Effective biological dose from occupational exposure during nanoparticle synthesis

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Abstract. Nanomaterial and nanotechnology safety require the characterization of occupational exposure levels for completing a risk assessment. However, equally important is the estimation of the effective internal dose via lung deposition, transport and clearance mechanisms. An integrated source-to-biological dose assessment study is presented using real monitoring data collected during nanoparticle synthesis. Experimental monitoring data of airborne exposure levels during nanoparticle synthesis of CaSO₄ and BiPO₄ nanoparticles in a research laboratory is coupled with a human lung transport and deposition model, which solves in an Eulerian framework the general dynamic equation for polydisperse aerosols using particle specific physical-chemical properties. Subsequently, the lung deposition model is coupled with a mathematical particle clearance model providing the effective biological dose as well as the time course of the biological dose build-up after exposure. The results for the example of BiPO₄ demonstrate that even short exposures throughout the day can lead to particle doses of 1.10·E+08 #/(kg-bw·8h-shift), with the majority accumulating in the pulmonary region. Clearance of particles is slow and is not completed within a working shift following a 1 hour exposure. It mostly occurs via macrophage activity in the alveolar region, with small amounts transported to the interstitium and less to the lymph nodes.

1. Introduction

Ultrafine particles due to their increased specific surface area may present an increased hazard and risk to the health of humans and workers. This is especially true for the case of nanoparticles. These particles are engineered to have novel, enhanced and specific properties, which may not be toxicologically tested.

Assessment of nanoparticle health impacts requires the characterization of the exposure and equally important the estimation of intake through lung deposition, translocation from the deposition sites and the clearance of the deposited particles. Retention in the respiratory system of ultrafine carbon particles, for instance, is significant and up to 75% retention has been observed 24-hours from exposure [1]. Additionally, studies suggest that the role of macrophages in ultrafine and nanoparticle clearance from the lungs may not be sufficient [2] and occurs at a lesser extent than their micro-sized counterparts [3].

A number of models have been developed examining particle uptake in the respiratory system. The International Commission on Radiological Protection [4] developed the ICRP66 model to calculate particle deposition and internal doses with size differentiated uptake parameters [4]. More models
have been developed since then, examining particle uptake as well as the distribution in the different organs of the body and clearance processes [5-7].

This paper presents an integrated source-to-biological dose study in which all above points, i.e., exposure, lung deposition and clearance of inhaled particles following exposure during nanoparticle production, are combined based on realistic data collected in an operating nanoparticle synthesis setting. The analysis of exposures incurred in real production settings of different particles allows for the examination of the differences and the importance of the aerosol dynamics in the internally delivered biological dose.

2. Methods

2.1. Methodology

Data from experimental monitoring of airborne exposure levels during the synthesis of nanoparticles in research laboratories is coupled with a transport and deposition model. This model considers aerosol dynamics to translate the exposure concentration to lung deposition based on the physical-chemical properties of the investigated particles. In a subsequent step, the lung deposition mathematical model is coupled with a mathematical model of particle clearance to provide the effective biological dose in target organs by inhalation for the exposed workers. The physiological parameters used were those of Caucasian adults undergoing light exercise.

2.1.1. Experimental monitoring. The experimental part involved detailed, size-resolved measurements of CaSO₄ and BiPO₄ airborne material during their synthesis. Number and mass particle concentrations as well as the size distributions of the airborne particles were monitored. A Scanning Mobility Particle Sizer (SMPS model 3936, TSI Inc) scanned in the 20 – 673 nm size range. Condensation Particle Counters (CPC 3022A and 3007, TSI Inc.) quantified number concentrations, while the DustTrak™ (model 8520, TSI Inc.) and SidePak™ (model AM510, TSI Inc.) monitored PM1 and PM10 mass concentrations, respectively. Besides monitoring results, the time-activity patterns of the workers present in the setting were also recorded during working hours. A survey on production, workers’ behavior and employment duration was completed by all researchers providing estimates of total exposure duration in such settings. The resulting doses estimated from the monitored exposure conditions represent a worst case scenario, as particle retention by personal protective equipment is not considered.

2.1.2. Lung deposition modelling. The lung deposition mathematical model used in this study is a mechanistic model that solves in an Eulerian framework the general dynamic equation for polydisperse aerosols, taking into account the processes of growth and coagulation when significant [8]. Deposition is determined in all generations of the respiratory tract. Particle deposition is assumed to be the result of the mechanisms of gravitational settling, Brownian diffusion, inertial impaction, and flow turbulence, acting simultaneously. The employed modeling approach is shown to be specifically appropriate for the study of the lung deposition of nanoparticles [8]. This model has been extensively validated against a large body of experimental and numerical respiratory data, for both inert and hygroscopic aerosols [4, 9-15].

2.1.3. Retention and clearance modelling. The particle retention and clearance mathematical model describes the distribution of the internalized dose in different target systems (interstitium and lymph nodes) beyond the portal of entry organ, which is in this case the lung [7]. Additionally the model describes the time course of the build-up of the dose after exposure. The model has been calibrated with data from various experimental studies [7].
3. Results

3.1. Monitoring results
During the synthesis of these compounds using the flame-spray pyrolysis technique, the production of CaSO₄ resulted in elevated airborne concentrations of 5 to 13 times the background concentration and size distributions peaked between 115 and 170 nm (Figure 1) [16]. The latter compound displayed similar airborne size distributions with the peak ranging between 135 and 165 nm. However, the airborne exposure levels were 37 to 42 times the background level, mainly due to a production system change.

![Figure 1. BiPO₄ number concentration during a single production. The estimated deposition fractions in the extrathoracic, tracheobronchial and pulmonary regions of the respiratory system are also plotted.](image)

Production runs lasted between 8 to 9 min on average, whereas total production time for CaSO₄ and BiPO₄ was 162 and 63 min, respectively. During this time workers were within 1 meter from the production unit. Exposure conditions relapsed back to background with 1-2 min after production ends.

3.2. Particle lung deposition
The lung deposition mathematical model was used to estimate the particle specific deposition fractions (DFᵢ) of the emitted particles in the extrathoracic (NOPL), tracheobronchial (TB), and pulmonary (PL) regions of the human respiratory system (Figure 1) [8]. The deposited particle dose in terms of number concentration of particles in these regions was then estimated (Equation 1) by using the total exposure time during production and physiological parameters of Caucasian adults undergoing light activity [4].

\[
D_i = \frac{C \cdot IR \cdot T}{BW} \cdot DF_i \quad \text{Equation 1}
\]

where \(D_i\) is the particle dose in region \(i\) of the respiratory tract (#/(kg-bw·working shift)), \(C\) is the particle number concentration (#/cm\(^3\)), \(IR\) the inhalation rate of a Caucasian adult (cm\(^3\)/h), \(T\) the duration of exposure per working shift (h/working shift), \(BW\) the body-weight of a Caucasian adult (kg-bw), and \(DF_i\) (-) the size differentiated particle deposition fraction in region \(i\) of the respiratory tract.

Figure 2a displays the variation in deposited particle dose for BiPO₄ in the different regions of the respiratory system per production run, as well as the total daily dose based on the exposure duration of 63 min. The total working shift deposited dose of BiPO₄ during synthesis amounts to 1.10·E+08 #/(kg-bw·8h shift). The maximum average deposited dose occurs in the pulmonary region and is 1.10·E+07 #/(kg-bw·8h shift).
3.3. Clearance Model

The particle specific pulmonary dose in terms of number concentration estimated with the lung deposition model was then fed to the retention and clearance model, assuming the same exposure conditions. Particle retention in the alveolar surface and clearance via macrophage activity and to the interstitium and subsequently to the lymph nodes was estimated. In the example of BiPO$_4$ exposure, the model shows that during exposure there is a steady build-up of particles in all four investigated regions. Once exposure ceases, clearance of inhaled particles from the alveolar free surface is very slow, whereas build-up continues throughout the remaining working shift in the other regions. Figure 2b shows the integrated particle dose over an 8h working shift following 63 min exposure at the beginning of the working day. Most particles within this time frame are retained in the alveolar region, whereas only a small fraction is transported to the interstitium and lymph nodes.

**Figure 2a.** BiPO$_4$ dose variation per production runs and daily dose

**Figure 2b.** BiPO$_4$ effective dose in alveolar, interstitium and lymph nodes, regions of the human body

4. Discussion and conclusion

The employed modeling approach is shown to be specifically appropriate for the study of the lung deposition of nanoparticles. On one hand, the Eulerian approach, contrary to the commonly employed Lagrangian approach, permits to properly account for the axial dispersion of the particles, which is of importance for very small particle sizes. On the other hand, the use of the general dynamic equation permits to fully account for aerosol processes, in particular hygroscopic growth and coagulation of very fine particles. Also, it allows expressing deposition in terms of a number of relevant exposure metrics, namely number or surface, and not only in terms of mass. This is of value because surface or number, as well as properties such as solubility are considered as more appropriate surrogates for describing the biological effects of nanoparticles.

The combination of the deposition model with the clearance model completes the description of the pathway from a worst-case external exposure to internal dose. Further research is required on the extension of this model to account for the distribution of the inhaled particles to other targets organs in the human body and to construct a mathematical description of the dose-response relationship. Further experimental data are needed to complete this step.
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