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Short term inhalation toxicity of a liquid aerosol of glutaraldehyde-coated CdS/Cd(OH)$_2$ core shell quantum dots in rats

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HIGHLIGHTS

- We examined the inhalation toxicity and translocation ability of coated CdS/Cd(OH)$_2$ quantum dots in rats.
- Broncho-alveolar lavage fluid examinations and microscopy were performed.
- Inflammatory process was observed by examination of broncho-alveolar lavage fluid.
- Quantum dots caused less toxicity compared to compounds with larger particle sizes.
- No translocation of the particles from lung to other organs were observed.
- Small particle sizes are not the only factor triggering the toxic response or translocation.

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ABSTRACT

Quantum dots exhibit extraordinary optical and mechanical properties, and the number of their applications is increasing. In order to investigate a possible effect of coating on the inhalation toxicity of previously tested non-coated CdS/Cd(OH)$_2$ quantum dots and translocation of these very small particles from the lungs, rats were exposed to coated quantum dots or $CdCl_2$ aerosol (since Cd^{2+} was present as impurity), 6 h/d for 5 consecutive days. Cd content was determined in organs and excreta after the end of exposure and three weeks thereafter. Toxicity was determined by examination of broncho-alveolar lavage fluid and microscopic evaluation of the entire respiratory tract. There was no evidence for translocation of particles from the respiratory tract. Evidence of a minimal inflammatory process was observed by examination of broncho-alveolar lavage fluid. Microscopically, minimal to mild epithelial alteration was seen in the larynx. The effects observed with coated quantum dots, non-coated quantum dots and $CdCl_2$ were comparable, indicating that quantum dots elicited no significant effects beyond the toxicity of the Cd^{2+} ion itself. Compared to other compounds with larger particle size tested at similarly low concentrations, quantum dots caused much less pronounced toxicological effects. Therefore, the present data show that small particle sizes with corresponding high surfaces are not the only factor triggering the toxic response or translocation.

1. Introduction

Quantum dots are crystalline nanoparticles exhibiting semiconductor properties, consisting of a crystalline core and a surrounding cap, which protects the core. They exhibit extraordinary optical and mechanical properties. However, increased application of quantum dots potentially leads to higher human exposure and therefore to concerns regarding health effects, since quantum dots, being nanoparticles, can easily penetrate biological

Abbreviations: BALF, broncho-alveolar lavage fluid; GSD, geometric standard deviation; ICP-MS, inductively coupled plasma mass spectrometry; MMAD, mass median aerodynamic diameter; SMPS, scanning mobility particle sizer; TEM, transmission electron microscopy.

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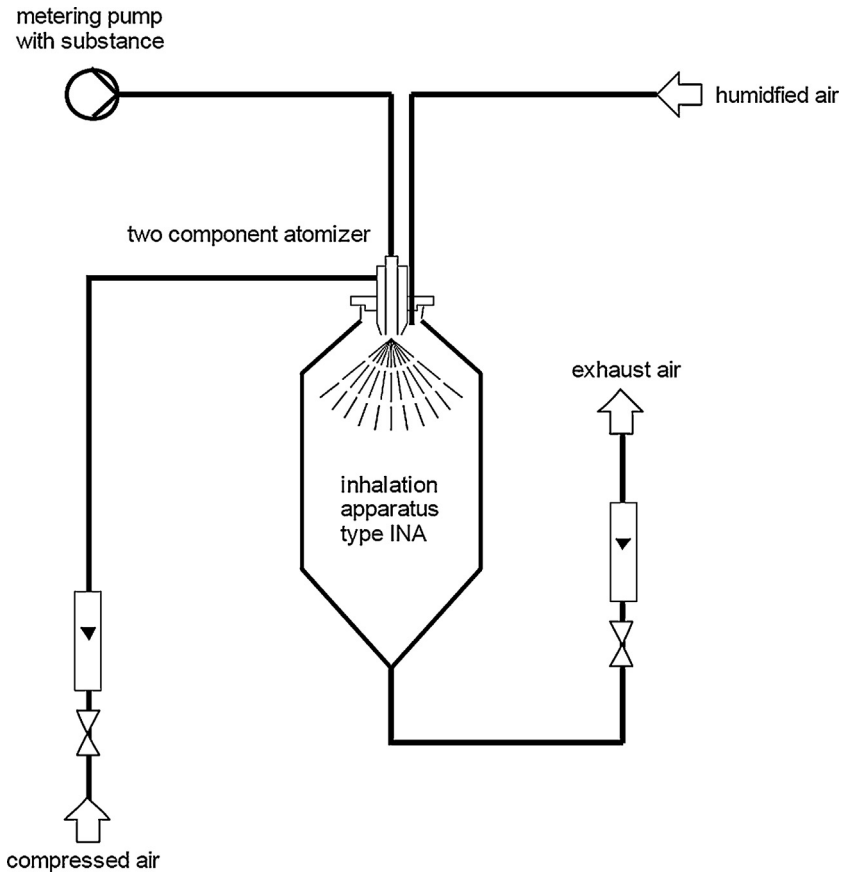

Fig. 1. Schematic diagram of the inhalation exposure chamber and aerosol generation.

barriers. Among the different possible exposure routes, inhalation is considered to be the most relevant one.

The results of available inhalation toxicity studies with nanomaterials have shown that in principle the lung is the primary target organ, with local inflammation being the most prominent effect. However, the extent of toxicity is dependent on many physico-chemical properties, like particle size distribution (Elder et al., 2005), surface area (Oberdörster et al., 1994), agglomeration state (Wick et al., 2007; Mercer et al., 2008), shape (Poland et al., 2008; Mühlfeld et al., 2012), charge (Karakoti et al., 2006), surface lipophilicity/hydrophilicity (Bottini et al., 2006), surface chemistry (e.g. partial oxidation, structural defects, and impurities) (Bottini et al., 2006; Muller et al., 2008; Fenoglio et al., 2008), and finally the amount of lung burden (Morrow, 1988). A detailed examination of the physico-chemical properties is therefore a crucial pre-requisite for the evaluation of the results with these nanomaterials. Furthermore, it has to be taken into account is the translocation of inhaled materials to other organs, as shown for ultrafine iridium and carbon particles (Kreyling et al., 2002; Oberdörster et al., 2004).

Usually, 28- or 90-day inhalation toxicity studies are carried out in order to generate data for a subsequent risk assessment. Since these studies are considerably time-consuming, a short-term inhalation test protocol was developed in order to test a larger amount of nanomaterials in a shorter time period. In this test protocol, male rats are exposed nose-only to different concentrations of the test compound, 6 h/d, for 5 days, followed by an approximately three week exposure free period. As an additional endpoint, broncho-alveolar lavage fluid (BALF) is examined for mediators indicative for pro-inflammatory and pro-fibrotic changes, increasing the predictivity of this short-term inhalation test for long-term effects. These results can be used as a basis for a quantitative risk assessment (Ma-Hock et al., 2009a; Van Ravenzwaay et al., 2009; Landsiedel et al., 2010; Klein et al., 2012).

Using this experimental design, exposure to $CdS/Cd(OH)_2$ core shell quantum dots at a concentration of 4.1 mg/m^3 (corresponding to 0.52 mg/m^3 Cd) caused a slight local inflammation in the lung, characterized mainly by increased polymorphonuclear neutrophils in BALF and by histopathological examination of the lung. There was no evidence of translocation of the material into the brain (Ma-Hock et al., 2012).

The aim of the present study was to investigate the inhalation toxicity of $CdS/Cd(OH)_2$ core shell quantum dots, which were coated with glutaraldehyde and to compare the results with the available data of the non-coated material. In order to differentiate between effects caused by nanomaterial and effects driven by release of Cd^{2+} ions, or Cd^{2+} ions present as impurity, a $CdCl_2$ aerosol was tested in parallel. Additionally, these very small quantum dots were used as model particles to proof the hypothesis on the particle size dependent transport of particles through the lung into other organs.

2. Materials and methods

2.1. Characterization of the test material

$CdS/Cd(OH)_2$ core shell quantum dots were produced by the Research Group on Nanostructures and Biological Interfaces (NIB), UFPE, Recife, PE, Brazil, as previously described (Ma-Hock et al., 2012). Coating was performed by adding a 0.01% glutaraldehyde solution (QD containing suspension; glutaraldehyde solution, ratio volume/volume 10:1) at room temperature under continuous stirring for 20 min. Evaluation of the characterization selected methods has been reported elsewhere (Wohlleben et al., 2013). In short, size and crystalline structure of coated quantum dots were characterized using transmission electron microscopy (TEM) and selected area diffraction. Impurities were determines by energy dispersive X-ray