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Regional deposition of inhaled aerosol constituents from Electronic Nicotine Delivery Systems (ENDS) in the respiratory tract

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ABSTRACT

Characterization of internal dose and potential health impact of inhaling aerosol from an Electronic Nicotine Delivery System (ENDS) requires understanding and estimation of the regional deposition and absorption of the aerosol constituents in the respiratory tract. The aerosol generated from ENDS is a highly unstable mixture of multi-constituent aerosols and their vapor constituents. The mixture undergoes rapid changes once inhaled into the respiratory tract. Measurement of the deposited dose is a formidable challenge and no reliable method is currently available. Hence, a model for the deposition of aerosol components and vapor constituent of an ENDS aerosol mixture was developed based on previously constructed models for particle deposition and vapor uptake in the respiratory tract. Constituent phase instability and rapid mass exchange within the aerosol mixture and with airway walls required the coupling of the aerosol and vapor phases for all constituents. The fate of the ENDS aerosol mixture was determined throughout the respiratory tract for a typical vaping scenario consisting of puff withdrawal, mouth hold, mixing of the puff with dilution air at the end of mouth hold, lung inhalation, lung hold, and exhalation. Model predictions indicated that over 90% of constituents with medium vapor pressure (e.g., nicotine and propylene glycol or PG) were delivered to the lung tissues by both aerosol deposition and vapor uptake, which occurred in all regions of respiratory tract. Low vapor pressure constituents (e.g., glycerin) mostly remained in the aerosols and were delivered to the lung by aerosol deposition alone. The dosimetry model is a useful tool to estimate the internal exposure to the constituents in the ENDS aerosol and can provide valuable insights for risk assessments.

1. Introduction

Heating and vaporization of typical solutions in Electronic Nicotine Delivery Systems (ENDS) produce far fewer constituents than a combustible tobacco products (Burstyn, 2014; Goniewicz et al., 2014). However, there is a growing concern regarding the health impact from the use of ENDS products due to the presence of potentially toxic components and increasing popularity particularly in the younger generation (NASEM The National Academies of Sciences, Engineering, Medicine, 2018; U.S. Centers for Disease Control and Prevention CDC, 2017). The aerosol mixture generated by ENDS may contain glycols, aldehydes, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbon (PAHs), tobacco-specific nitrosamines (TSNAs), metals, silicate particles and other elements. The number and level of known toxicants generated is on average much lower than in cigarette smoke (Flora et al., 2016;

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Nomenclature

A	Cross-sectional area
C_j	Constituent j vapor concentration
C_{j_0}	Concentration of vapor constituent j at mouth opening
$C_{j,max}$	Maximum attainable concentration for constituent j in the air
C_d	Aerosol number concentration
$C_{d_{i,k}}$	Aerosol concentration in length interval i and time interval k
C_{d_i}	Aerosol concentration at the initial or entry location of an airway
C_{d_0}	Aerosol concentration at mouth opening
D_d	Aerosol diffusion coefficient
D_j	Diffusion coefficient of vapor constituent j
DF_j	Deposition fraction of constituent j
UF_j	Uptake fraction of constituent j
Kn	Knudsen number
L_j	Latent heat of evaporation of for constituent j
Q	Air flow rate
Q_{in}	Inhalation flow rate
$\bar{R}$	Aerosol gas constant
T_d	Droplet temperature
T_∞	Air temperature
T	Inhalation, pause, or exhalation time
V_p	Puff volume
a_j	Activity coefficient
c_{dj}	Specific heat of constituent j in liquid form
i	Length interval
j	Constituent index
k_a	Thermal conductivity of air
m_d	Aerosol mass
$m_{d_{i,k}}$	Aerosol mass in airway length interval i and time interval j
m_{d_o}	Aerosol mass at mouth opening
m_j	Mass of liquid constituent j in a single aerosol
T	Elapsed time
x_j	Mole fraction of constituent j in the aerosol
y_j	Mass fraction of constituent j in the aerosol
$y_{j_{i,k}}$	Mass fraction of constituent j in the aerosol for length interval i and time interval k
y_{j_o}	Inlet mass fraction at mouth opening
z	Axial direction
z_i	Inlet axial coordinate of a segment or an airway
$\Delta\lambda_d C_d$	Number of aerosols deposited per unit time per unit volume
$\Delta\lambda_j C_j$	Mass of vapor constituent j absorbed by wall tissues per unit time per unit volume
$\Delta\eta_j$	Uptake efficiency of vapor constituent j
$\Delta\eta_{d_{i,k}}$	Deposition efficiency of aerosols in length interval i and time interval k
β	Coagulation kernel
ρ_d	Aerosol mass density
ρ_j	Density of constituent j in the droplet
σ_j	Surface tension of constituent j in the aerosol
S_j	Saturation ratio of vapor constituent j
$V_d(z)$	Distal volume at depth z
M_j	Molecular weight of constituent j
TLV	Total lung volume
$\Delta T_k k^{th}$	time interval
MF_j	Total mass fraction of constituent j
N_c	Number of constituents in the puff
N_i	Number of length intervals
N_k	Number of time intervals
T_{res}	Residence time in an airway

Goniewicz et al., 2014; Visser et al., 2015). However, the level varies greatly across products mainly due to the applied temperature used to evaporate the e-liquid. In addition, there are about 8000 flavors that are used in e-liquids on the market (Zhu et al., 2014). The health effects of many of these flavors when heated and inhaled have not been studied (Barrington-Trimis, Samet, & McConnell, 2014). Determining the fate of these compounds in the respiratory tract is key to assessing their health impact from short and long term exposure. In this paper, the terms ENDS and electronic cigarette (EC) are used interchangeably.

Volatility of the aerosol mixture from ENDS devices poses a challenge in characterization after generation and assessments of the internal dose following inhalation. There are only a few studies on deposition and uptake measurement of the electronic cigarette (EC) aerosols in the respiratory tract (Liu et al., 2017; St. Helen, Havel, Dempsey, Jacob, & Benowitz, 2016). Substantial efforts were made to develop predictive dosimetry models as an alternative to measurements and also to gain insight into the physics of cigarette smoke transport and deposition in the respiratory tract, which allows correlating exposure characteristics to biological outcomes (e.g., Broday & Robinson, 2003; Kane, Asgharian, Price, Rostami, & Oldham, 2009; Martonen, 1992; Muller, Hess, & Scherer, 1990; Martonen & Musante, 2000; Robinson & Yu, 1998, 2001). These predictive models were created for traditional combustible cigarette particles out of necessity as models for environmental aerosols greatly under-estimated the internal dose of cigarette particles (Kane et al., 2009). These models included additional mechanisms such as electronic charge (Stober, 1984), droplet hygrocopicity (Davies, 1988; Longest & Xi, 2008), and colligative effects (Martonen, 1992; Phalen, Oldham, & Mannix, 1994). Charge effects did not increase aerosol deposition appreciably and hygroscopicity partially accounted for enhanced deposition (Robinson & Yu, 2001). There were also uncertainties regarding the significance of colligative effects in confined spaces such as in lung airways. To overcome the shortcoming, an initial cloud dimension was selected (Martonen, 1992), which decreased with lung depth due to dilution of the particle mixture with the reserved air (Broday & Robinson, 2003). As a result, model predictions (Asgharian, Price, Yurteri, Dickens, & McAughey, 2013) approached measurements (Baumberger, 1923; Dalhamn, Editors, & Rylander, 1968; Foster & Gaffney, 1958; Hinds, First, Huber, & Shea, 1983; McAughey, Prichard, Black, Hoare, & Knight, 1991; Mitchel, 1962; Polydorova, 1961).

The above modeling efforts often fail to include the thermodynamics of aerosol mixture. Tissue dose of an aerosol mixture through the vapor route may be significant, providing an alternative explanation over the cloud effects for increased deposition and uptake when compared with inert aerosols. Recently, Pichelstorfer, Hofmann, Winkler-Heil, Yurteri, and McAughey (2016) proposed a stochastic dosimetry model to predict the internal dose of inhaled combustible and electronic cigarette particles. The model accounted for droplet-vapor interaction by phase change, hygroscopicity, and particle coagulation. The investigators predicted nicotine