992 AUTOMATED SELF-SIMILARITY ANALYSIS OF AIRWAYS IN THE SPRAGUE DAWLEY RAT.

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The rat is extensively used as an animal model for respiratory disease and inhalation toxicity. A quantitative description of the rat lung morphometry is therefore foundational to mathematical models of gas-exchange and particle deposition in the rat, and forms the basis for realistic boundary conditions for multiscale models of rat lung mechanics. A morphometric analysis across animals can also define a distribution of important morphometric parameters and thus help to define a 'normative' animal upon which to base generalizations of experimental and computational findings. We developed an automated method for tabulating morphometric data from magnetic resonance images of the rat bronchial tree, and a succinct morphometric framework for comparisons among animals. This method was validated against hand measurements of lung casts. Once airway geometries were segmented from MRI data, morphometric and statistical analysis were performed in under five minutes per lung. Computer-generated measurements of airway diameters averaged 0.13 mm (95% C.I. -0.16 mm to -0.09 mm) smaller than the corresponding measurements obtained manually, while airway lengths averaged 0.13 mm longer, but the difference was not statistically significant. Fits to the six variable parameter vector for 28 'branches' per lung were excellent and in agreement with the parameterization of the manual measurements. Parameterization of the left and right principle paths down to the terminal bronchioles, was predictive of the lung as a whole. Comparisons among a growing library of rat lung geometries have established a normative geometry of the Sprague Dawley bronchial tree. This method is also useful for in vivo hyperpolarized 3He gas imaging studies to characterize the compliance of the entire tree from the few airways resolvable with this modality to improve 3D model development under toxicant-induced disease conditions. Funded by NHLBI RO1 HL073598-01

993 SIMULATION OF INSPIRATORY AIRFLOW IN THE B6C3F1 MOUSE NASAL PASSAGES.

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Studies of nasal lesions induced by inhaled gases such as chlorine, formaldehyde and hydrogen sulfide routinely include data from both rats and mice. Anatomically accurate computational fluid dynamics (CFD) models of the F344 rat nose have been previously made to correlate lesion incidence and localized tissue dose. These correlations and human CFD models have enabled risk estimation in humans. Confidence in these methods will be increased if the CFD modeling approach predicts similar correlations in the mouse. A three-dimensional reconstruction (3D-R) of both sides of the nasal passages of an adult, male B6C3F1 mouse (approx. 30 g) was constructed from digital photographs of 50-μm serial-step sections through a minimally-fixed, frozen tissue specimen. The locations of squamous, transitional, respiratory, and olfactory epithelium were mapped into the 3D-R using light microscopy and Mimics (Materialise, Ann Arbor, MI). A tetrahedral mesh with 2.5 million cells was generated using ICEM-CFD (ANSYS, Canonsburg, PA). Steady-state inspiratory airflow was simulated using Fluent (Fluent, Inc., Lebanon, NH) at an estimated minute volume of 24.5 ml/min by imposing a pressure drop between the nostrils and nasopharynx of 65 Pa. Major routes of predicted airflow were similar to those in the rat and were located anteriorly in dorsal, middle lateral and middle meati with lesser streams in dorsal medial and ventral medial meati. Posteriorly, major airflow streams were located in the ventral medial meatus with lesser streams forming Z-shaped patterns adjacent to the dorsal septum and medial aspects of the first and third ethmoturbinates. Countercurrent backflow was observed adjacent to the fifth and sixth ethmoturbinates (terminology from Mery et al., Toxicol. Pathol. 22:353-372, 1994). As in the rat, inspiratory airflow passing olfactory-lined areas originated from the dorsal medial meatus anteriorly. These results will provide a means for interspecies comparison of predicted correlations of tissue dose and response and thereby increase confidence in their use for estimating risks to human health.

994 DOSIMETRY PREDICTIONS OF INHALED HEXAMETHYLENE DIISOCYANATE IN THE HUMAN RESPIRATORY TRACT.

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Hexamethylene diisocyanate (HDI) is a reactive chemical used in the commercial production of polyurethane products. Toxic effects in animals exposed to HDI vapor include respiratory tract irritation, degeneration of olfactory epithelium, and pathological changes in the alveolar airways. Concerns for human exposure to HDI are focused on potential responses of the tracheobronchial or pulmonary regions of the lung, including airway hypersensitivity and reversible reductions in lung function, with the main health concern being the potential of the isocyanate to initiate occupational asthma. In this study, a dosimetry model was developed to predict localized tissue dose of inhaled HDI vapor in the human respiratory tract for nasal or oronasal breathing. The model consisted of an anatomically accurate computational fluid dynamics model of the human nasal passages that was linked to a lung dosimetry model. Airflow and HDI transport in the nasal passages were simulated using the finite element software FIDAP (Fluent, Inc.). Transport of HDI through lung and oral airways was simulated by convection and axial dispersion and was implemented in MATLAB (Mathworks, Inc.). The nasal and lung components of the dosimetry model included tissue phases where absorption of HDI was governed by diffusion and first-order clearance. Nasal or oronasal breathing was used depending on the inspiratory airflow rate for different activity states. Tissue dose was predicted in the nasal and oral passages and in all generations of the lung. The simulations predicted that the upper respiratory tract and upper bronchial airways received the highest tissue dose, yet there was still penetration of HDI vapor to the pulmonary airways. These tissue dose estimates in human tracheobronchial and alveolar regions can be correlated with corresponding dosimetry predictions in rats that are known to cause adverse responses.

995 NANOPARTICLE DEPOSITION IN THE RAT NASAL CAVITY: PREDICTION OF DOSE TO THE OLFACTORY EPITHELIUM.

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Potential health risks associated with inhalation of nanoparticles are mostly unknown. A recent study in rats showed that nanoparticles depositing in the olfactory region can translocate along nerve axons to the olfactory bulb in the brain (Oberdoerster et al., Inhal. Toxicol. 16:437-445, 2004). An accurate estimate of the dose of inhaled nanoparticles to the rat olfactory epithelium will assist in understanding potential toxic effects and extrapolating such findings to humans. The goal of this study was to quantify nanoparticle deposition in the rat nasal cavity and, more specifically, the olfactory region. A three-dimensional, anatomically-accurate computational fluid dynamics model of the rat nasal airways was developed. A tetrahedral mesh was created in ICEM-CFD (Ansys, Inc.) with major epithelial types mapped onto its surface. Airflow and nanoparticle transport were simulated using Fluent software (Fluent, Inc.) for airflow rates corresponding to 1, 1.5 and 2 times the resting minute volume of 288 ml/min and particle sizes from 1 to 100 nm. For these particle sizes, particle deposition is dominated by diffusion, thus an Eulerian approach was used in the computations. Simulations predicted that nasal deposition decreased with increasing particle size: more than 90% of 1-nm particles and less than 1% of 100-nm particles were filtered by the nose. Olfactory deposition was maximal for particles with diameters of 2-6 nm, with 5 to 9 % of the inhaled particles deposited in the olfactory region. Deposition fractions were somewhat influenced by airflow rate, with higher airflow leading to (1) fewer particles being extracted by the nose and (2) a shift in the spatial distribution of deposited particles, with more deposition in the olfactory region. These results will help decrease uncertainty associated with estimates of potential health risks from inhaled nanoparticles. (Supported by CDC/NIOSH #000HCCEE-2006-36673.)

996 A MODEL OF NANOPARTICLE TRANSPORT AND DEPOSITION IN THE NASAL AND LUNG AIRWAYS OF HUMANS AND RATS.

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Recent studies have suggested that airborne nanoparticles may pose a greater threat of toxicity merely due to their small sizes. With increasing production, there is a concern over the health effects of inhaled engineered nanoparticles. Functional relationships of nasal deposition fraction of nanoparticles as a function of physical and physiological parameters were developed and fitted to deposition measurements in nasal airway casts of humans and rats. The resulting semi-empirical models were incorporated in a mathematical model of nanoparticle deposition in the lung that accounted for axial diffusion and dispersion. Model predictions in human and rat lungs were confirmed by comparing with available lung deposition measurements in the literature. In both species, nanoparticles were found to deposit primarily in nasal passages with a small amount entering lung airways. Nearly all particles below 5 nm were deposited in nasal airways. For particles below 10 nm in diameter, lung deposition was confined to upper airways of the tracheobronchial region. Transport and deposition of nanoparticles in the alveolar region occurred

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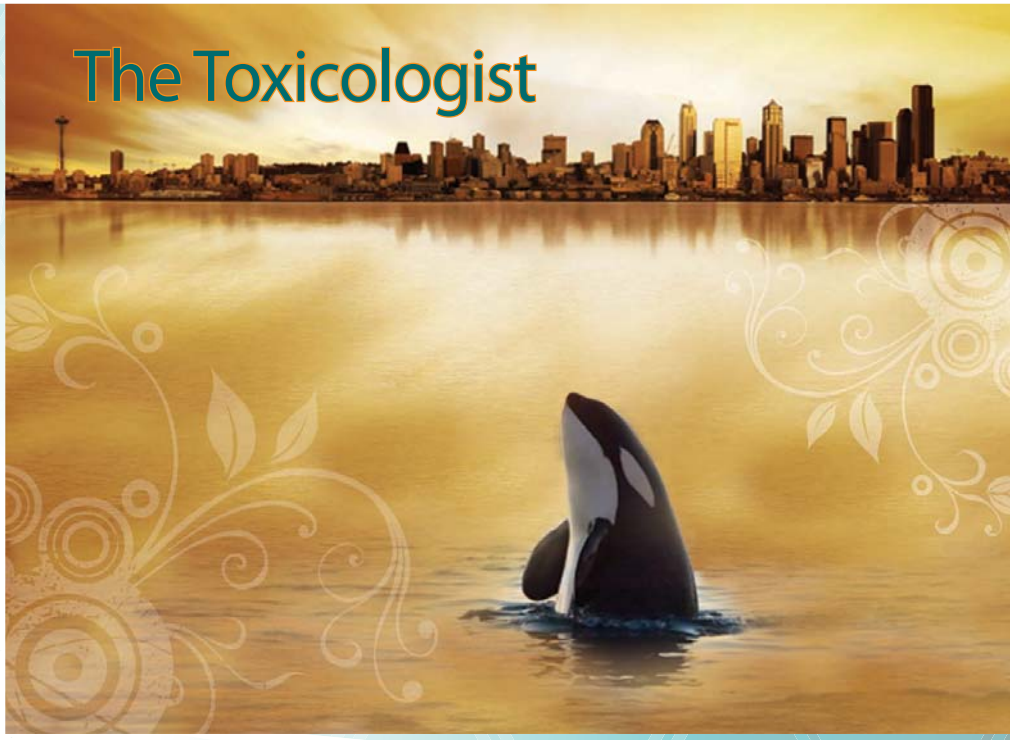

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