Dosimetry Models of Inhaled Flavoring Compounds in ENDs Aerosols and Estimation of Tissue Concentrations in the Mouse and Human Respiratory Tracts

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Abstract Number: 4030
Poster Board Number: F502
Location: ToxExpo, Hall B

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BACKGROUND

Exposure to flavoring compounds in electronic nicotine delivery systems (ENDS) aerosols via inhalation raises potential health concerns. Although many flavoring compounds in ENDs products have been evaluated and affirmed as GRAS (Generally Recognized as Safe), this evaluation does not directly apply to exposure via inhalation. To better assess health risks, physiologically based pharmacokinetic (PBPK) models have been used for interspecies and route-to-route extrapolation.

In this study, we developed PBPK models specifically for ENDs aerosols, which consist of flavoring compounds in the gas phase and suspended fine particles, to estimate their tissue-level concentrations in the mouse and human respiratory tracts.

METHOD

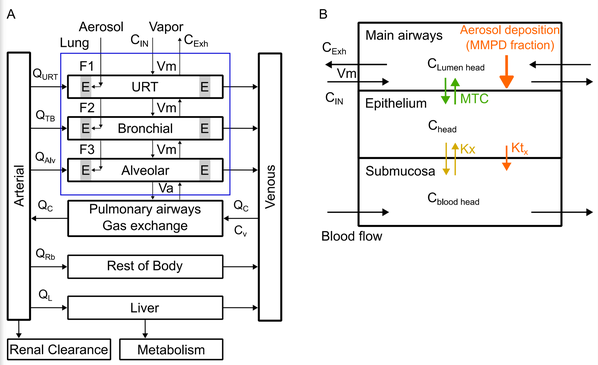
We combined the PBPK model with the multiple-path particle dosimetry (MPPD) lung deposition model because of the multiphase characteristics of the ENDs aerosol (Figure 1). The PBPK contained a multicompartment respiratory tract model based on anatomical location and functional structure, comprising three regions of the respiratory tract (the upper respiratory tract [URT], the tracheobronchial region [TB], and the alveolar region) and a pulmonary compartment representing the gas-exchange regions of the lung. Each region was further divided into a lumen for air passage, surrounded by epithelium and submucosal tissue layers, which facilitate the transport of absorbed chemicals across the anterior respiratory tract compartments. The model structure was the same across mice and humans, incorporating species-appropriate anatomy and physiology. Chemicals' gas vs. particle phases were estimated using Panko's (2017) approach, with activity coefficients calculated using the UNIFAC method (Fredenslund et al., 1975). The MPPD model was executed for a mass median aerodynamic diameter of 0.8 μm with a geometric standard deviation of 1.4 μm for the ENDs aerosols. Tissue concentrations of nicotine and 38 select flavoring compounds in each previously defined region were calculated, and z-score normalized to compare the deposition of flavors within and between mice and humans. A correlation analysis was conducted to examine the impact of modeling parameters on the results.

MPPD-PBPK MODEL

Table 1 –The MPPD model predicted different deposition patterns of particles in mice and humans.

Tissue	Mice	Humans
URT	53.3%	0.9%
TB	2%	6%
Alveolar	2%	15%

Figure 1 – The PBPK model schematic for nicotine and flavor compounds.



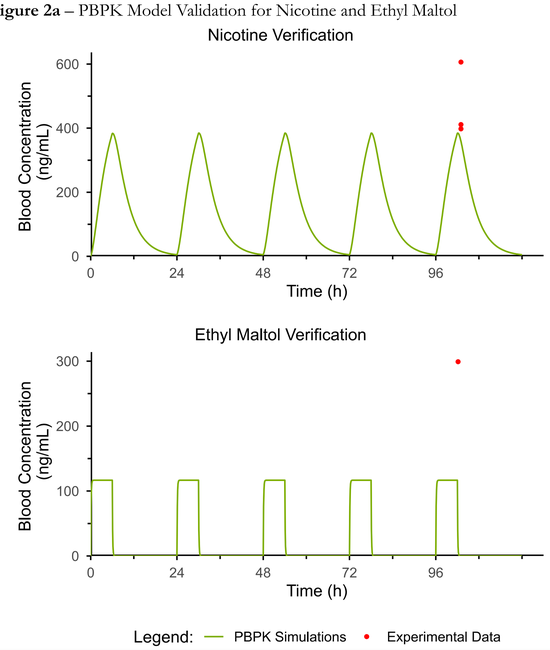
Panel A depicts the primary organs included in the model, along with the anatomical lung sub-compartments relevant to inhalation exposure. QL, QRb, QTB, QURT, and QAlv denote blood flow to each tissue compartment (liver (L), rest of the body (Rb), tracheobronchial region (TB), upper respiratory tract region (URT), and alveolar region, respectively). QC denotes the cardiac output, CV the venous concentration, and CIN the inhaled vapor concentration. F1, F2, and F3 indicate the aerosol fraction deposited in each region of the respiratory tract.

Panel B illustrates lung functional tissue sub-compartments and the movement of chemicals within the lumen and across the tissue, where "C" denotes concentration, "MTC" the mass transfer coefficient from the lumen to the epithelium, and "Kt_x" and "Kx" the tissue mass transfer parameters (epithelium to submucosa) for aerosols and vapors, respectively.

MODEL VALIDATION

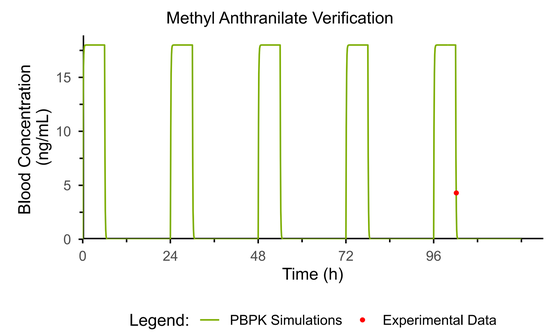
The MPPD-PBPK model was validated using plasma nicotine concentrations from a mouse inhalation study and subsequently applied to flavoring compounds (Figures 2a and 2b).

Figure 2a – PBPK Model Validation for Nicotine and Ethyl Maltol



MODEL VALIDATION Cont.

Figure 2b – PBPK Model Validation for Methyl Anthranilate.



FLAVOR CLUSTERS

Clustering mouse tissue concentrations identified 5 groups of flavoring compounds: (1) 4 with high blood and low respiratory levels (low liver clearance), (2) 20 with low blood and respiratory levels, (3) 7 with low blood and high respiratory (alveolar) levels, (4) 5 with low blood and high levels across all respiratory regions, and (5) 2 with low blood and high respiratory (URT) levels.

Table 2– Clustering of tissue concentrations. Steady-state maximum tissue concentrations were z-score normalized and analyzed using hierarchical clustering. Human tissue concentrations were merged to mice chemical clusters.

Chemical	CAS	Z-score mice				Z-score human	
		$Cven_{max}$	$Cturt_{max}$	$Ctalv_{max}$	$Cttb_{max}$	$Cturt_{max}$	$Ctalv_{max}$
Dihydroactinidiolide	17092-92-1	-0.22	2.49	-0.73	-0.18	5.87	-0.81
Ambrox	6790-58-5	-0.20	4.81	1.63	1.06	-0.25	0.5
alpha-Damascone	43052-87-5	-0.27	0.41	3.04	2.39	-0.29	0.5
Linalool	78-70-6	-0.26	0.02	2.13	1.59	-0.24	1.92
D,L-Citronellol	106-22-9	-0.22	1.12	1.45	2.99	-0.05	3.29
p-Mentha-8-thiol-3-one	38462-22-5	-0.25	0.74	1.39	1.89	-0.27	0.31
Eugenyl acetate	93-28-7	-0.15	0.83	0.49	1.50	-0.09	1.42
para-Cymene	99-87-6	-0.20	-0.41	1.19	0.04	-0.32	-0.63
Methyl cinnamate	103-26-4	-0.30	-0.24	1.51	0.68	-0.28	0.81
(E,Z)-2,6-Nonadienal	557-48-2	-0.36	-0.23	1.3	0.63	-0.27	1.06
delta-Nonalactone	3301-94-8	-0.34	0.08	-0.18	0.29	-0.13	0.88
Isopulegol	89-79-2	-0.29	-0.12	0.62	0.64	-0.21	1.81
3-Methyl-2,4-nonanedione	113486-29-6	-0.33	0.38	0.12	0.68	-0.18	0.49
Piperitone	89-81-6	-0.34	0.27	0.4	0.88	-0.2	0.75
Methyl anthranilate	134-20-3	-0.35	-0.25	-0.52	-0.32	-0.17	0.49
2-Methyl-4-phenyl-2-butanol	103-05-9	-0.37	-0.47	-0.17	-0.52	-0.33	-0.89
para-Dimethoxybenzene	150-78-7	-0.37	-0.44	0.02	-0.40	-0.31	-0.28
cis-3-Hexenol	928-96-1	-0.27	-0.5	-0.53	-0.72	-0.33	-0.74
Acetal	105-57-7	-0.30	-0.5	-0.56	-0.72	-0.32	-0.45
Isobutyraldehyde	78-84-2	-0.31	-0.5	-0.53	-0.74	-0.33	-0.61
Benzyl alcohol	100-51-6	-0.26	-0.42	-0.79	-0.73	0.45	-0.78
Ethyl lactate	97-64-3	-0.28	-0.44	-0.8	-0.74	0.4	-0.75
2-Methylbutyric acid	116-53-0	-0.24	-0.42	-0.77	-0.68	0.03	-0.08
2-Acetylthiazole	24295-03-2	-0.17	-0.41	-0.78	-0.71	0.3	-0.52
Ethyl 2-methylbutyrate	7452-79-1	-0.45	-0.5	-0.77	-0.77	-0.33	-1.18
Triethyl citrate	77-93-0	-0.33	-0.39	-0.75	-0.75	-0.17	-0.79
Furaneol	3658-77-3	-0.37	-0.44	-0.77	-0.76	-0.15	-0.88
Ethyl maltol	11/8/40	-0.36	-0.46	-0.78	-0.77	-0.26	-0.91
Ethyl vanillin	121-32-4	-0.33	-0.29	-0.69	-0.72	-0.32	-0.75
alpha-Pinene	80-56-8	-0.42	-0.5	-0.61	-0.72	-0.33	-1.18
Isoamyl alcohol	123-51-3	-0.29	-0.46	-0.64	-0.65	-0.25	0.64
1-Penten-3-one	1629-58-9	-0.33	-0.48	-0.66	-0.69	-0.28	0.24
Ketoisophorone	1125-21-9	-0.35	-0.41	-0.74	-0.67	-0.16	-0.29
2-Methoxy-4-methylphenol	93-51-6	-0.37	-0.44	-0.69	-0.66	-0.32	-0.69
2-Acetylpyrrole	1072-83-9	0.99	-0.45	-0.71	-0.68	-0.25	-0.91
2,5-Dimethylpyrazine	123-32-0	1.60	-0.45	-0.7	-0.65	0.28	-0.9
Acetanisole	100-06-1	4.56	-0.22	-0.1	-0.04	-0.1	-0.41
3-Ethylpyridine	536-78-7	3.07	-0.3	-0.34	-0.26	0.18	0.31

CORRELATION ANALISIS

Table 1 – Correlation analysis between tissue concentrations and physico-chemical properties: the n-octanol:water partition coefficient (logKow), molecular weight (MW), water solubility (logWS), and vapor pressure (logVP).

correlation coefficient	Mice				Human	
	$Cven_{max}$	$Cturt_{max}$	$Ctalv_{max}$	$Cttb_{max}$	$Cturt_{max}$	$Ctalv_{max}$
MW	-0.13	0.56	0.43	0.47	-0.16	0.28
logKow	-0.14	0.70	0.72	0.67	0.06	0.43
logWS	0.21	-0.57	-0.63	-0.53	0.42	-0.33
logVP	-0.03	-0.32	-0.19	-0.27	0.06	-0.20

DISCUSSION

MPPD-PBPK model

The MPPD-PBPK model developed in this study well recapitulated *in vivo* data from mouse studies for nicotine and two flavors (Methyl anthranilate and ethyl maltol). Model predictions fall within a factor of 2 for Nicotine and 2.6 for Ethyl Maltol. For Methyl Anthranilate, the measurement falls within the simulation's elimination phase.

Flavor Clusters

Clustering by tissue and venous concentrations reveals that some flavors have high concentrations in specific regions of the respiratory system in mice. For example, Dihydroactinidiolide and Ambrox are especially high in the URT, and alpha-Damascone, Linalool, D,L-Citronellol, and p-Mentha-8-thiol-3-one are high in the TB and alveolar regions. Elevated concentrations in TB and the alveolar region are also visible for para-Cymene, Methyl cinnamate, (E,Z)-2,6-Nonadiena, Isopulegol, and Piperitone.

One prominent feature of cluster analysis is species divergence, suggesting limitations in using rodent models as direct proxies for humans, especially in the URT, potentially due to anatomical differences.

Correlation Analysis

The analysis examined the relationship between chemical-specific parameters and the compounds' maximum normalized concentrations measured during the final week at steady state. Based on the correlation analysis, we can draw several key conclusions: The distribution of flavoring compounds in respiratory tissues appears to be primarily driven by their physicochemical properties, particularly their lipophilicity (LogKow) and molecular weight, rather than by partition coefficients or phase distribution. More lipophilic compounds (higher LogKow) tend to preferentially accumulate in respiratory tissues, especially in the alveolar region. This affinity suggests that lipophilic flavorings may have longer residence times in respiratory tissues, potentially increasing their local effects. The inverse relationship between water solubility (LogWS) and tissue concentrations reinforces the importance of lipophilicity - less water-soluble compounds tend to accumulate more in respiratory tissues.

CONCLUSIONS

We developed dosimetry models for ENDs aerosols to predict tissue concentrations in the respiratory tracts of humans and mice. The results indicate species-specific deposition patterns in humans and in mice and suggest that lipophilic compounds tend to accumulate in respiratory tissues regardless of their partitioning in particle/vapor phases. The correlation analysis indicates that the behavior of flavoring compounds is more predictable based on their physicochemical properties in the mouse model than in the human model. Therefore, the use of a generic dosimetry model for human exposure may require additional caution to ensure relevance and accuracy.

Citations:
1. Pankow, J. F. (2017). Calculating compound dependent gas-droplet distributions in aerosols of propylene glycol and glycerol from electronic cigarettes. *Journal of Aerosol Science*, *107*, 9–13. https://doi.org/10.1016/J.JAEROSCI.2017.02.003
2. Fredenslund, A., Jones, R. L., & Prausnitz, J. M. (1975). Group-contribution estimation of activity coefficients in nonideal liquid mixtures. *AIChE Journal*, *21*(6), 1086–1099. https://doi.org/10.1002/aic.690210607