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Research Article

Multiple Path Particle Dosimetry Modeling Employability to Complement *in-vitro* Ultrafine Particle Toxicity Study

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Abstract

This paper demonstrates how computationally prediction can be done on inhaled ultrafine aerosol particles that are transported, disseminated, and deposited in the respiratory tracts of laboratory mice. Poyldisperse ultrafine particles (UFP) range between 1 nm and 100 nm in diameter. Multiple Path Particle Dosimetry (MPPD), a probabilistic computational simulation software was used to mimic in-vitro experimental conditions. In this work, the physical, mechanical and electrical properties of the UFPs were used as input parameters in MPPD. Additionally, pulmonary physiologic and morphometry input variables for BALB/c mice strain were applied to the simulation. Finally, the UFP deposition results of the computational simulation study were compared with in-vitro UFP deposition trends published in scholarly journals, and fitting agreements were found. Mutually both in-silico (computational modeling) and in-vitro studies complemented each other in determining the UFP toxicity burdens in fetal mice.

Introduction

During growth of a fetus in the uterus of mother's womb, mom's exposure to particulate matters (PMs) causes infant respiratory morbidity and mortality [1,2]. Studies are necessary to understand PMs in-utero exposure due to the breathing of polluted air. The ambient air pollution can be caused by PMs originated from various sources such as cigarette smoking in the household, industrial workplace, road-vehicle exhausts etc. The PM concertation of a typical full flavor cigarette smoke per puff is in the order of 109/ml. The particles size (diameter) distribution is in the range of 10 nm to 1µm, and the count median aerodynamic diameter (CMAD) 193 ± 1.43 nm [3,4]. This does not include the water associated with the smoke aerosol, or the volatile organic compounds lost due to evaporation. The CMAD for exhaled smoke is 230 ± 5nm [5].

Diesel vehicle's emission is a complex mixture of hundreds of constituents in either gas or PM form. These emissions consist of fine particles including a high number of ultrafine particles (UFPs). Studies showed that these diesel exhaust particles (DEPs) are highly respirable and have a large surface to mass ratio where respiratory organs can adsorb them easily [6]. Furthermore, ambient fine and ultrafine particles, of which vehicle is an important component, contribute to cardiopulmonary morbidity and mortality and lung cancer.

Engineered UFPs are purposefully developed in many industrial applications (e.g., carbon black, fumed silica, titanium dioxide, iron oxide, quantum dots, and carbon nanotubes) [7,8]. High-energy processes such as synthesis, spraying, machining, and industrial bagging are correlated with the release of large numbers of predominantly fine particles and UFPs. The wide application of engineered UFPs has induced increasing exposure to humans and the environment, which has led to substantial concerns on their biosafety. Significant exposures largely occur at industrial workplaces when industrial safeguards and personal protection schemes are not followed as recommended.

Among these PMs, the role of ultrafine particles (UFPs) which are of aerodynamic diameter of less than 100 nm in causing asthma and other chronic obstructive pulmonary diseases (COPD) is still inconclusive. Asthma and COPDs are conditions in which a human's airways turn out to be inflamed, constricted or swell, and produce added mucus, which makes it problematic or discomfort to respire.

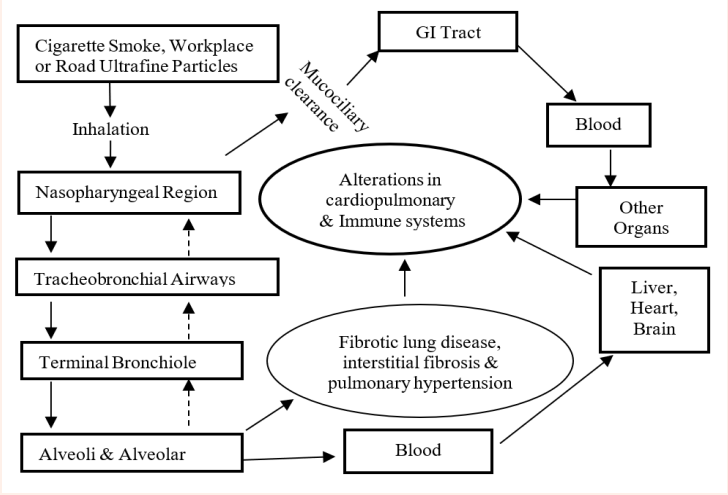

Figure 1: Translocation of inhaled ultrafine particles, alteration of cardiopulmonary and immune response.

Studies reported that within the first few hours after inhalation of UFPs, because of extracellular transfer of blood is the means of clearance, 1 to 10 nm particles are cleaned much quicker than particles in the size range of 10 nm to 100 nm, with a retained fraction about 80% after 24 hours [9]. Figure 1 illustrates the links of translocation of inhaled UFPs, alteration of cardiopulmonary and immune responses. When ambient air is dominated by UFPs, various recent epidemiologic investigations reported that increased susceptibility to lower pulmonary infections with in-utero exposure, and consequently increased wheeze and asthma risk in offspring early life [10-12].

As literature showed the offspring's respiratory illnesses due to in-utero exposure to the UFP toxicity burdens need to be supported by further investigations focusing on several dosimetric and mechanistic aspects such as

a) Quantification of the UFP deposition in different regions of the mouse lung, an animal model in relation to human conditions of increased susceptibility
b) UFP translocation to interstitial and extra-pulmonary tissues by exhibiting various biomarker activities like eosinophilic inflammation, antigen-specific IgE reactivity, airway hyper-responsiveness, and the predominance of T helper (Th) 2 cell-associated cytokine production typically express the phenotypic response
c) Characterization of animal models in relation to human conditions of increased susceptibility [13].

To accomplish these goals, understanding of the pathophysiological processes, identification of biomarkers associated with in-utero inhalation of UFPs at home and in the workplace and analysis of the offspring's respiratory distress and pulmonary immune response is necessary. By employing diesel exhaust nanomaterials (DEPs), a representative of UFPs exposure to BALB/c fetal mice strains, Rychlik et al. [14] reported pulmonary immunosuppression of the offspring of these laboratory animals. However, very limited in-vitro or in-vivo techniques are available to accurately quantify inhaled dose distribution and deposition in the upper lung airway, tracheobronchial and alveolar regions of fetal mouse lungs. Therefore, it is warranted to undertake in-silico (computational) studies to understand the in-vitro (in-utero) exposure to ambient UFPs. In order to achieve such objective, this study employed the Multiple Path Particle Dosimetry (MPPD), a probabilistic computational simulation software to mimic in-vitro experimental conditions.

Materials and Methods

The major objectives of this study were as follows: predict inhaled UFPs deposition in various regions of fetal mouse lungs, compare these computational results with in-vitro study data, and, quantify the deposition using the concentration fractions in various compartments of the mouse respiratory tract. Inhaled UFPs from workplace, roadside, atmosphere or biological sources flow and deposit in the lung airways using five electromechanical deposition mechanisms such as inertial impaction, sedimentation or gravitational settling, Brownian diffusion, interception, and electrostatic charge forces [15].

To better understand particle dosimetry and the deposition patterns of UFPs, this study employed empirically derived expressions based semi-empirical multiple path particle dosimetry (MPPD, version 3.4) computational software. MPPD was developed by Applied Research Associates (ARA) Inc., Albuquerque, NM, USA [16]. The ARA has provided the GNU license to undertake this study.

The UFPs were diesel exhaust nanomaterials (DEPs), a primary component of traffic-related pollutants and composed of polydisperse particulates in the range between 10 nm and 1000 nm in diameter. The mice inhaled aerosols were three types: fresh air (FA) with no DEPs, low-density (LD) with 100μg/m³ and high-density (HD) with 500μg/m³ DEPs. The test subjects were four BALB/c neonatal mice with whole body exposure for 6 hours/day for 18 days.

The MPPD model can run single or batch jobs with age-specific mouse lung geometries, and plots can be drawn for deposited fraction with respect to the inhaled mass vs. lung generations or compartments. The model paraments can be the default values or user-chosen parameters of respiratory airway morphometry, inhalation properties, exposure boundary conditions, deposition and clearance. Setting loop continues until the user accepts upon reviewing entire simulation protocol.

Results and Discussion

The mathematical model of MPPD analysis in mice adopted following assumptions: the lung airways are shaped as cylinders; they expand and contract homogeneously during a breathing sequence; PM concentration is unchanging across the airway cross section; PM deposition is accounted for by a loss term in the 1-D flow model; the loss term is associated to net deposition efficiency of PMs by various electro-aerodynamic mechanisms for which systematic mathematical equations had been defined [15,17].

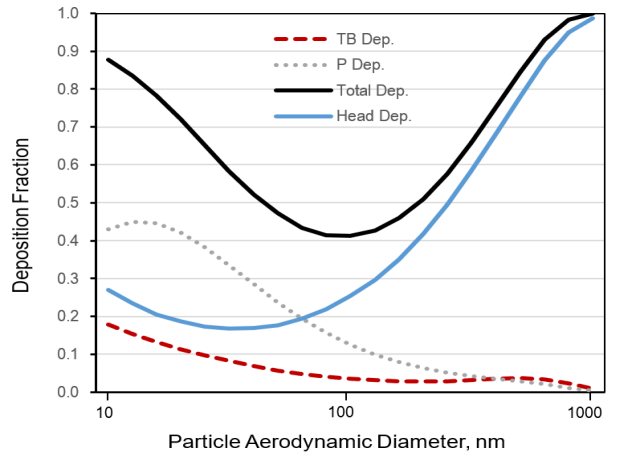

Figure 2: In-silico modeling results of various compartments (Head, tracheobronchial (TB), pulmonary (P)) and entire respiratory-airway deposition fraction of inhaled UFPs for the particle diameter range of 10 nm to 1000 nm in the BALB/c mouse lung.

The conventional PM dosimetry recommendations are particles' either number or mass concentrations within a fixed aerodynamic size. So, as the present MPPD simulation model calculated both deposition and clearance of UFPs in the mouse lung. Figure 2 illustrates the high-density (HD) DEPs size distributions that were deposited in various lung regions. Here the total lung dose of 10 nm size particles is the highest (88%) while 120 nm size particles is the lowest (42%). Thereafter, the deposition again increases with particle size and reaches near 100% for 1000 nm (1.0μm).

Table 1 shows the compartment-wise deposition efficiency of fresh air (FA), low density (LD), and high density (HD) of inhaled UFPs. The FA did not contain any UFPs, so the model showed almost all them deposited in the Head (mouth-throat-larynx) region. The MPPD model takes it as the base result i.e., 0% inhaled particles passed beyond Head region. For LD DEPs about 41% UFPs were deposited combinedly in the Head (25.21%), tracheobronchial (TB) (3.45%) and pulmonary (P) (12.52%) or alveolar regions. In case of HD DEPs, deposition efficiencies are 47% combinedly in three regions. Individually these HD UFPs deposition efficiencies were 17.69%, 5.4%, and 23.77% for Head, TB and P regions, respectively.

Table 1: Modeling results of 50nm LD and HD UFPs in the BALB/c female mouse lung.

UFP	Head	TB	P	Total
FA, 0 μg/m³ DEPs	100%	0%	0%	100% air, no UFPs
LD, 100 μg/m³ DEPs	25.21%	3.45%	12.52%	41.18% of all inhaled UFPs
HD, 500 μg/m³ DEPs	17.69%	5.74%	23.77%	47.20% of all inhaled UFPs

Note: UFPs: Ultrafine particles, FA: Fresh Air, LD: Low density aerosol, HD: High density aerosol, DEPs: Diesel exhaust particles, Head: mouth-throat-larynx, TB: Tracheobronchial, P: Pulmonary

Based on the simulation results, the proposed MPPD model has demonstrated the predictive power as a supplement to physical *(in-vitro)* models for assessing fine and ultrafine PMs deposition in the realistic airways of extrathoracic (Head),

tracheobronchial tree and pulmonary alveolar sacs like other mechanistic computational models referred by Beckman et al. [18]. For example, the simulated tracheobronchial deposition quantity is very much representative of lower respiratory infection biomarkers reported by Rychlik et al. [14].

Conclusions

Mutually both in-silico and in-vitro studies complemented each other in determining the UFP toxicity burdens in fetal mice. Computational simulation of lung burdens of harmful UFPs supported by in-vitro results of broncho-inflammatory illnesses on laboratory animals can overcome risks associated with investigations on detailed human inhalation, particle flow and transport processes which are restrictive from time, cost, and ethical perspectives. These understandings may be the keys to foster developing of effective drug delivery methods or determining the air pollution toxicity burdens.

Limitation

The MPPD model simulation has a limitation. While its deposition model does not specify a bound for uncertainties related with model assumptions, the model provides average predictions for deposition fractions per airway generation of the lower lungs due to dissimilarity in airway dimensions and breathing mechanism.

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