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DOSIMETRIC CONCEPTS OF PARTICLE LUNG INTERACTIONS. *WOLFGANG G. KREYLING Manuela Semmler Winfried Möller Francesca Alessandrini Shinji Takenaka Holger Schulz*

Rodent animal models are frequently used for toxicological studies after inhalative exposure to air-borne particulate matter. Therefore, total and regional particle deposition is an essential prerequisite for dose estimates and for extrapolation of toxicological results to assess human health risk. Indeed very limited data on total and regional deposition in rodents exist for ultrafine particles in the size range of 10 -100 nm. Recent experimental data will be compared with existing theoretical predictions and the observed differences will be discussed. In addition, the deposition differences observed between young and adult rats will be discussed.

Insoluble particles deposited on the respiratory epithelium will be labeled (opsonized) with specific biomolecules to be recognized by alveolar macrophages (AM) which form the first defense line against particulate matter. As a result AM will migrate towards such a labeled particle to incorporate (phagocytize) it for further digestion or dissolution / absorption or for transportation. While AM phagocytosis of particles > 0.5 µm is usually accomplished within a few hours after deposition, ultrafine particles (UP) are less effectively recognized and phagocytized. Therefore UP can interact with epithelial cells getting access into these cells and beyond into the tissue and blood circulation. Therefore, they will be no longer accessible for removal by broncho-alveolar lavage (BAL). Based on BAL data over six months of UP retention this transport will be discussed which has fuelled the debate about UP access to the vascular circulation.

Once deposited on the respiratory epithelium particles are likely to interact with endogenous proteins depending on the molecular structure and composition of the particle surface. Interacting with an insoluble particle proteins will not recognize what is inside the particle but only react with the molecules at the particle surface. So, the vast amount of a reactive molecule species located only at the particle surface determines the interaction and may eventually cause adverse outcomes although this molecule may only add a small fraction to the particle mass.The larger the particle surface area is the more interaction will occur. UP < 40 nm have a similar size as large proteins. Therefore they may form complexes whose biokinetic fate may be determined by the protein and no longer by the UP. Such a complex may be small enough for transport across membranes while this will occur less likely for a micron-sized particle-complex. Preliminary studies using different types of ultrafine particles confirm different binding patterns to a number of proteins. At the same time UP may induce functional changes of proteins being another mechanism by which particularly UP - with their large surface area - may induce protein mal-functioning which subsequently may lead to the pathogenesis of adverse health effects.

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DEPOSITION OF SPHERICAL AND FIBER AEROSOLS IN HUMAN ORAL AND UPPER TRACHEOBRONCHIAL AIRWAYS. *YUNG SUNG CHENG, Wei-Chung Su, Yue Zhou, Lovelace Respiratory Research Institute, Albuquerque, NM*

Inhalation exposure of spherical ambient and occupational aerosols may have serious health consequences including lung cancers and other respiratory diseases. The deposition pattern in the respiratory tract as a function of particle size is the information critical to understanding respiratory dosimetry and defining the index of exposure for health protection purposes. Physical replicas of human respiratory tract have been used to study the microdosimetry of inhaled particles. Increasingly, mathematical deposition models have been used to assess the dosimetry of inhaled fiber aerosol. However, current lung dosimetric models for fibers in the human respiratory tract are based on theoretical equations, which have not been verified with experimental data. The purpose of this study is to investigate the effects of aerosol size and breathing rate on the deposition pattern in a realistic human airway cast with a defined geometry for spherical and fiber aerosol. We also compared the experimental results to theoretical equations. The human airway cast used in this study included the oral cavity, pharynx, larynx, trachea, and three generations of bronchi. The oral portion of the cast was molded from a dental impression of the oral cavity in a human volunteer, while the other airway portions of the cast were made from a cadaver. Spherical PSL particles and carbon fibers diameter (3.74 mm) were used for the deposition study. The aerosol was generated with a small-scale powder disperser (Model 3433, TSI Inc., St Paul, MN). Regional fiber deposition was measured at a constant inspiratory flow rate of 15 to 60 L min-1. Deposition in each segment of oral and TB tree is measured by cutting the cast into sections corresponding to each region. The deposition efficiency in the oral region was found to be a unique function of the Stokes number, which combined the inertial particle size and flow rate for both spherical and fiber aerosol. In the tracheobronchial region, deposition in the first four generations were similar for both spherical and fiber aerosol as a function of Stokes number, which is reasonable as in the size range the impaction is the dominant deposition mechanism. The experimental data also in reasonable agreement with deposition theory of Cai and Yu (1988). Therefore, the airway replica consisting of oral, laryngeal, and tracheobronchial airways can be used to investigate deposition patterns and dosimetry of inhaled particles in air pollutants, occupational hazards, or pharmaceutical applications. (This research was supported by the National Institute for Occupational Safety and Health under the Grant 1R01 OH03900).