GA07 / P19

Comparative analysis of inhalation exposure to e-cigarette vapors with different puffing behaviors using PBPK-CFD approach

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Abstract: *The purpose of this study is to develop a numerical prediction method for assessment of human health risks caused from the inhalation exposure of various contaminants generated by electronic cigarettes (e-cigarettes). In this study, the inhalation exposure to contaminants, generated from e-cigarette smoking under two types of puffing behaviors was quantitatively estimated adapting a coupled physiologically based pharmacokinetic (PBPK)–computational fluid dynamics (CFD) model to a numerical respiratory tract model. Heterogeneous contaminants concentration distributions inside the respiratory tract were predicted through transient CFD simulations. For evaluating adsorption flux onto respiratory tissue surface, tissue surface contaminants concentrations of respiratory tract were calculated by using two concepts: partition coefficient between air-phase and tissue-phase and analogy of flux conservation. Contaminants concentration distributions inside the tissue were analyzed by using PBPK model. Through the coupled PBPK-CFD analyses, we indicated total fractions of contaminants inhaled from e-cigarette: (i) adsorbed onto tissue surface of respiratory tract, (ii) transported to deeper bronchial regions, and (iii) released into the indoor environment by exhalation.*

Keywords: Inhalation exposure, CFD, Numerical respiratory tract model, PBPK model

1. INTRODUCTION

Electronic cigarettes (e-cigarette) have recently been perceived as the safer alternatives to conventional cigarettes in terms of first-, second-, and third-hand exposure smoking throughout the world. Although e-cigarette vapor is generally generated through a non-combustion process, it has been confirmed to include some contaminants such as aldehydes, which affect human health and indoor environment. In addition, puffing behaviours (short and long puffing) have potential impact on the human health in terms of inhalation exposure. Thus, it is essential to develop a predictive framework to analyse the comparative health impact caused by the e-cigarette smoking with different puffing behaviours. Correspondingly, this study focuses on a qualitative and quantitative assessment of e-cigarette vapor exposure in the human respiratory tract using PBPK–CSP–CFD analyses.

2. METHODS

2.1 Numerical respiratory tract model

As shown in Figure 1, the numerical respiratory tract model considered in this study includes the oral cavity, pharynx, larynx, trachea, and bronchial tubes reproduced around fourth bifurcation, and have 38 outlets, and excludes nasal cavity region for reducing the computational load. We confirmed that the flow patterns in the respiratory tract is independent on the existence of nasal cavity region before the inhalation exposure analysis using the respiratory tract excluding nasal cavity region. The airway model has already been developed based on CT data extracted healthy human male. This model consists of approximately 2×10^6 polyhedral elements and very fine prism layers in the near-wall region. Moreover, for simulation of the inhalation of e-cigarette vapor, a circular inlet opening having a diameter of 8.0mm was set to simulate a stream of vapor coming from the mouth directly into the pharynx region. In addition to the inhalation period, an elliptical outflow opening having an area of 1.2cm2 was set to reproduce the shape of mouth opening in the exhalation period.
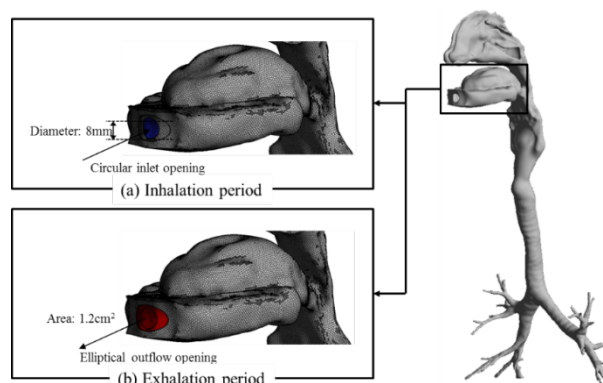

Fig. 1. Numerical respiratory tract model.

2.2 Transient puffing profiles

To investigate the effect of puffing behaviours in terms of total respiratory uptake, two types of puffing profiles based on the measurement data from Vansickel et al. were prepared in this study. The exhalation duration of two profiles was set a same value of 1.8s due to the fact that no difference was observed in exhalation duration between cigarette smokers and e-cigarette users (Farslinos et al., 2013). The exhalation profile was described by sine function based on the exhalation duration and inhaled volume. In this study, two types of transient puffing profiles shown in Figure 2 were set in the inlet/outflow opening (see Figure 1) as inflow boundary condition.
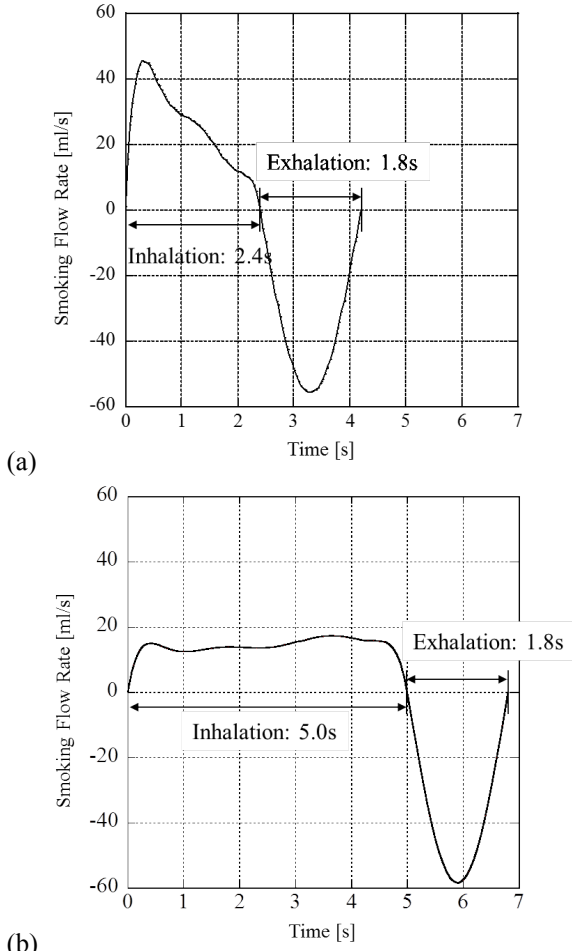
(a)

(b)

Fig. 2. Transient puffing profiles. (a) short puff (b) long puff

2.3. PBPK–CSP–CFD analyses

In this study, we focused on formaldehyde, acetaldehyde, acrolein, benzene, toluene, glycerol, and nicotine as representative contaminants of e-cigarette vapors, and we applied the PBPK–CFD model constructed by Tian and Longest (2010) to the numerical respiratory tract model. In the PBPK–CFD model, the convection and diffusion of the contaminants in the airway are analysed using CFD, while their absorption/diffusive transport, metabolic clearance, and elimination in the respiratory tissue which composes three layers: mucus, epithelium, and sub-epithelium, are predicted by the PBPK model. The concept and governing equations of the PBPK–CFD model are shown in Figure 3.

In this simulation, in order to analyse the adsorption/desorption fluxes with numerical stability, we applied the double boundary film theory based on the partition coefficient and the flux conservation between the air and tissue phases as the Dirichlet boundary condition. Based on equations of partition coefficient and flux conservation, the wall surface concentrations of the air and tissue phases can be represented by equations (1) and (2), respectively:

$$C_{a,0} = \left(C_{a,1} + \frac{D_t}{D_a}\frac{\Delta x_a}{\Delta x_t} C_{t,1} \right) \Big/ \left(1 + \frac{D_t}{D_a}\frac{\Delta x_a}{\Delta x_t} P_{t:air} \right) \quad (1)$$

$$C_{t,0} = \left(C_{t,1} + \frac{D_a}{D_t}\frac{\Delta x_t}{\Delta x_a} C_{a,1} \right) \Big/ \left(1 + \frac{D_a}{D_t}\frac{\Delta x_t}{\Delta x_a} \frac{1}{P_{t:air}} \right) \quad (2)$$

where $C_{a,0}$ and $C_{t,0}$ are wall surface contaminant concentrations of the air and tissue phases, and $C_{a,1}$ and $C_{t,1}$ are defined as the concentrations of the closest elements to the wall surface of the air and tissue zones. The wall surface contaminant concentrations are calculated using a sufficient number of iterations.

The numerical and boundary conditions used for the inhalation exposure analyses are summarized in Table 1. The chemically relevant parameters shown in Table 2 and used in the coupled PBPK–CFD analyses conducted in this study.
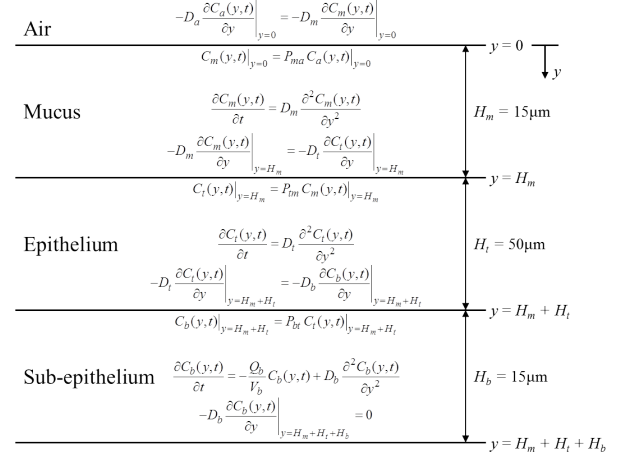

Fig. 3. PBPK–CFD model.

3. RESULTS

Figure 4 shows the time series of the formaldehyde concentration distributions in the respiratory tract model under short puffing condition, and Figure 5 shows the time series of the formaldehyde adsorption flux distributions on the mucus surface of the respiratory tract model. The mass rate of formaldehyde transported to the 4th generations of the bronchial tube and exhaled to the indoor environment was very high compared to the other contaminants because the most of inhaled formaldehyde was adsorbed onto the mucus surface of tongue region and upper palate. The distributions and contributions of contaminants generated from e-cigarette puffing under the short puffing and long puffing conditions are summarized in Table 3. The long puffing behaviour leads to elevated contaminants uptakes in the respiratory tract model compared to the short puffing behaviour. Therefore, if the total puff volume is almost same, the long puffing behaviour with a lower puff intensity will induce higher total adsorption than the short puffing behaviour with a higher puff intensity. When we drew a comparison between contaminants in terms of the adsorption rate onto the mucus surface, the adsorption rate of formaldehyde, glycerol, and nicotine, having significant higher partition coefficient, were very high. Furthermore, the diffusion coefficient and metabolic rate cause the differences of the adsorption rate between these three contaminants. On the other hand, the adsorption rate of benzene and toluene, which have very low partition coefficient, is very small. It leads to high rate of exhalation by way of mouth opening and remaining airway without adsorption.

Table 1. Numerical and boundary conditions for inhalation exposure analyses.

Turbulence Model	Low Re number type k–ε model (Abe–Kondoh–Nagano Model)
Mesh	9.0M mesh elements (unstructured and prism)
Algorithm	SIMPLE (unsteady)
Scheme	Convection term: Second upwind scheme
Inflow boundary	Q_{in} = transient cigarette smoking profiles (see Figure 2) $k_{in} = 3/2\,(U_{in} \times 0.1)^2$, $\varepsilon_{in} = C_\mu{}^{3/4} k_{in}{}^{3/2} l_{in}$ T_{in} = 45 °C C_{in} = 0.7 µg/ml (formaldehyde), 0.22 µg/ml (acetaldehyde)
Outflow boundary	Boundary type: Pressure boundary
Wall treatment	Velocity: no slip Temperature: $T_{wall\ surface}$ =36.4 °C Contaminant: calculated by equations (3) and (4)

Table 2. Physical properties of target chemicals

	Formaldehyde	Acetaldehyde	Acrolein
Diffusivity [cm²/s]			
Air (D_a)	0.18	0.124	0.105
Mucus (D_m)	2.00×10^{-5}	1.23×10^{-5}	1.12×10^{-5}
Tissue (D_t)	6.67×10^{-6}	4.10×10^{-6}	3.73×10^{-6}
Blood (D_b)	3.03×10^{-6}	2.67×10^{-6}	2.46×10^{-6}
Partition coefficient (P)			
Mucus:Air (P_{ma})	3.65×10^{4}	165	101
Tissue:Mucus (P_{tm})	0.831	0.824	0.826
Blood:Tissue (P_{bt})	1.0	1.0	1.0
Octanol:water (P_{ow})	2.24	0.457	0.977
Blood:air (P_{ta})	3.03×10^{4}	136	83.1
Metabolism			
K_m [µg/m³]	2.01×10^{5}	1.1×10^{9}	5.0×10^{2}
V_{max} [µg/m³/s]	1.96×10^{7}	3.93×10^{7}	1.12×10^{5}
K_f [1/s]	1.8×10^{-2}	3.573×10^{-2}	2.0×10^{-2}

|	Benzene	Toluene	Glycerol	Nicotine
Diffusivity [cm²/s]				
Air (D_a)	0.088	0.087	0.0877	0.065
Mucus (D_m)	9.8×10^{-6}	8.6×10^{-6}	9.3×10^{-6}	9.38×10^{-6}
Tissue (D_t)	3.23×10^{-6}	2.87×10^{-6}	3.1×10^{-6}	3.13×10^{-6}
Blood (D_b)	2.20×10^{-6}	2.08×10^{-6}	2.08×10^{-6}	1.73×10^{-6}
Partition coefficient (P)				
Mucus:Air (P_{ma})	2.65	2.31	3.25×10^{9}	8.18×10^{6}
Tissue:Mucus (P_{tm})	1.36	2.98	0.826	0.881
Blood:Tissue (P_{bt})	1	1	1	1
Octanol:water (P_{ow})	135	537	0.977	14.8
Blood:air (P_{ta})	3.61	6.88	2.68×10^{9}	7.21×10^{6}
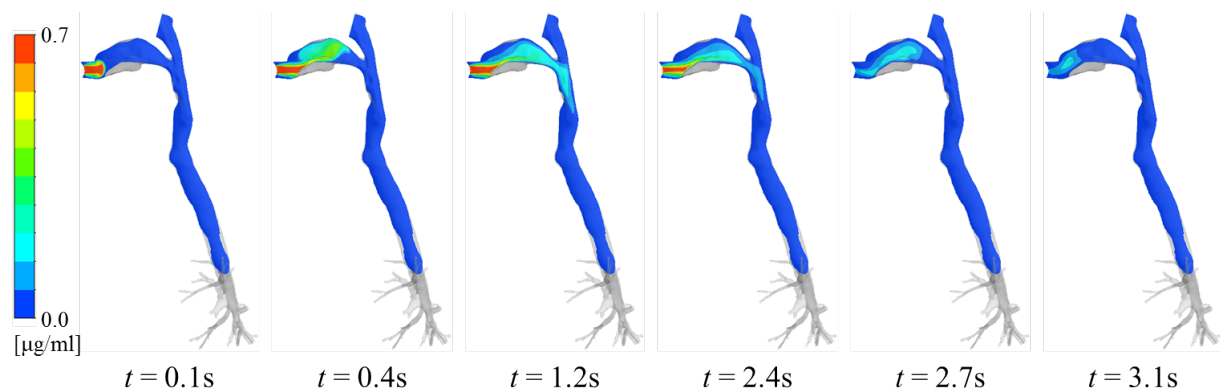
Fig. 4. The time series of the formaldehyde concentration distributions in the respiratory tract model under short puffing condition
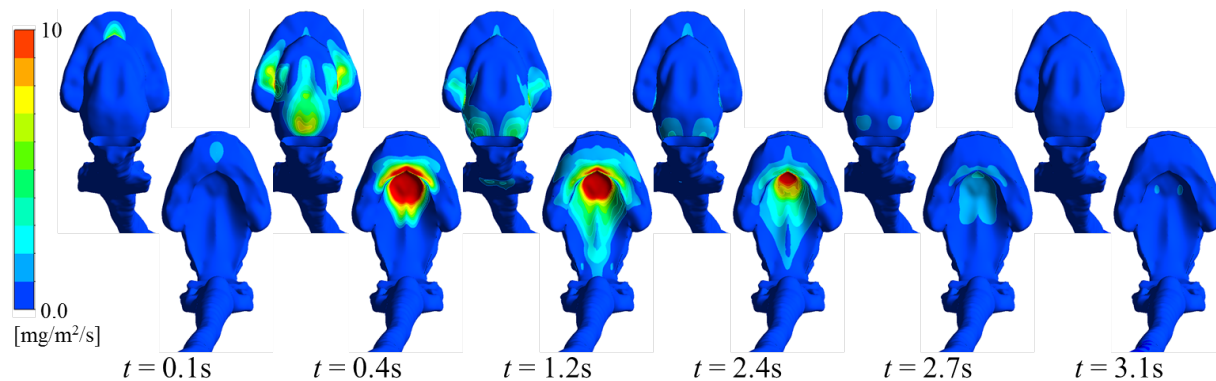
Fig. 5. The time series of the formaldehyde adsorption flux distributions on the mucus surface of the respiratory tract model

Table 3. Distributions/contributions of contaminants generated from e-cigarette puffing.

		Total mass of inhalation (µg)	Total mass of exhalation by way of mouth opening (µg)	Total mass of adsorption on air-mucus interface (µg)	Total mass of contaminants remaining airway without absorption (µg)
Short puff	Formaldehyde	45.82 (100%)	2.02 (4.4%)	43.79 (95.6%)	0.006 (0.0%)
	Acetaldehyde	14.40 (100%)	2.95 (20.5%)	10.96 (76.1%)	0.50 (3.4%)
	Acrolein	1.31 (100%)	0.35 (27.2%)	0.86 (65.8%)	0.09 (7.0%)
	Benzene	0.108 (100%)	0.066 (61.7%)	0.002 (1.8%)	0.039 (36.5%)
	Toluene	0.205 (100%)	0.126 (61.4%)	0.005 (2.5%)	0.074 (36.1%)
	Glycerol	2173 (100%)	204.8 (9.4%)	1956 (90.0%)	12 (0.6%)
	Nicotine	17.67 (100%)	2.18 (12.4%)	15.26 (86.3%)	0.22 (1.3%)
Long puff	Formaldehyde	47.92 (100%)	2.18 (4.6%)	45.71 (95.3%)	0.02 (0.1%)
	Acetaldehyde	15.06 (100%)	2.53 (16.8%)	12.20 (81.0%)	0.34 (2.2%)
	Acrolein	1.37 (100%)	0.30 (22.2%)	0.99 (72.3%)	0.07 (5.5%)
	Benzene	0.113 (100%)	0.065 (58.1%)	0.0024 (2.1%)	0.045 (39.7%)
	Toluene	0.215 (100%)	0.124 (57.6%)	0.006 (3.1%)	0.084 (39.3%)
	Glycerol	2273 (100%)	198 (8.7%)	2061 (90.7%)	14 (0.6%)
	Nicotine	18.48 (100%)	2.02 (10.9%)	16.20 (87.6%)	0.26 (1.5%)

4. DISCUSSIONS AND CONCULUSIONS

We have been tackling the development of numerical respiratory tract model for coupled PBPK–CFD analyses and have reported preliminary analysis results. In our previous study, we analyzed the formaldehyde adsorption flux distribution using the normalized partition coefficient concept in which the reaction-diffusion resistance in the tissue was reduced to a surface reaction and PBPK analysis was omitted (Kuga, et al., 2017). Moreover, we analyzed formaldehyde and acetaldehyde adsorption flux distribution using coupled PBPK–CFD model with two compartments; mucus + epithelium and sub-epithelium which can simultaneously analyze the diffusive transport in respiratory tissues (Kuga, et al., 2018). In this study, for improvement of prediction accuracy of inhalation exposure, we modified the model separating mucus and epithelium compartments and elaborately estimated the physical parameters of target chemicals. The modification has theoretically improved the prediction accuracy of our simulation. Based on our understanding, the numerical simulation of the respiratory tract using coupled PBPK–CFD analyses might be the only effective, quantitative and reasonable way to conduct inhalation exposure assessments. Furthermore, the differences of the adsorption rates of different chemical contaminants are considerable. Hence, coupled PBPK–CFD analyses which can predict the dynamics of various chemicals in the air and tissue phases of the respiratory tract should be developed. In this study, we modified coupled PBPK–CFD analyses and estimated the effect of different puffing behavior against the first- and second-hand human health risks of inhalation exposure of e-cigarette smoke.

5. REFERENCES

[1] Vansickel, A. R., Edmiston, J. S., Liang, Q., Duhon, C., Connell, C., Bennett, D., & Sarkar, M. 2018.Regulatory Toxicology and Pharmacology, 98, 250-256.

[2] Farsalinos, K. E., Romagna, G., Tsiapras, D., Kyrzopoulos, S., & Voudris, V. 2013. International journal of environmental research and public health, 10(6), 2500-2514.

[3] Tian, G., & Longest, P. W. 2010. Journal of biomechanical engineering, 132(5), 051003.

[4] Kuga, K., Ito, K., Yoo, S. J., Chen, W., Wang, P., Liao, J., ... & Kumagai, K. 2017. Indoor and Built Environment, 27(7), 898-916.

[5] Kuga, K, Yoo, SJ, Ito, K, Chen, W, Wang, P, Fowles, J, Kumagai, K, Shusterman, D. 2018. Roomvent-Ventilation, 283-288