the respective workplace background levels (Table 1), and (c) concentration levels in packing of $pTiO_2$ material (Table 3).

The number dose rate during synthesis was at the same level and during the pouring event, ten times lower than the UBG number dose rate (see Tables 2 and 3). The

Table 4: Proposals for occupational exposure limits (OELs) in the number and mass concentrations as time-weighted average concentrations for up to 10 h per day during a 40-h work week, and the calendar year average air quality limit values for PM_{10} and $PM_{2.5}$.

Substance	OEL[a], [cm^{-3}]	OEL, [$\mu g\ m^{-3}$]	Reference
$nTiO_2$	40000	300	IFA (2010); NIOSH (2011)
$pTiO_2$	-	2400	NIOSH (2011)
Nanodiamonds	40000	-	IFA (2010)
DPM[b]	-[c]	5	EPA (2002)
Urban background:			
PM_{10}	-	40	EC (2008)
$PM_{2.5}$	-	25	EC (2008)

[a]For ENPs with sizes in between of 1 to 100 nm, see definition from IFA (2010)
[b]Diesel particulate matter, particle diameter $< 2\ \mu$m, see definition from EPA (2002).
[c]DPM particles below < 100 nm are classified as ultrafine particles.

ENM mass dose rates during synthesis and in the spill of NDs were respectively 80 and 1.7 times lower than the UBG dose rate. The mass dose rate during the pouring event was 1150 times higher than UBG mass dose rate. This was mainly because of the fact that the worker did not wear a respirator. During the 10 minute pouring activity that particular worker was exposed to approximately ten times more $nTiO_2$ particles in mass than UBG particles during 24-hours.

Workplace background particle number dose rates were systematically higher than ENM number dose rates (see Tables 1 and 2). Only during the $nTiO_2$ pouring activity was the workplace background particle mass dose rate lower. The mass dose during 10 minute pouring activity was similar to the mass dose of background PM received during the whole work shift. This shows that the dose of background PM, both in terms of units of number and mass, may be significantly higher than the dose of ENMs. ENM doses were reduced due to the use of respirators and the short duration of ENM exposure. The workplace background PM originated during synthesis mainly from some unknown indoor sources, in the packing area from both outdoor and indoor sources, and in ND handling from outdoor sources. Since the nature of the background particles was not known, their risk could be not estimated.

During packing of the $pTiO_2$ material, the average particle number dose rate was clearly highest (Table 3). These were mainly newly produced diesel particulate matter (DPM;

Figure 9d) from forklifts and sulphuric acid particles. DPM is classified as carcinogenic to humans (Group 1, IARC, 2012). This means that during an 8-h work shift, a worker receives a 6 times higher dose in terms of particle number than the UBG particles during 24-hours. The calculated mean mass concentration in the $pTiO_2$ packing area for particles below 2 μm in diameter was 90 μg m^{-3} (ρ_{eff} = 1 g cm^{-3}, mobility and optical diameters assumed to be the same). However, because this mass originated mainly from $pTiO_2$ particles, the proposed OEL limit was not exceeded (Table 4).

During synthesis, the TiO_2 NPs were mainly deposited in the alveolar region whereas in the $nTiO_2$ pouring and the ND spill event, they deposited in the head airways both in units of number and mass (Table 2). Table 3 shows that incidental particles in the $pTiO_2$ packing area and UBG PM were deposited mainly in the alveolar region. This might impact on the dose potential biological response. Especially for insoluble particles such as TiO_2 and soot particles, the deposition region clearly influences clearance, e.g. via mechanisms such as particle translocation and accumulation in the extrapulmonary organs (Geiser and Kreyling, 2010). Thus, in a worker's inhalation exposure risk assessment, the risk of particles from incidental sources needs to be considered in addition to estimating the worker's ENM exposure risk.

Perspectives on exposure assessment

PM exposure is usually considered as the fraction of particles which are smaller than a pre-defined cut-size, such as PM_{10} or $PM_{2.5}$. These size limits are loosely based on health effects, i.e. particles over 10 μm in diameter do not enter efficiently into the respiratory system during inspiration. For some pollutants, such as asbestos, there are specific exposure limits (fibres cm^{-3}) but this is not usually the case for different particle pollutants. In recent years, the risks of exposure to ENMs have triggered a demand for source specific exposure assessment in addition to the traditional PM_x exposure assessment.

A source specific exposure assessment usually requires size-resolved concentration measurements and at least measurements undertaken at two sampling points. Therefore, these kinds of measurements were conducted in this study with the SMPS and a 3-way valve in the ND exposure assessment and with the SMPS and two CPCs during the synthesis procedure. This requires expensive instrumentation and a well-trained user. One solution to overcome this problem would be to identify and characterize particle

sources or emissions from processes, and then estimate their influences on indoor air quality from their emission strengths. Subsequently, one could measure the concentration difference between background particles (from outdoor or incoming ventilation air) and the indoor concentration (room or ventilation exhaust air), for example with a diffusion charger. This would provide information about the indoor sources influencing the indoor air quality.

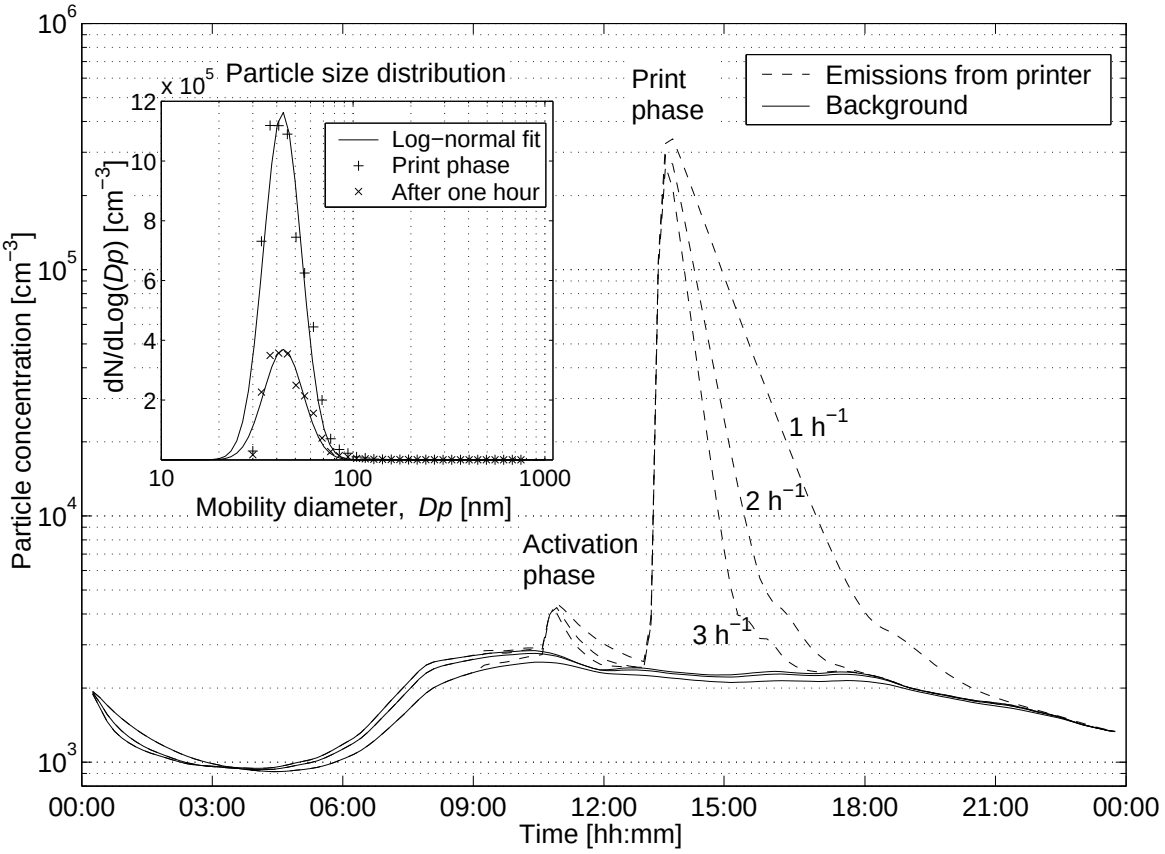

Figure 10: Laser printer influence on a modeled 62 m^3 office room indoor particle concentration. The background concentration was 10-year average concentration measured in Kumpula, Helsinki, and filtered with a EU7 filter. Sub-plot shows peak particle number size distribution during the print phase (+), and after one hour (×), with ventilation rate 1 h^{-1}.

Source specific exposures can be defined either with measurements or with indoor aerosol modelings when the sources have been characterized (**Paper I**; Koivisto et al., 2012). An example of this kind of modeling is shown in Figure 10. Hussein et al. (2013) performed exposure and dose modelings for a large population exposed to urban aerosol particles. In such model emissions from local indoor or outdoor sources may be applied.

This information in association with epidemiological studies could be used to estimate the influence of different PM sources on human health. Indoor aerosol modelings can be of assistance in designing indoor environments where sources of particles affecting the indoor air quality are taken into account. For example, Figure 10 shows how the effect of the ventilation rate on the indoor particle concentration was studied.

In a complete inhalation exposure and risk assessment, both gaseous and PM pollutants need to be considered. In that situation, gas-particle interactions such as new particle formation, condensation and evaporation must be assessed (see research programs funded by The Finnish Work Environmental Fund no. 112132 and no. 112133).

The optimal risk assessment measurement metrics are still an open question. The traditional forms of occupational hygiene exposure and risk assessment rely on OEL values given in units of concentration per volume. However, currently there is a discussion about how best to measure dose with respect to the risk or risk exposure (see Nanosolutions research program and Qui, 2012). This will require the measurement of the overall dose that should be weighted in consideration of the overall dose-response. For example, this kind of metric could take into account the chemical activity (Neubauer et al., 2011) or the photoemission properties (Lee and Sundheim, 1989).

6 Review of papers and the author's contribution

Paper I describes how an indoor aerosol model can be used to characterize particle emissions and predict the influence of the source on indoor air concentrations. The experiments were designed by K. Hämeri, T. Tuomi, and R. Niemelä. The modelings were performed by T. Hussein. The author carried out the major part of the work regarding the experimental setup, measurements, data analysis and manuscript writing under the supervision of K. Hämeri.

Paper II presents a novel exposure protocol to study biological responses of synthesized nanoparticles. The author designed and constructed in conjunction with M. Miettinen the experimental setup used in the inhalation studies under the supervision of J. Jokiniemi and K. Hämeri. The author along with E.M. Rossi H.K. Lindberg, and G.-C. Falck was responsible for the inhalation studies which were designed by H. Alenius, H. Norppa and K. Savolainen. The respiratory parameters of mice were investigated by M. Mäkinen under the supervision of A. Korpi. The particle characterization was conducted by J. Riikonen, E. Vanhala, and M. Vippola. The author performed instrument calibration, aerosol measurements, data analysis, lung deposition analysis and manuscript writing under the supervision of K. Hämeri.

Paper III presents one method for estimating a worker's calculated regional inhalation dose. It was applied to estimate regional inhalation dose rates and doses of nanoparticles to which workers were exposed. The study provides fundamental data for risk assessment of airborne nanoparticles, regulations, dose metrics, as well as assessing the magnitude of doses in nanoparticle synthesis. M. Aromaa was responsible for the nanoparticle synthesis under the supervision of J. Mäkelä. T. Hussein estimated the effect of the particles' hygroscopic growth to lung deposition. The author was responsible for the measurements, data analysis, lung deposition estimations and manuscript writing under the supervision of K. Hämeri.

Paper IV reports titanium dioxide (TiO_2) factory workers' source specific exposure and dose to airborne particles. The study highlights the importance of estimating a worker's source-specific exposure and source-specific risk assessment. The author and J Lyyränen were responsible for measurements which were supervised by A. Auvinen, T. Tuomi, J. Jokiniemi and K. Hämeri. Particle analysis was performed by E. Vanhala. The author analyzed data, estimated lung depositions and wrote the manuscript under the supervision of K. Hämeri.

7 Conclusions

This thesis investigates the exposure of workers to engineered nanomaterials (ENMs). The exposure scenarios were the synthesis of TiO_2 nanoparticles (NPs), the packing of $nTiO_2$ particles, and the handling of nanodiamonds. It was revealed how it is possible to distinguish background particles from ENM concentrations with different measurement techniques and indoor aerosol modelings. The regional inhalation doses of particles to which workers were exposed were estimated from the ENM size-fractional concentrations and by using a lung deposition model.

During TiO_2 synthesis the main deposition region was the alveolar region whereas during ENM handling it was the head airways. The proposed occupational exposure limits (OELs) were exceeded only momentarily during packing of $nTiO_2$ particles in units of mass. A worker's risk to suffer inflammatory or genotoxic effects during $nTiO_2$ packing was assessed by estimating the dose to which the worker was exposed and extrapolation of dose-biological response of $nTiO_2$ in mice. It was found that in this case the risk was negligible because the worker's dose was 310 μg while the inflammatory and genotoxic effects were only expected to occur at the doses exceeding 3.0 mg and 20 mg, respectively. However, the dose translation from mice to humans was preliminary and it was mainly conducted in order to illustrate how one could exploit existing toxicological data in a risk assessment in an occupational setting.

The ENM exposures and doses were compared with the levels of background particles occurring in a workplace, during packing of $pTiO_2$ particles, and a modeled 24-hour average exposure to urban PM. This study indicated that workers were exposed to high number concentrations in different workplaces when compared to 24-hour average urban PM exposure. The exposure concentrations were dominated by background particles originating from local incidental sources and outdoor concentrations that penetrate to indoors. During packing of $nTiO_2$ particles, work shift dose of ENMs were at the same level as the dose of background particles when expressed in units of mass. In other respects, the work shift ENM doses were lower than workplace background PM doses. This was because of the brief ENM exposure compared to whole work shift duration and use of respirators by workers while working with ENMs. During packing of $pTiO_2$ material, a worker was identified to be potentially at the highest risk when compared to the other ENM exposures in this study. This was because of he was exposed to a high diesel particulate matter number concentration for a long period. This

shows that essential to estimate source specific exposures and risks in order to identify the most relevant risk factors in an occupational environment.

This study revealed how best to exploit indoor aerosol modelings in a characterization of indoor particle emitters and how to estimate their influence on indoor air concentrations. These modeled concentrations may be used to estimate exposures, doses, and risks attributable to particle emitters in different work scenarios. These predicted exposure levels may be used in epidemiological studies. Indoor aerosol modelings may also be used to design safer indoor environments by minimizing the influences of these emitters on the indoor air concentrations.

In summary, the main outcomes of this thesis are:

- ENM exposures and doses were characterized in different workplace's and were compared with the workplaces background particle exposures and the exposure to average urban background particles
- In these workplaces, it is proposed that exposure metrics in NP synthesis should be related to D_p^0 and during ENM handling to the D_p^3
- Regional doses revealed that synthesized NPs were deposited mainly in the alveolar region and in ENM handling in head airways both when assessed units of number or mass
- An exposure protocol was introduced for studying the toxicities of synthesized NPs and this was used to estimate the tocicity of TiO_2 NPs
- Risk assessment was performed by applying proposed OELs and for nTiO_2 by using dose and dose-biological responses obtained from toxicological studies conducted in experimental animals
- One can exploit indoor aerosol modelings to characterize sources and then estimate how these will influence the indoor air concentrations

This study describes how to assess a worker's risk for being exposed via source specific inhalation exposure. It provides some methods to answer commonly asked questions, such as "What does this exposure mean?" or "Are we at a high risk to suffer some disease?".

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