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Simulations of submicron aerosol deposition at an air–liquid interface for *in vitro* toxicology

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ABSTRACT

Submicron particles released during the lifecycle of nano-enabled products and as a byproduct of air pollution and occupational processes are a potential health risk. Recent advancements to *in vitro* model systems have been proposed to assess the toxicity of particulate materials resulting from inhalation. The reliability of these models depends on the introduction and deposition of aerosolized particles on cells at an air–liquid interface. However, chamber geometry, gas flow rate, electric field, and other process parameters significantly impact how particles deposit at this interface. Here, we carried out finite element modeling to describe the transport and deposition of submicron aerosolized particles. Simulations were performed using multiphysics software on a typical *in vitro* exposure chamber design, and results were compared to analytical approximations for deposition efficiency. Deposition experiments were also systematically carried out to validate the modeling predictions. Our results show how deposition depends on various process parameters. To achieve efficient deposition without focusing, the electric field strength and gas flow rate must be balanced; at high gas flow rates, higher electric fields are required to achieve deposition. Further, we find that AC electric fields at the appropriate frequency can increase deposition above DC fields at similar strengths. Overall, the study establishes simulation approaches for the design of *in vitro* aerosol deposition chambers and relates key process parameters to deposition, which is critical to controlling the dose of submicron aerosols in *in vitro* toxicology experiments.

1. Introduction

Understanding health risks associated with environmental and occupational exposure to aerosolized submicron particles is becoming increasingly important. There is growing evidence that cardiopulmonary disease is related to the inhalation of

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Nomenclature

AC	alternating current
C_{amb}	ambient exposure concentration
C_{exp}	experimental exposure concentration
D	particle diffusion coefficient
DC	direct current
h	height of the inlet tube discharge from the air–liquid interface
HEPA	high efficiency particle air
$J_{y=0}$	particle flux at the air–liquid interface
J_R	regional particle flux (respiratory tract)
MPPD	multiple path particle deposition
n_e	number of electron charges
PBS	phosphate buffered saline
Q	flow rate
r	deposition radius
r_0	discharge radius
SA_{ALI}	air–liquid interface surface area
SA_R	regional surface area (respiratory tract)
SEF	surface enhanced fluorescence
SMPS	scanning mobility particle sizer
V	applied voltage potential
V_{ch}	chamber volume
V_p	particle volume
V_R	regional volume (respiratory tract)
v_E	electrical drift
v_s	sedimentation velocity
y	vertical distance traveled by a particle
Z_p	electrical mobility
ϵ_{theor}	theoretical deposition efficiency, analytical
$\epsilon_{theor,ns}$	heoretical deposition efficiency, no screen, semi-empirical
ϵ_{exp}	experimental deposition efficiency
ρ_p	particle density
τ	residence time
χ_R	regional deposition fraction (respiratory tract)

ambient particulate matter in the sub-2.5 μm size range (Brook et al., 2010; Borm & Donaldson, 2007; Pope et al., 1995). Occupational exposure to welding fume, crystalline silica, and diesel exhaust, all of which contain submicron particles, has been shown to cause acute and chronic pulmonary diseases (Kaye et al., 2002; Fubini et al., 1995; Hart et al., 2009). The adverse health effects of occupational exposure to aerosol particles have been mitigated by the addition of engineering controls and education (NIOSH, 2014). However, new potentially dangerous materials and processes are constantly under development. For example, engineered nanoparticle materials (≤ 0.1 μm) are being implemented in a broad array of emerging applications, which will undoubtedly lead to inhalation exposure during their lifecycle (Maynard & Aitken, 2007). Therefore, it is essential to establish methods for characterizing the toxicity of new materials as they are being developed.

In vitro studies can serve as a simpler, less costly and faster alternatives to animal studies for toxicity assessment (Stokes & Wind, 2010). However, there are shortcomings in correlating *in vitro* endpoints with whole organism responses (Hartung, 2013; Sayes et al., 2007). Therefore, there is a critical need to improve *in vitro* techniques to better predict the toxicity of particulate matter (Stokes & Wind, 2010). Previous *in vitro* studies have been typically carried out by dispersing particles in cell culture media and administering to cells under static conditions (Chairuangkitti et al., 2013; Braydich-Stolle et al., 2010; Carlson et al., 2008; Grabinski et al., 2007; Hussain et al.; 2005). During the dispersion step, complex agglomerates are formed consisting of particles and adsorbed media components (Nel et al., 2009; Murdock et al., 2008). The size distribution and fractal structure of agglomerates are complicated to characterize (Cho et al., 2013) and affect transport properties, leading to incorrect assessment of dose (Cho et al., 2011; Teeguarden et al., 2007). Additionally, cell culture media does not have the same properties as bodily fluids, so agglomeration trends will inevitably be different from *in vivo* (Han et al., 2012).

Exposure of cells grown at the air–liquid interface to aerosolized particles has been found to be a more accurate model than liquid dispersions, particularly in the assessment of toxicity resulting from inhalation (Lenz et al., 2009; Lichtveld et al., 2012). Further, lung cells prefer to grow at the air–liquid interface and certain cells display differentiated features when grown using this approach, making it necessary to bring in particles from the gas phase (Huh et al., 2010; Wengst & Reichl, 2010). Particles that are stable in aqueous media are typically aerosolized using a nebulizer or electrospray (Brandenberger et al., 2010; Kim et al., 2010). Particles which are not stable in aqueous media can be aerosolized from a dry powder (Baron et al., 2008). Additionally, a wide range of nanoparticle materials can be synthesized directly in the gas phase (Chiang & Sankaran, 2007; Jaworek & Sobczyk, 2008; Biskos et al., 2008). Online measurements *via* electrical mobility allow the particle size distribution to be monitored in parallel to cell exposure (Comouth et al., 2013). Therefore, it is possible to predict the deposition rate more accurately for aerosol than traditional static exposure to aqueous dispersions.

Experimental systems for exposing cells at an air–liquid interface to aerosol particles have been designed and reported over the last decade (Raemy et al., 2011; Brandenberger et al., 2010; Müller et al., 2010; Lenz et al., 2009; Paur et al., 2008; Aufderheide, 2005; Knebel et al., 2002). In general, these systems rely on sedimentation and diffusion forces for deposition. Parametric aerosol dosimetry has been investigated for sedimentation and diffusion forces (Fujitani et al., in press; Comouth et al., 2013; Desantes et al., 2006; Tippe et al., 2002). However, sedimentation and diffusion forces are not strong enough to efficiently deposit submicron sized particles from a gas flow (Melling, 1997). Several recent studies have recognized this issue and incorporated electric fields to enhance deposition (Savi et al., 2008; Volckens et al., 2009; Grigg et al., 2009; Saffari et al., 2012; Aufderheide et al., 2011; Stevens et al., 2008). However, aerosol deposition in the presence of an electric field has not been thoroughly studied and remains a challenge for modeling dosimetry and toxicology by *in vitro* exposure systems.