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Computational fluid dynamics simulations of submicrometer and micrometer particle deposition in the nasal passages of a Sprague-Dawley rat

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ABSTRACT

Computational fluid dynamics (CFD) simulations were conducted in a model of the complete nasal passages of an adult male Sprague-Dawley rat to predict regional deposition patterns of inhaled particles in the size range of 1 nm to 10 μm. Steady-state inspiratory airflow rates of 185, 369, and 738 ml/min (equal to 50%, 100%, and 200% of the estimated minute volume during resting breathing) were simulated using Fluent™. The Lagrangian particle tracking method was used to calculate trajectories of individual particles that were passively released from the nostrils. Computational predictions of total nasal deposition compared well with experimental data from the literature when deposition fractions were plotted against the Stokes and Peclet numbers for micro- and nanoparticles, respectively. Regional deposition was assessed by computing deposition efficiency curves for major nasal epithelial cell types. For micrometer particles, maximum olfactory deposition was 27% and occurred at the lowest flow rate with a particle diameter of 7 μm. Maximum deposition on mucus-coated non-olfactory epithelium was 27% for 3.25 μm particles at the highest flow rate. For submicrometer particles, olfactory deposition reached a maximum of 20% with a particle size of 5 nm at the highest flow rate, whereas deposition on mucus-coated non-olfactory epithelium reached a peak of approximately 60% for 1–4 nm particles at all flow rates. These simulations show that regional particle deposition patterns are highly dependent on particle size and flow rate, indicating the importance of accurate quantification of deposition in the rat for extrapolation of results to humans.

1. Introduction

Inhalation toxicology studies frequently rely on laboratory animals to study the effects of inhaled particles and gases. Quantitative estimates of respiratory tract dose can then be used to derive dose–response relationships for subsequent

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extrapolation to humans for health risk assessment. Nasal filtering efficiency is important to quantify not only to determine the amount that reaches the lung in nose-breathing animals, but also since the nose is a target site for large microparticles and small nanoparticles. The nasal geometries of rats and humans are both quite complex, yet they contain significant anatomical differences that lead to differences in airflow and particle deposition patterns between species. An accurate assessment of regional particle deposition in the rat nasal passages is therefore essential for extrapolating potential toxicological effects from inhaled particles to human exposure scenarios.

Many experimental studies have been conducted to measure particle deposition in the upper respiratory tract of rats using *in vivo* methods (Gerde et al., 1991; Kelly et al., 2001a; Raabe et al., 1977, 1988; Wolff et al., 1984) and *in vitro* experiments with replica molds (Cheng et al., 1990; Kelly et al., 2001b; Wong et al., 2008). *In vivo* exposures have the advantage of simulating real physiological conditions, but experiments can be difficult and costly and may involve a large number of animals that subject results to high variability. Studies using replica molds are reproducible and can easily accommodate multiple flow rates and particle sizes, but may not perfectly replicate exposure conditions found *in vivo*. Nevertheless, nasal molds have been shown to be adequate surrogates for live animals for estimating nasal particle deposition and both techniques have provided consistent nasal deposition results (Kelly & Asgharian, 2003).

Experimental studies have shown that high diffusional deposition ($>70\%$) in the rat nose occurs for particles in the low nanometer size range ($\sim$5 nm), with deposition efficiency decreasing to less than 10% as particle size approaches 200 nm due to decreased Brownian diffusion effects (Cheng et al., 1990; Wong et al., 2008). As particle size increases above 1 μm, increased particle inertia causes further deposition, with efficiencies approaching 100% for particles >5 μm (Kelly et al., 2001a, 2001b). These studies also showed a strong influence of flow rate on deposition efficiency. As flow rate increases, deposition of nanoparticles decreases due to decreased residence times for particles to deposit by diffusion, whereas deposition of micrometer particles increases due to increased particle inertia.

While current experimental methods have provided detailed estimates of particle deposition in rats over a wide range of particle sizes, regional deposition is difficult to measure due to lack of a reliable measurement technique to quantify dose in specific locations in the rat nose. Information on regional particle deposition patterns in the rat is important for many applications in risk assessment and drug delivery due to differences in metabolism, blood flow, and tissue types. For example, localized dose estimates at standard cross-sections for nasal histopathology can be used to correlate dose and response for nasal toxicity studies (Dorman et al., 2004; Mery et al., 1994), nanoparticles that deposit on olfactory epithelium have been shown to translocate to the brain (Oberdorster et al., 2004; Tjalve & Henriksson, 1999), and inhaled drug particles may be targeted to vascularized nasal mucosa for maximal drug absorption in pharmacokinetic studies (Hirai et al., 1981).

Computational fluid dynamics (CFD) models offer an attractive option to study airflow and particle deposition in complex geometries such as those found in the respiratory system. Many recent studies have used CFD models of the rat nasal passages to analyze airflow patterns (Kimbell et al., 1997; Minard et al., 2006; Yang et al., 2007a), predict uptake of reactive gases (Kimbell et al., 2001; Schroeter et al., 2006, 2008), and study olfactory uptake of nanoparticles and odorant molecules (Garcia & Kimbell, 2009; Jiang & Zhao, 2010; Yang et al., 2007b). But to date, no CFD studies using rat nasal models have simulated total or epithelial deposition of micrometer particles. In this study, a CFD model of the complete nasal passages of an adult male Sprague-Dawley rat was used to predict total and regional deposition patterns of inhaled submicrometer (1 nm to 1 μm) and micrometer (1–10 μm) particles in the rat nose.

2. Methods

2.1. Rat nasal model

A three-dimensional model of the rat respiratory tract was previously developed from magnetic resonance (MR) images of an adult male Sprague-Dawley rat weighing approximately 600 g (Minard et al., 2006; Timchalk et al., 2001). The model consisted of the complete nasal passages (i.e., left and right nasal passages), nasopharyngeal duct, larynx, trachea, and several generations of the lung. Further details regarding the development of the model can be found in Minard et al. (2006) and Timchalk et al. (2001). For this study, the model was truncated at the anterior trachea to focus on particle deposition in the upper respiratory tract and to be consistent with the geometries of nasal replica molds that were used in earlier *in vitro* particle deposition experiments and are used for model validation (Fig. 1).

The locations of the different epithelial types were identified from earlier histological measurements (Gross et al., 1982; Mery et al., 1994) and were mapped onto the three-dimensional surface of the nasal model. Epithelial locations in the Sprague-Dawley rat model were compared with those from a previous Fischer 344 rat nasal model to ensure that the epithelial mappings were consistent (Garcia & Kimbell, 2009). The entire nasal surface of the rat model was partitioned into Dry Squamous, Wet Squamous, Transitional, Respiratory, and Olfactory regions. The remaining surfaces consisting of the nasopharyngeal duct, larynx, and anterior trachea were designated the NP Duct/Larynx region (Fig. 1). The Dry Squamous region is located at the extreme anterior nose and consists of non-mucus-coated epithelium. The Wet Squamous, Transitional, Respiratory, and NP Duct/Larynx regions are all mucus-coated epithelial types. The Olfactory region comprises the approximate extent of olfactory epithelial cells.

An unstructured tetrahedral mesh was generated in the rat nasal model using ICEM-CFD^{TM} (ANSYS, Inc.). Individual mesh elements were smoothed until the aspect ratio of all elements was above 0.3 to ensure that the mesh did not contain