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RESEARCH ARTICLE

Assessing the potential exposure risk and control for airborne titanium dioxide and carbon black nanoparticles in the workplace

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Abstract
Purpose This study assessed the potential exposure risks for workers in the workplace exposed to airborne titanium dioxide nanoparticles (TiO_2-NPs) and carbon black nanoparticles (CB-NPs). The risk management control strategies were also developed for the NP engineering workplace.
Methods The method used in this study was based on the integrated multiple-path particle dosimetry model to estimate the cumulative dose of nanoparticles (NPs) in the human lung. The study then analyzed toxicological effects such as pulmonary cytotoxicity and inflammation and evaluated the health risk associated with exposure to NPs in the workplace. Risk control measures such as the use of ventilating systems and N95 respirator protection are also discussed.
Results and discussion This study found that: (1) the cumulative dose of CB-NPs was greater than that of TiO_2-NPs in human lungs; (2) there is a potential health risk to workers exposed to TiO_2-NPs and CB-NPs in the absence of control measures in the workplace, with higher health risks associated with CB-NPs than TiO_2-NPs; and (3) the use of a ventilating system and an N95 respirator offers greater protection in the workplace and significantly reduces the health risks associated with NP exposure.
Conclusion The present risk management control strategy suggests that the most effective way to reduce airborne NPs is to incorporate the use of a ventilating system combined with N95 respirator protection. This will enable the concentrations of TiO_2-NPs and CB-NPs to be reduced to acceptable exposure levels.

Keywords Titanium dioxide · Carbon black · Nanoparticles · Workplace · Risk assessment

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1 Introduction

Nanotechnology has become an important industry in the twenty-first century, playing a significant role in the generation of new products and applications through the development of nanoparticles (NPs) that exhibit varying characteristics such as particle size, surface area, crystal structure, surface chemistry, and surface charge (Handy and Shaw 2007). The properties differ substantially from those bulk particles of the same composition, allowing the NPs to perform exceptional feats of conductivity, reactivity, and optical sensitivity. However, possible undesirable results of these capabilities are harmful interactions with biological systems and the environment, with the potential to generate toxicity (Nel et al. 2006). At present, little information is available about the human health and environmental risk of NPs in the workplace. These different types of NPs pose a hazard to exposed workers.

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Accordingly, there is a need for assessing the health risk for workers (Crosera et al. 2009). Bergamaschi (2009) also indicated that among possible exposure routes, occupational cohorts are likely to have earlier and higher exposures than the general populations/consumers, and that may occur through inhalation, ingestion, and dermal absorption. While dermal absorption and ingestion are potential entry routes for engineered NPs, the inhalation route has received the most marked attention for workplace exposure. Certainly, workers in the workplace will be most at risk from exposure to NPs especially through inhalation (Schmoll et al. 2009). NPs can enter the human body mainly by inhalation, resulting in pulmonary inflammation or cytotoxicity (Nel et al. 2006; Oberdörster et al. 2005). With the development of an increasing variety of NPs, there is a need to investigate the potential influence of NPs on human health.

Titanium dioxide (TiO_2) accounts for 70% of the total production volume of pigments worldwide. Titanium dioxide nanoparticles (TiO_2-NPs) are used in sunscreens and plastics to block ultraviolet light and also act as catalysts. Carbon black (CB) is a powdered form of elemental carbon that is manufactured using the hydrocarbon pyrolysis process. Over 90% of CB production in the world is used for the reinforcement of rubber, while the remaining proportion is used for printing inks, paints, lacquer, and additives for industry (Wellmann et al. 2006). The annual consumption rate of CB in the world was nearly 10,100,000 t in 2010, with the most part being produced domestically. Carbon black nanoparticles (CB-NPs) are a relatively conductive carbon material composed of 90–99% elemental carbon. It is readily available and has been widely applied in the industry because of its low price (Yang et al. 2007).

Current research indicates that TiO_2-NPs and CB-NPs can produce adverse health effects (Chio and Liao 2008; Liao et al. 2009; Morfeld et al. 2006; Sayes et al. 2006). Gurr et al. (2005), Pulskamp et al. (2007), Oberdörster et al. (2000), and Elder et al. (2005) performed in vitro and in vivo studies which demonstrated that TiO_2-NPs and CB-NPs result in cytotoxicity and inflammatory response. Gurr et al. (2005) demonstrated that TiO_2-NPs in the absence of photoactivation can induce oxidative damage to human bronchial epithelial cells. Their results indicated that treatment with 10 μg/mL TiO_2-NPs (20 nm) for 24 h did not cause observable cell cycle delay; however, treatment with 10 μg/mL TiO_2-NPs (20 nm) for 3 days caused cell growth inhibition. Pulskamp et al. (2007) reported on cells treated with 5, 10, 50, and 100 μg/mL of CB-NPs (14 nm) for 24 h and indicated that exposure to CB-NPs resulted in a decrease of cell viability. Oberdörster et al. (2000) demonstrated that mice exposed to doses of 6, 25, and 100 μg of insoluble or poorly soluble TiO_2-NPs (20 nm) for 24 h induce significantly inflammatory effect in the lower respiratory tract. Elder et al. (2005) demonstrated that rats were exposed to three CB-NP dose levels of 1, 7, and 50 mg/m^3 for 13 weeks and allowed to recover for 1 day. Their results detected that exposure to high concentrations of CB-NPs produced lung tumors in rats.

Ventilation is the most widely implemented control measure that facilitates the efficient collection of NPs. Pui et al. (2008) indicated that ventilation systems are able to effectively reduce the concentration of silver NPs in the air. Moreover, the high diffusion capacity of NPs allows for their collection within disposable masks with relative ease. Huang et al. (2004) confirmed that commercial respirator filters rely heavily on the presence of an electrostatic charge on the fibers of the filter to provide adequate filter efficiencies. It was shown that a reduction in electrostatic charge resulted in a considerable increase in particle penetration, with the most penetrating particle size noticeably shifted from the nanometer to the sub-micrometer range.

The multiple-path particle dosimetry (MPPD) model is a computational model that can be used for estimating human airway particle dosimetry. The MPPD model calculates the deposition and clearance of monodisperse and polydisperse aerosols in the respiratory tracts of human for particles ranging in size from ultrafine (10 nm) to coarse (20 μm). The models are based on single-path and multiple-path methods for tracking air flow and calculating aerosol deposition in the human lung (CIIT Centers for Health Research 2006). In this study, the MPPD model was applied for assessing the internal particle concentration in the lungs.

The general dose–response model indicates that the higher the concentration of a chemical substance, the greater is its influence on the organism. Therefore, how a dose–response relationship is determined becomes important. In 1910, Hill developed a model to describe the dose–response relationship (Hill 1910). This study uses a Hill model commonly used in pharmacodynamic modeling to predict the effects of TiO_2-NPs and CB-NPs on human health, particularly with regard to pulmonary cytotoxicity and inflammation.

Although evidence for the health risks associated with NP exposure has yet to be established, many NP-related products are commercially available. To ensure high standards of occupational health and safety in a workplace where there is a high risk of NP exposure, health risk assessment and risk management is required in all workplaces (RSRAE 2004). In 2004, The Royal Society and the Royal Academy of Engineering devised a preliminary scheme for risk assessment on nanotechnology which clearly states that despite a lack of scientific evidence on the health risk of NP exposure, its potential danger and toxicity cannot be ignored even in the absence of evidence. The European Commission also recommends that health risk assessment, exposure analysis, effect analysis, and the establishment of risk management

strategies should be implemented in all workplaces (ECCHCP 2004).

Workers employed within the nanotechnology field are subject to high exposure (Bartis and Landree 2006; Bergamaschi 2009; Brouwer 2010; Crosera et al. 2009). As such, this study assessed the exposure risk of TiO_2-NPs and CB-NPs among workers in the field in order to investigate the effectiveness of existing control measures used in NP engineering workplace. The objectives of this study were fourfold: (1) to estimate the dose of TiO_2-NPs and CB-NPs inhaled into human lungs using the MPPD model; (2) to analyze the dose–response profiles for pulmonary cytotoxicity and inflammation using the Hill equation model; (3) to evaluate the exposure risk to TiO_2-NPs and CB-NPs in the workplace; and (4) to evaluate the efficiencies of using a ventilating system alone, N95 respirator protection alone, or a combined ventilating system with N95 respirator protection.

2 Materials and methods

Based on the foundation of probabilistic risk assessment, this study investigated the inhalation risk to workers exposed to TiO_2-NPs and CB-NPs in the workplace. Within acceptable exposure risk conditions, the study explored the differences in NP dose reduction by means of ventilation and N95 respirator protection (Fig. 1).

2.1 Hazard identification

Hazard identification was the first step of risk assessment (Fig. 1a). The step was the determination of whether a particular chemical was or was not causally linked to particular health effects. Gurr et al. (2005) demonstrated that TiO_2-NPs in the absence of photoactivation can induce oxidative damage to human bronchial epithelial cells. Oberdörster et al. (2000) also indicated that insoluble or poorly soluble TiO_2-NPs (<0.1 μm) induce significantly greater inflammatory effect in the lower respiratory tract than chemically identical particles of the size of the accumulation mode (0.1–1 μm). The high surface area per given mass of insoluble or poorly soluble TiO_2-NPs appears to be an important determinant of their inflammatory potency. Low-dose endotoxin inhalation can sensitize the respiratory tract to enhance the inflammatory response of TiO_2-NPs.

Pulskamp et al. (2007) reported that exposure to CB-NPs resulted in a decrease of cell viability and revealed that CB-NPs are able to generate reactive oxygen species in a cell-free system, which may also contribute to enhanced oxidative stress. Elder et al. (2005) also demonstrated that exposure to high concentrations of CB-NPs produces lung tumors in rats, but not mice or hamsters, presumably due to secondary genotoxic mechanisms involving persistent lung inflammation and injury. Lung inflammation and histopathology were more severe and prolonged in rats than in mice and hamsters.

2.2 Exposure analysis in the workplace

Analyses of NP concentrations, size distribution, and the intended use of the manufactured TiO_2-NPs and CB-NPs were carried out. NP concentrations and size distribution data were obtained from a TiO_2-NP manufacturing laboratory and a CB plant from studies by Chen et al. (2007) and Kuhlbusch et al. (2004), respectively. Chen et al. (2007) reported a method for the continuous generation of TiO_2-NPs by dielectric barrier discharge process and measured the number size distribution in the production process in a manufacturing laboratory. Kuhlbusch et al. (2004) measured the NPs of number size distributions during forklift operation near the sampling instrumentation that workers may be exposed to in the bag filling areas in CB plants. The NPs were most likely attributed to exhaust emissions from forklift and gas heater running. Based on very conservative assumptions, we adopted the experimental data to assess the potential exposure risk in CB plants due to workers who may be exposed to part of CB-NPs. Therefore, we reconstructed the TiO_2-NP concentration of continuous generation in a manufacturing laboratory (Chen et al. 2007) while CB-NP concentration during forklift use in CB plants (Kuhlbusch et al. 2004).

This study simulated NP distribution probability according to investigations in the workplace by Chen et al. (2007) and Kuhlbusch et al. (2004). Since it is usually more accepted to quantify NP exposure levels using the surface area dose (Sager and Castranova 2009), exposure analysis of number concentration was converted to surface area dose (Fig. 1b) using the equation given below (Maynard 2003):

$$\mathrm{SA} = N\pi {d_\mathrm{S}}^2, \tag{1}$$

$$d_\mathrm{S} = \mathrm{CMD}\, e^{\mathrm{Ln}^2\sigma_\mathrm{g}}, \tag{2}$$

where SA is the surface area concentration (m^2/m^3); N is the number concentration (particles/m^3); d_S is the particle diameter of average surface area (m); CMD is particle count median diameter (m); and σ_g is geometric standard deviation. The airborne TiO_2-NP and CB-NP number concentration distributions were measured according to Chen et al. (2007) and Kuhlbusch et al. (2004). In this study, we considered the d_S of TiO_2-NPs and CB-NPs approximate to 20 and 14 nm for consistency with effect analysis of pulmonary cytotoxicity and inflammation studies. The primary data of exposure analysis (Table 1)

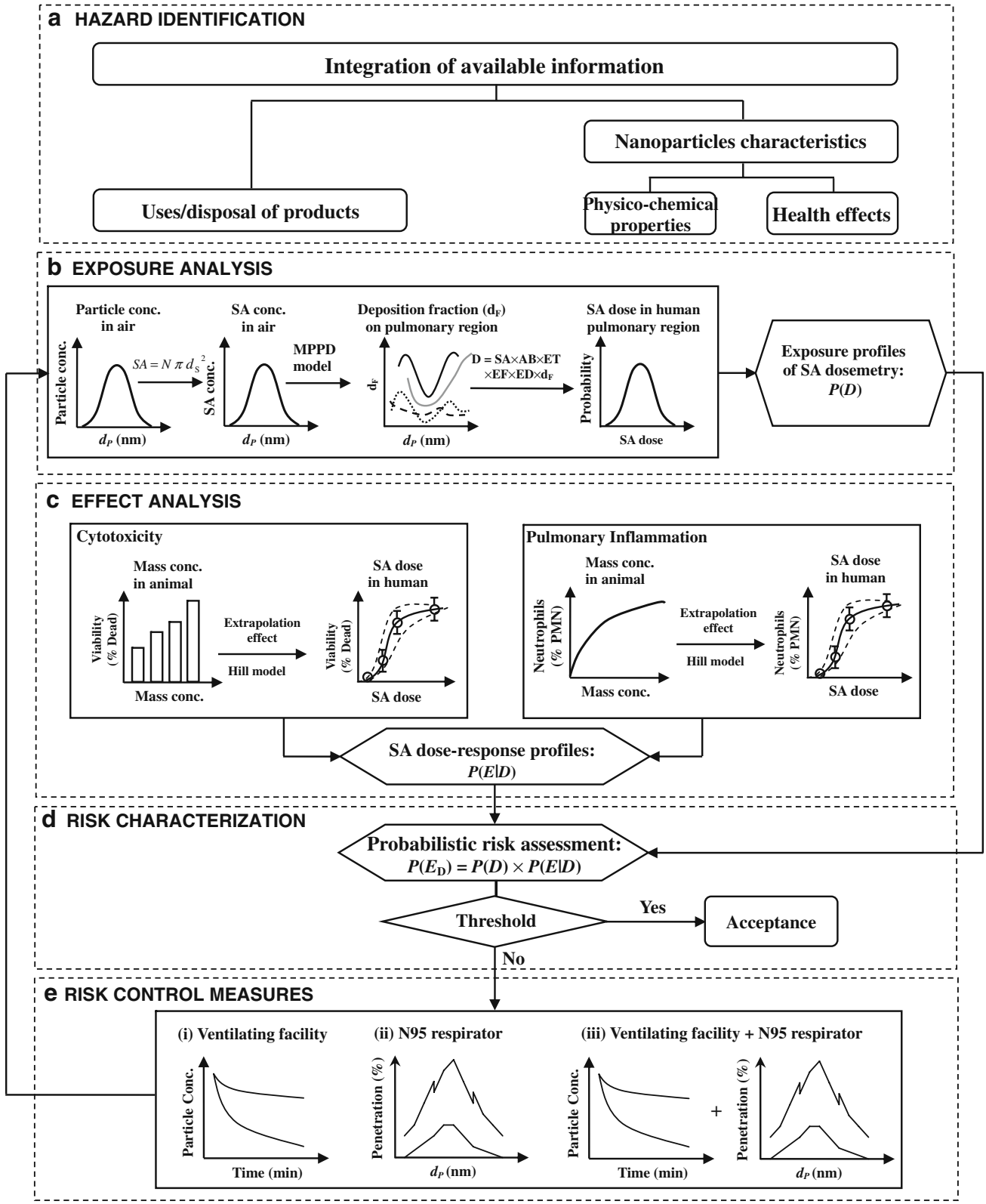

Fig. 1 Schematic for risk management of airborne engineered NPs

Table 1 Primary data used to analyze the exposure models

Primary data	TiO_2-NPs[a]	CB-NPs[b]
Particle size (nm)	20	14
Number concentration (particles/cm^3)	7.1×10^3–1.8×10^4	1.3×10^5–1.7×10^5
Process	Using the atmospheric pressure plasma enhanced NP synthesis process obtained at different applied voltages to generating TiO_2-NPs	Operating the forklift near the instrumentation in different CB plants
Workplace	TiO_2-NP manufacture laboratory	CB plant

[a] Adapted from Chen et al. (2007)

[b] Adapted from Kuhlbusch et al. (2004)

were obtained from Chen et al. (2007) and Kuhlbusch et al. (2004).

The MPPD model was used to estimate the diameter and deposition fraction distribution of NPs in varying regions of the lung. The lung regions include head, tracheobronchial, and pulmonary region. The exposure model based on surface area dosimetry gives the following:

$$D = \mathrm{SA} \times AB \times ET \times EF \times ED \times d_{\mathrm{F}}, \tag{3}$$

where D is cumulative surface area-based NP dose of exposure (m^2); AB is the rate of inhalation (1.07 m^3/h; ICRP 1995); ET is the time of exposure (8 h/day); EF is the frequency of exposure (240 days/year); ED is the duration of exposure (30 years); and d_{F} is the deposition fraction of NPs in the lung regions (dimensionless).

2.3 Effect analysis for workers

Effect analysis was undertaken with regard to pulmonary cytotoxicity and inflammation. Pulmonary inflammation was quantified according to the number of infiltrating polymorphonuclear neutrophils (PMN), which is one of the first immune cells to migrate to sites of inflammation. The data for the effect of TiO_2-NPs and CB-NPs on lung cell cytotoxicity were obtained from Gurr et al. (2005) and Pulskamp et al. (2007), and the data for PMN counts were derived from the research of Oberdörster et al. (2000) and Elder et al. (2005). Gurr et al. (2005) demonstrated that TiO_2-NPs (particle size ~20 nm) in the absence of photoactivation can induce oxidative damage to human bronchial epithelial cells. Pulskamp et al. (2007) indicated that rat alveolar macrophage cells exposed to CB-NPs (particle size ~14 nm) can decrease cell viability. Oberdörster et al. (2000) demonstrated that TiO_2-NPs (~20 nm) can cause a significant acute pulmonary inflammatory response for lung lavage in mice at 6, 24, and 48 h after intratracheal instillation of different doses. Elder et al. (2005) reported on lung inflammation in rats induced by subchronic inhalation of CB-NPs (~14 nm) of different doses for 13 weeks. Oberdörster et al. (2000) and Elder et al. (2005) used PMN to represent a sensitive indicator of pulmonary inflammation. So we used PMN counts to represent pulmonary inflammation and compare the risk difference of TiO_2-NPs and CB-NPs. The primary data of effect analysis are obtained from Gurr et al. (2005), Pulskamp et al. (2007), Oberdörster et al. (2000), and Elder et al. (2005) in Table 2.

Combining the toxicological effect with the Hill equation model allowed us to formulate the equation for optimal effect profile (Fig. 1c):

$$E(D) = \frac{E_{\mathrm{MAX}} \times D^n}{ED_{50}^n + D^n}, \tag{4}$$

where $E(D)$ is the effect for a specific surface area-based NPs dose D; E_{MAX} is the maximum measured effect; ED_{50} is the cumulative surface area-based NP dose yielding half the maximal effect E_{MAX} (m^2); D is the cumulative surface area-based NP dose deposited in the human lung regions (m^2); and the exponent n is a fitted Hill coefficient. A value of $n>1$ indicates a positively cooperative reaction. We used TableCurve 2D (version 5.01, AISN Software Inc., Mapleton, OR, USA) to optimize the dose–response profile with significance set at $p<0.05$.

We treated the ED_{50} value in Eq. 4 probabilistically. The cumulative distribution function (CDF) of the predicted effect function for a given surface area-based cumulative NP dose is expressed as a conditional CDF:

$$P(E|D) = \Phi\left(\frac{E_{\mathrm{MAX}} \times D^n}{ED_{50}^n + D^n}\right), \tag{5}$$

where $\Phi(\bullet)$ is the cumulative standard normal distribution.

In this study, for TiO_2-NP-induced cytotoxicity effect, we integrated the exposure of D for tracheobronchial region with the cytotoxicity effect for human bronchial epithelial cells, whereas for TiO_2-NP-induced pulmonary inflammation effect, we integrated the exposure of D for pulmonary region with the pulmonary inflammation effect for intra-

Table 2 Primary data used to analyze the effect models of pulmonary cytotoxicity and inflammation

Primary data	Cytotoxicity		Inflammation	
	TiO_2-NPs[a]	CB-NPs[b]	TiO_2-NPs[c]	CB-NPs[d]
Particle size (nm)	20	14	20	14
Experiment method	Cell culture: human bronchial epithelial cells (MTT assay)	Cell culture: rat alveolar macrophage cells (MTT assay)	Animal: mice Exposure route: intratracheal instillation	Animal: rats Exposure route: inhalation
	Dose: 0.01, 0.5, 1, 2, 4, 8, 10 μg/mL	Dose: 5, 10, 50, 100 μg/mL	Dose: 6, 25, 100 μg	Dose: 1, 7, 50 mg/m^3
	Duration: 3 days	Duration: 24 h		Duration: 1 day
Response	Viability (% dead): 8.6 ± 0.5, 27.2 ± 4.6, 39.6 ± 3.1, 39.9 ± 5.7, 54.1 ± 5.4, 64.7 ± 2.6	Viability (% dead): 20.0 ± 4.2, 50 ± 3.9, 62.2 ± 3.6, 80.0 ± 1.5	PMN (%): 1.4 ± 1.8, 18.7 ± 3.6, 45.6 ± 7.6	PMN (%): 0.8 ± 2.2, 17.6 ± 4.8, 48.0 ± 3.1

[a] Adapted from Gurr et al. (2005)

[b] Adapted from Pulskamp et al. (2007)

[c] Adapted from Oberdörster et al. (2000)

[d] Adapted from Elder et al. (2005)

tracheal instillation in mice. For CB-NP-induced cytotoxicity effect and pulmonary inflammation effect, we estimated the exposure of D for pulmonary region with the cytotoxicity effect for rat alveolar macrophage cells and the pulmonary inflammation effect for inhalation in rats, respectively.

2.4 Risk characterization

Risk characterization provides an estimate of risk for the given sample, which in this study comprised workers in the nanotechnology industry workplace. Risk to a specific target organ with dose D can be calculated as the proportion of the group that is expected to have that tissue dose multiplied by the conditional probability of adverse effects for the given dose D. Risk characterization integrates the results of the exposure analysis and the effect analysis mentioned above using the probabilistic risk concept to estimate the health risk of workers exposed to TiO_2-NPs and CB-NPs. This is given by Fig. 1d:

$$P(E_D) = P(D) \times P(E|D), \tag{6}$$

where $P(E_D)$ is the probabilistic risk of exposure to a specific cumulative dose D of NPs; $P(D)$ is the probability of surface area-based cumulative dose D of NPs in the pulmonary region of the human lung; and $P(E|D)$ is the CDF of the adverse effect, given the surface area-based cumulative NPs dose D of the pulmonary region of the human lung.

2.5 Risk control measures

The efficacies of three different control measures in reducing TiO_2-NP and CB-NP concentrations were evaluated. These included: (1) a ventilating system (HVAC filter and updraft hood), (2) personal N95 respirator protection, and (3) a ventilating system (HVAC filter) combined with N95 respirator protection (Fig. 1e). The HVAC filter is a heating, ventilation, and air conditioning system. At present, its application has been mainly for the maintenance of indoor air quality. The efficiency of reducing NP concentration using the ventilating system can be expressed as the following (Pui et al. 2008):

$$\frac{dN}{dt} = \frac{QN(1-\eta) - QN}{V} + I \tag{7}$$

where N is the concentration of NPs (particles/cm^3); Q is the ventilation flow velocity (L/min); V is the volume of the workplace (m^3); η is the efficiency of ventilation that reduces NP concentration; and I is the rate of NPs entering a controlled volume from any source or infiltration (particles/cm^3/min).

Data on ventilation flow velocity (Q) and efficiency of ventilation (η) were obtained from two sources: (1) Pui et al. (2008) indicated that an open-loop wind tunnel could be used to recirculate air through a room with a Viledon HVAC filter (Freudenberg Nonwovens L.P., Hopkinsville, KY, USA) at Q=50,970 L/min, η=67.99%, and (2) Institute of Occupational Safety and Health, Taiwan (IOSH, Taiwan 2007), which used a general updraft hood with Q=7,056 L/min, η=60%. The volume (V) of the workplace was 280 m^3 and the rate of NP entry into the controlled volume from a particular source or via infiltration (I) was 479.27 particles/cm^3/min according to Pui et al. (2008).

The fiber filtration efficiency of the N95 respirator is dependent on NP diffusion and interception mechanics. In

this study, diffusion and interception mechanics were considered since the diameter of TiO_2-NPs and CB-NPs approximate to 20 and 14 nm according to Chen et al. (2007) and Kuhlbusch et al. (2004). The penetration efficiency of NPs through an N95 respirator was 0.003% for TiO_2-NPs and 0.0016% for CB-NPs, as derived from the effect of inhalation flow rate observed by Bałazy et al. (2006).

2.6 Uncertainty analysis

Uncertainty arises from the estimation of both exposure and effects. In order to reduce the uncertainties between intraspecies, interspecies, and short-term to longer term differences, we consider the uncertainty factor (UF) in this study. The $P(E|D)$ of TiO_2-NPs on human bronchial epithelial cell cytotoxicity was then derived by the overall UF of 100. The overall UF of 100 comprises a UF of 10 for intraspecies differences (human variability) and 10 for extrapolation from short-term to longer term data. The $P(E|D)$ of CB-NPs on rat alveolar macrophage cells cytotoxicity was then derived by the overall UF of 1,000. The combined UF of 1,000 represents UFs of 10 to account for interspecies differences (animal-to-human extrapolation), 10 for intraspecies differences (human variability), and 10 for extrapolation from short-term to longer term data. Furthermore, the $P(E|D)$ of TiO_2-NPs for pulmonary inflammation was then derived by the overall UF of 10,000 (10 for animal-to-human extrapolation, 10 for human variability, 100 for acute-to-chronic extrapolation; USEPA 1995). The $P(E|D)$of CB-NPs for pulmonary inflammation was then derived by the overall UF of 1,000 (10 for animal-to-human extrapolation, 10 for human variability, 10 for subchronic-to-chronic extrapolation; Ahlers et al. 2006).

Due to uncertainty within a particular dataset, such as that related to exposure analysis of number concentration and dose–response function, equation variables were defined in terms of a probability density function (PDF) derived from a limited number of observations. The software program Crystal Ball® (version 7.3, Decisioneering, Inc., Denver, CO, USA) was used to analyze data and to estimate distribution parameters. The selected distribution type was based on statistical criteria. To provide an estimate for each of the model parameters, Monte Carlo (MC) analysis was performed to generate the probability distributions. The chi-square (χ^2) and Kolmogorov–Smirnov (K-S) goodness-of-fit were used to determine the optimal fitted distributions for MC simulation.

To explicitly account for this uncertainty and its impact on the estimation of $P(E_D)$ and $N(t)$, an MC simulation was applied. To test the convergence and the stability of the numerical output, we performed independent runs at 1,000, 4000, 5,000, and 10,000 iterations, with each parameter sampled independently from the appropriate distribution at the start of each replicate. Inputs were assumed to be independent, largely because of limitations in the data used to derive model parameters. The result showed that 10,000 iterations were sufficient to ensure the stability of results.

3 Results and discussion

3.1 Personal exposure assessment

In this study, we reconstructed the TiO_2-NP (particle size ~20 nm) concentration of continuous generation in a manufacturing laboratory (Chen et al. 2007) while CB-NP (particle size ~14 nm) concentration during forklift use in a CB plant (Kuhlbusch et al. 2004). Selected log-normal distributions had acceptable χ^2 and K-S tests in optimizations that used either the geometric mean (gm) or geometric standard deviation (gsd), expressed as LN(gm, gsd). Figure 2 illustrates PDFs of the optimized log-normal distribution, with the gm and gsd shown for the various concentrations of TiO_2-NPs. TiO_2-NP and CB-NP concentrations were LN(11,255.7 particles/cm^3, 1.36) and LN (148,433.7 particles/cm^3, 1.07), respectively (Fig. 2).

Figure 3 shows the relationship between particle diameter and the deposition fraction of TiO_2-NPs and CB-NPs in

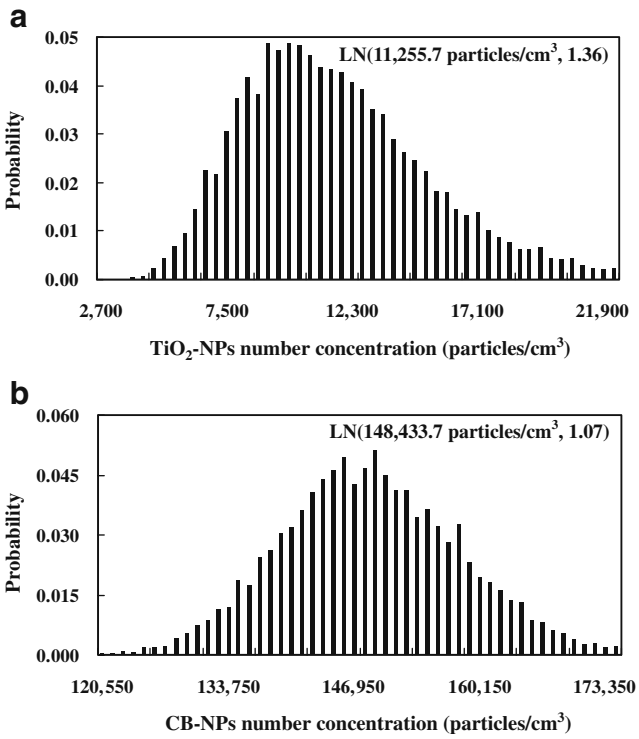

Fig. 2 Probabilistic density distributions of TiO_2-NP concentration in a TiO_2-NP manufacturing laboratory (**a**) and CB-NP concentration in a CB plant (**b**)

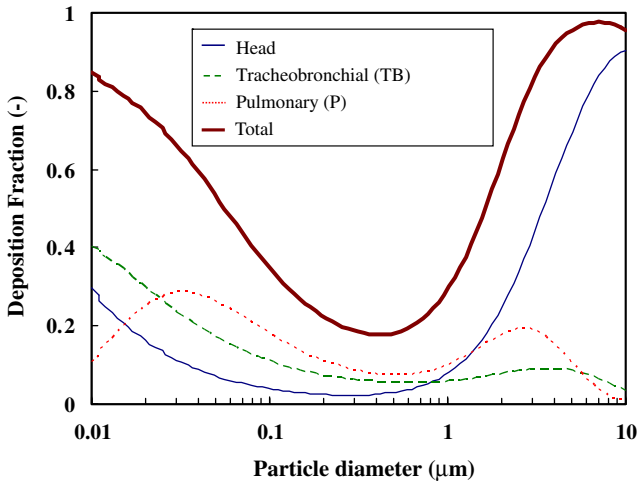

Fig. 3 Deposition fraction estimations in different lung regions by the MPPD model

the pulmonary region of the human lung by the MPPD model. Figures 4b, d and 5b, d illustrate the predicted PDFs by incorporating Eqs. 1 and 2 into Eq. 3, which resulted in PDFs relative to surface area-based TiO_2-NP and CB-NP doses in the pulmonary region of the lung. Figures 4b and 5b depict the PDFs relative to surface area-based TiO_2-NP dose, while Fig. 4d and 5d show the PDFs relative to surface area-based CB-NP dose. The surface area-based cumulative dose of TiO_2-NPs inside the pulmonary region of the lung was LN(0.21 m^2, 1.36), whereas the surface area-based cumulative dose for CB-NPs was LN(3.29 m^2, 1.07). These results suggested that the cumulative dose of CB-NPs was greater than the cumulative dose of TiO_2-NPs inside the pulmonary region of the lung.

3.2 Dose–response assessment

The dose–response relationships for pulmonary cytotoxicity and inflammation for TiO_2-NPs are shown in Figs. 4c and 5c. These results indicated that the effective dose that corresponded to a 10% increase in cytotoxicity-related adverse effects (EC_{10}) for TiO_2-NPs was 0.014 m^2 (95% CI=0.009–0.023 m^2), while the EC_{10} of TiO_2-NPs for pulmonary inflammation was 0.065 m^2 (95% CI=0.053–0.089 m^2). The dose–response relationships for cytotoxicity and pulmonary inflammation for CB-NPs are shown in Figs. 4e and 5e. Results indicated that the EC_{10} of CB-NPs for causing pulmonary cytotoxicity and inflammation was 0.023 m^2 (95% CI=0.011–0.047 m^2) and 0.60 m^2 (95% CI=0.49–0.71 m^2), respectively.

3.3 Risk estimation

We applied the plotted probabilities calculated from the outcome of the MC simulation method to estimate the risks associated with exposure to TiO_2-NPs and CB-NPs in the workplace. The MC simulation method was used to simulate 10,000 iterations to obtain the risk curves with the best fit. Figure 4a shows the risk curve for cytotoxicity, with the probability that 50% or more of workers are affected by TiO_2-NPs (risk=0.50) being approximately 44.7% (95% CI=41.1–49.3%, per 100) and 80.8% (95% CI=74.7–89.7%) by CB-NPs. Figure 5a shows that the exceedance risk of pulmonary inflammation (measured as PMN increase) that was caused by TiO_2-NPs (per 100, risk=0.50) was approximately 35.5% (95% CI=31.4–39.9%), whereas an exceedance risk of 43.8% (95% CI=41.6–46.1) was observed for CB-NPs.

Figures 4a and 5a show that with regard to pulmonary cytotoxicity and inflammation, the exposure risk for CB-NPs was approximately two times higher than TiO_2-NPs. There were two main reasons why this was so: (1) According to the exposure dose analyses, CB-NP doses were significantly higher in the lung compared to TiO_2-NPs, and (2) in the context of pulmonary cytotoxicity and inflammation, dose–response analyses showed that CB-NPs caused greater harm than TiO_2-NPs. Based on the exceedance risk, there is a potential health risk for workers exposed to TiO_2-NPs and CB-NPs. However, the CB-NP concentration and size distribution data are most likely attributed to exhaust emissions from forklift and gas heater running. Based on very conservative assumptions, we adopted the experimental data to assess the potential exposure risk in CB plants due to workers who may be exposed to part of CB-NPs.

3.4 Risk management

This study assessed the effectiveness of three risk control measures: (1) a ventilating system (HVAC filter and updraft hood), (2) an N95 respirator protection, and (3) a ventilating system (HVAC filter) combined with an N95 respirator protection. The effect of having a ventilating system with a HVAC filter and an updraft hood in reducing TiO_2-NP and CB-NP concentration are shown in Fig. 6a, b, respectively. These figures show that the use of a ventilating system can effectively reduce NP number concentration. This is primarily mediated by the HVAC filter which reduces the concentration of TiO_2-NPs and CB-NPs to a greater degree than an updraft hood alone. The ventilation flow velocity Q for the HVAC filter (Q= 50,970 L/min) and the updraft hood (Q=7,056 L/min) was the most influential factor in determining ventilation effectiveness as a change in ventilation flow velocity Q resulted in a change in ventilation effectiveness.

However, we compared the concentration of no control measure and three control measures in Table 3. The results demonstrated that 90th percentiles of concentration for no

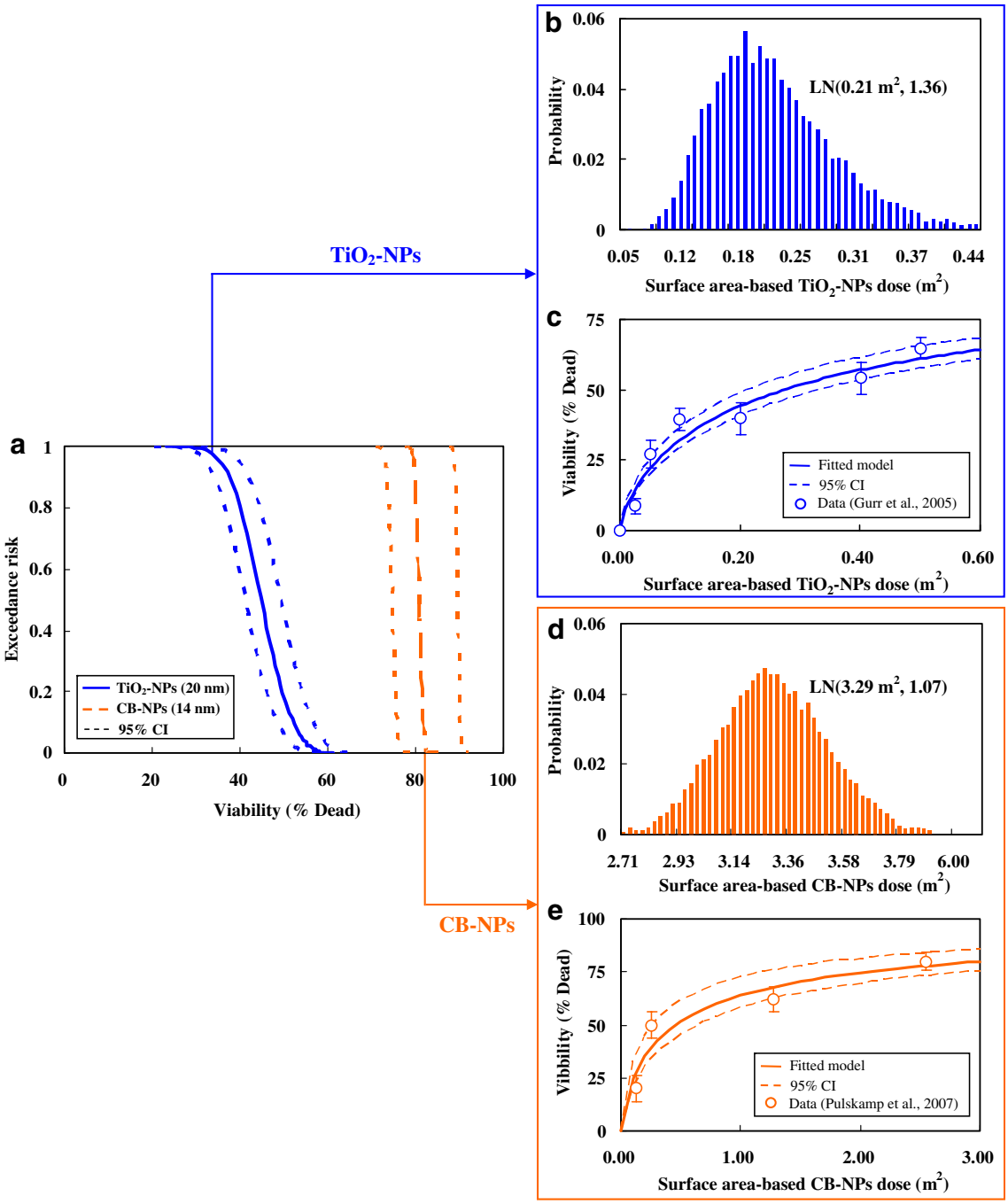

Fig. 4 Cytotoxicity risk assessment. **a** Exceedance risk (dead cell viability) functions with 95% confidence interval for airborne NPs, those with exposure profiles integrated with dose–response profiles. **b** Exposure profiles of TiO_2-NPs. **c** Dose–response profiles of TiO_2-NPs. **d** Exposure profiles of CB-NPs. **e** Dose–response profiles of CB-NPs

control measure, HVAC filter ventilation, updraft hood ventilation, N95 respirator protection, and HVAC filter ventilation combined with N95 respirator protection were 17,760, 13,533, 17,734, 46, and 35 particles/cm^3, respectively, showing that the N95 respirator protection alone and the combined HVAC filter ventilation with N95 respirator protection were more effective than using the ventilating system alone.

This study defines EC_{10} as an acceptable number concentration for exposure assessment. The acceptable airborne TiO_2-NP and CB-NP median number concentration that does not induce cytotoxicity is 780 and 1,030 particles/cm^3, respectively (Figs. 4e and 5e), while the acceptable airborne TiO_2-NP and CB-NP median concentration that does not induce pulmonary inflammation is 3,430 and 27,000 particles/cm^3, respectively (Figs. 4e and

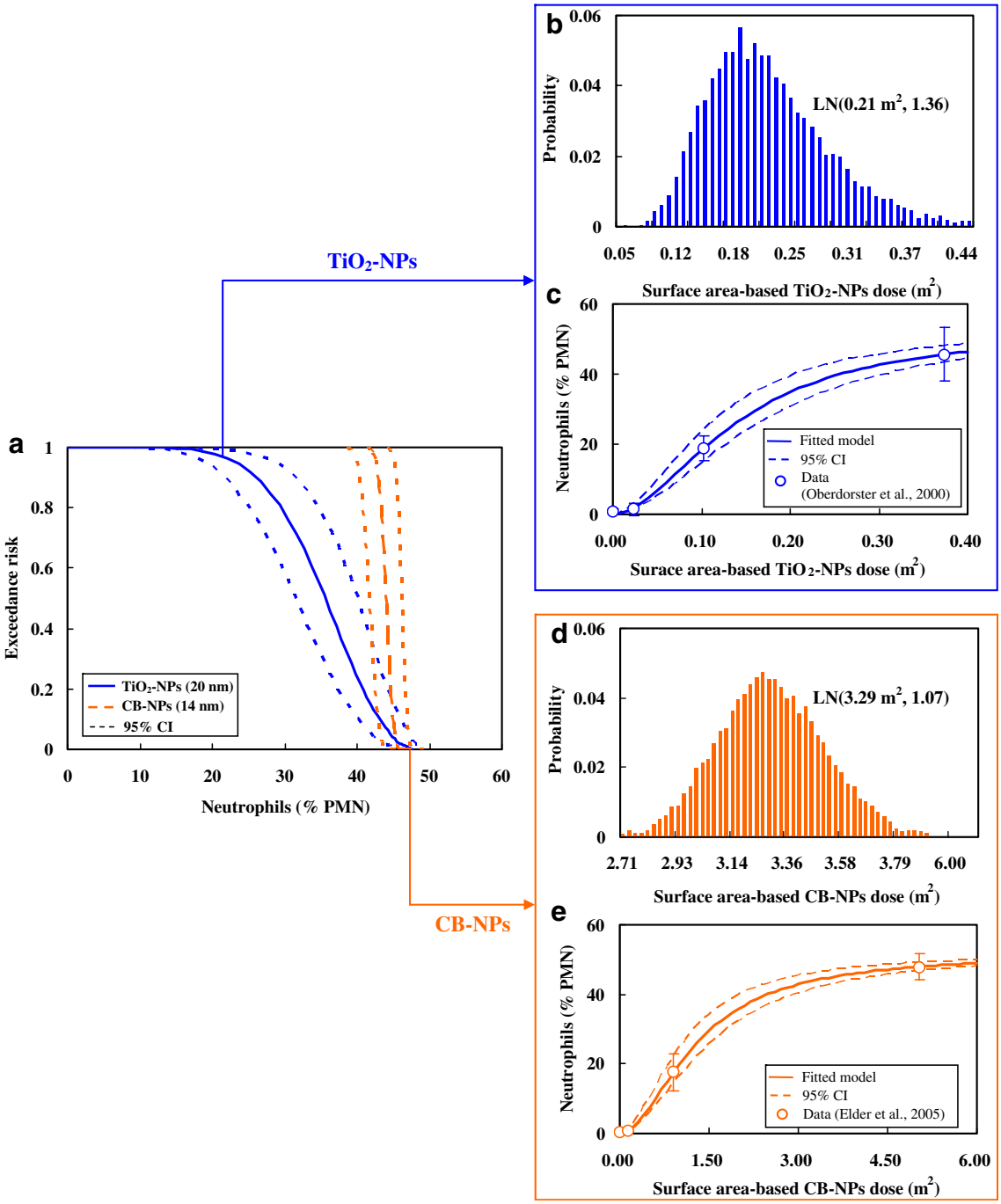

Fig. 5 Pulmonary inflammation risk assessment. **a** Exceedance risk (lung neutrophils) functions with 95% confidence interval for airborne NPs, those with exposure profiles integrated with the dose–response profiles. **b** Exposure profiles of TiO_2-NPs. **c** Dose–response profiles of TiO_2-NPs. **d** Exposure profiles of CB-NPs. **e** Dose–response profiles of CB-NPs

5e). The use of N95 respirator protection and the combined ventilating system with N95 respirator protection reduced the median TiO_2-NP concentration to 31 and 12 particles/cm^3, respectively, while the median CB-NP concentration was reduced to 194 and 12 particles/cm^3, respectively (Table 3). These reductions brought both TiO_2-NP and CB-NP concentrations within levels that were acceptable for the prevention of pulmonary cytotoxicity and inflammation. Therefore, the use of an N95 respirator protection and the combined ventilating system and N95 respirator protection can effectively reduce the concentration of TiO_2-NPs and CB-NPs to an acceptable exposure range in the workplace environment. In particular, an N95 respirator protection was able to effectively reduce exposure risk.

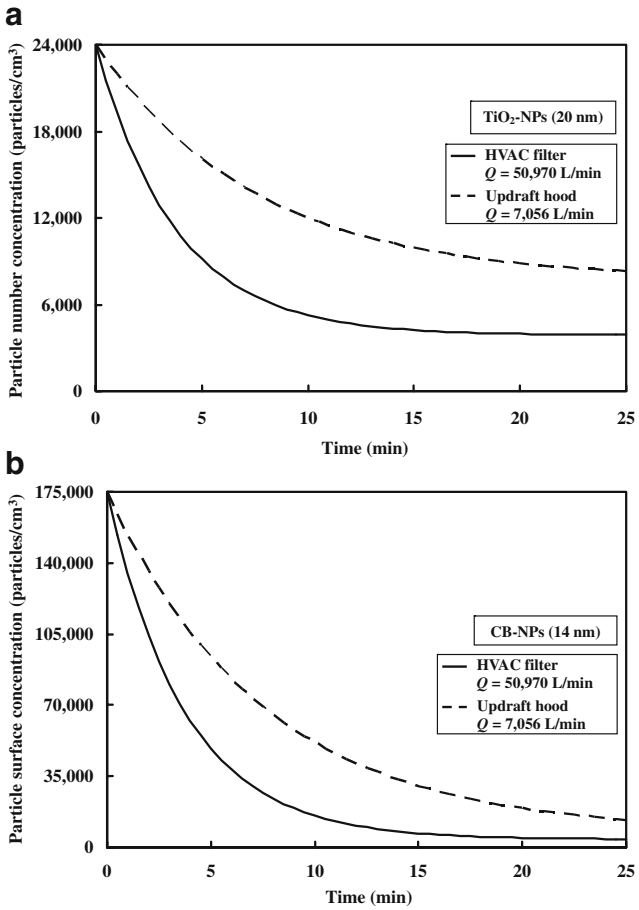

Fig. 6 Variation of TiO_2-NP (**a**) and CB-NP (**b**) concentration with time in the presence of a HVAC filter and an updraft hood

3.5 Limitations

Large manufacturers are aware of the risks associated with the introduction of new nano-level products. The occupational safety of such NPs presents many challenges with regard to concentration measurements and toxicity tests for exposure and effect analysis. The risk-based theoretical treatments described herein give detailed mechanistic information but are challenging to apply directly to the uncertainty analyses of the data. Capturing uncertainty is a key element in risk assessment. Uncertainty arises from the estimation of both exposure and effect analyses. Fortunately, the strength of our results rests on the robustness of both the proposed MPPD model and the Hill model.

The results of this study suggest that the Hill model-based dose–response profiles and the MPPD model exposure approach can be used to relate human lung cytotoxicity and pulmonary inflammation to risk profiling. Our analysis may provide a wider context for the interpretation of regional TiO_2-NP- and CB-NP-related inhalation risk profiling. Although more complex models may be necessary to answer specific research questions regarding risk or management strategies, our model allows risk analysis to be undertaken to determine the potential effects of NP exposure in the workplace. We used MPPD and Hill equation models considered from the TiO_2-NP/CB-NP exposure analysis and pulmonary cytotoxicity/inflammation effect analysis based on conservative assumption to simulate potential exposure risk for real populations of workers in the workplace. We also used the different control strategies such as ventilating system (HVAC filter and updraft hood), personal N95 respirator protection, and

Table 3 Comparison of different control measures to reduce the concentration of airborne engineered NPs in the workplace

Control measure	Concentration (particles/cm^3) for various percentiles				
	10th	25th	50th	75th	90th
TiO_2-NPs					
No control measure	8,070	9,713	11,892	14,348	17,760
(1) Ventilating facility					
HVAC filter	3,918	3,997	4,537	7,404	13,533
Updraft hood	7,904	9,587	11,854	14,677	17,734
(2) N95 respirator protection	21	25	31	37	46
(3) Ventilating facility (HVAC filter) combined with N95 respirator protection	10	11	12	19	35
CB-NPs					
No control measure	138,190	142,632	149,320	149,675	161,015
(1) Ventilating facility					
HVAC filter	4,261	4,929	9,519	33,900	86,008
Updraft hood	15,958	25,050	41,768	70,771	113,273
(2) N95 respirator protection	180	185	194	195	209
(3) Ventilating facility (HVAC filter) combined with N95 respirator protection	6	7	12	44	112

ventilating system (HVAC filter) combined with an N95 respirator protection to simulate the efficacy of three control measures.

3.6 Control measure implications

These risk analyses indicated a higher potential health risk to workers exposed to TiO_2-NPs and CB-NPs in the absence of control measures in the workplace, with greater risks associated with CB-NPs than TiO_2-NPs. This study also investigated the effectiveness of using three control measures by applying ventilating facility (HVAC filter and updraft hood), N95 respirator protection, and a combination of both on reducing airborne NP exposure in the workplace. The use of an N95 respirator protection effectively reduced the concentration of TiO_2-NPs and CB-NPs to an acceptable exposure risk.

We considered the concentration of NPs, ventilation flow velocity, volume of the workplace, efficiency of ventilation that reduces NP concentration, and rate of NPs entering a controlled volume from any source or infiltration parameters. Our findings demonstrated that protective devices and systems were able to reduce the exposure of workers to NP number concentration in the workplace. The findings are consistent with the recently reported observation by Han et al. (2008) and Old and Methner (2008) that the engineering control strategies reduce the concentration of airborne nanomaterials in the workplace.

Evaluation of the cumulative NP dose in the lung using the MPPD model showed that the cumulative dose of CB-NPs was higher than TiO_2-NPs. Without any control measures in place and where the probability that 50% or more of workers are affected by NPs (risk=0.50), 44.7% of cytotoxicity effects were attributed to TiO_2-NPs while 80.8% were attributed to CB-NPs. In addition, 35.5% of pulmonary inflammation effects were caused by TiO_2-NPs while 43.8% were caused by CB-NPs. Assessment of exposure risk illustrated that TiO_2-NPs and CB-NPs in the air were not within an acceptable safety range and, as a result, may pose a threat to the health of workers. Moreover, it was determined that greater risk was associated with CB-NPs than TiO_2-NPs.

Although respiratory personal protective equipment may cause physical burden to the workers and unable to provide eye protection, however, as a precautionary measure, it is often recommended that workers take steps to reduce their exposure to airborne NPs through the use of respiratory protective devices (Shaffer and Rengasamy 2009). Recent studies (Kim et al. 2010; Golanski et al. 2010) indicated that the electrostatic filtration system can effectively remove the NPs. The electrostatic filtration systems have higher efficiency for NPs than traditional ventilating systems; however, electrostatic filtration is under development and needs higher cost and technique to accomplish. The control measures will be considered in the future when the technology is more mature and popular. If the electrostatic filtration system could be applied, the physical burden from respiratory personal protective equipment and inability to provide eye protection from normal filter masks may be avoided.

4 Conclusions

This study assessed the potential exposure risks for workers in the workplace exposed to airborne TiO_2-NPs and CB-NPs. Potential risk control measures were also developed for such workplaces. This study concluded that: (1) the cumulative dose of CB-NPs was greater than that of TiO_2-NPs in human lungs; (2) there is a potential health risk to workers exposed to TiO_2-NPs and CB-NPs in the absence of control measures in the workplace, with higher health risks associated with CB-NPs than TiO_2-NPs; and (3) the use of a ventilating system and an N95 respirator offers greater protection in the workplace and significantly reduces the health risks associated with NP exposure. This study suggests that the most effective way to reduce airborne NPs is to incorporate the use of a ventilating system combined with an N95 respirator protection.

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