



A Dosimetry Model for Estimating Tissue Concentrations of Inhaled Flavoring Compounds in Mouse and Human Respiratory Tracts

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Agenda

ENDS Flavors: From Exposure to Target Tissue Dose

MPPD-PBPK Model for Multiphasic ENDS Aerosols

Tissue Dose in Respiratory Tracts of Mice and Humans

Conclusion



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ENDS Flavors: From Exposure to Target Tissue Dose

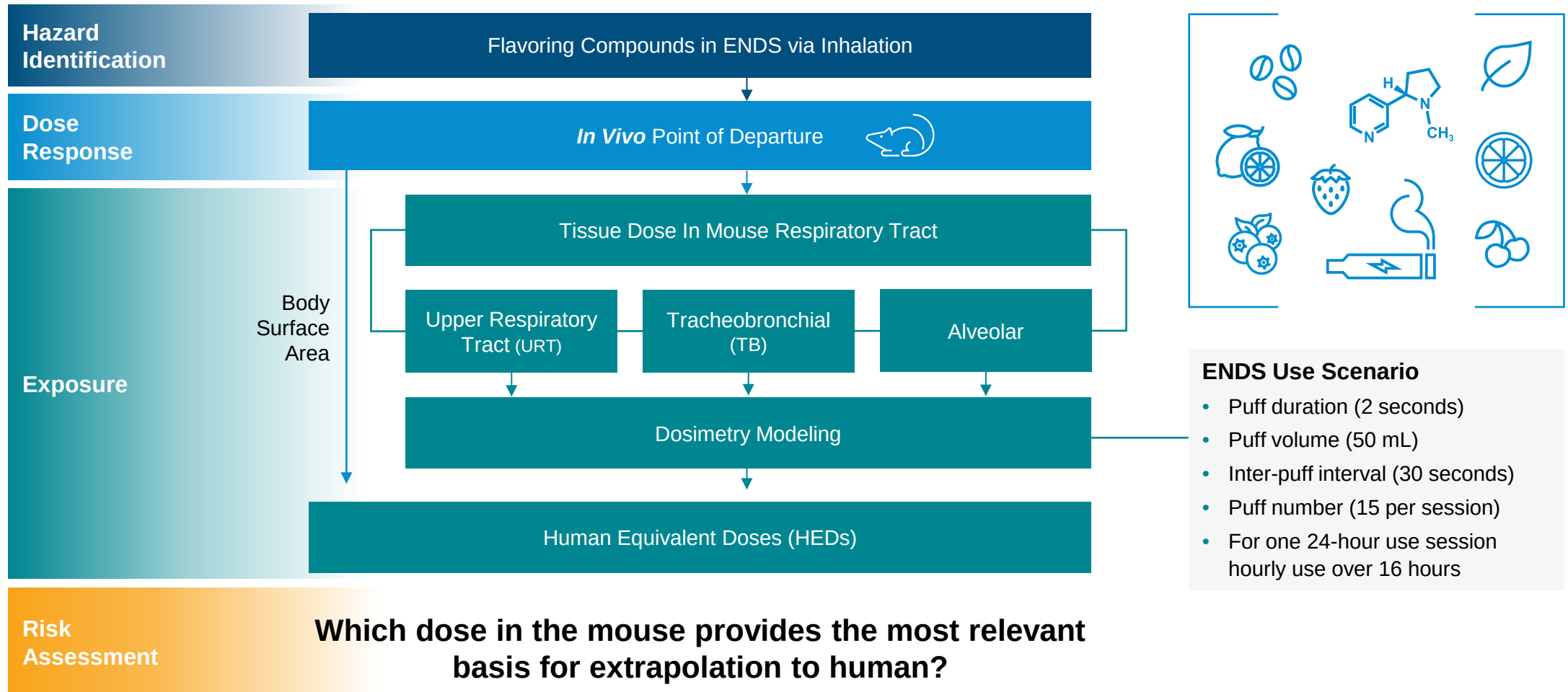
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MPPD-PBPK Model

ENDS aerosols = Gas phase + Suspended fine particles

A Combined Model

MPPD (multiple-path particle dosimetry) + PBPK (physiologically based pharmacokinetics)

Vapor/Particle partitioning calculated at equilibrium

PBPK: Multicompartmental for Mice and Humans

URT
upper respiratory tract

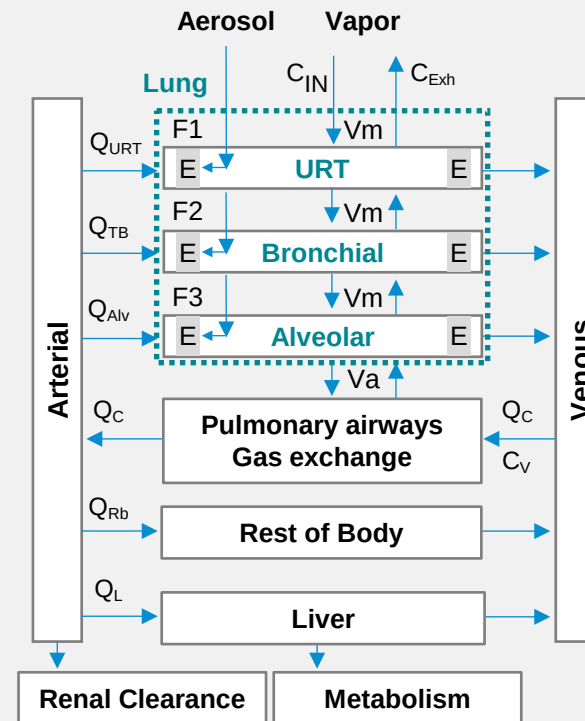
TB
tracheobronchial region

ALV
alveolar region

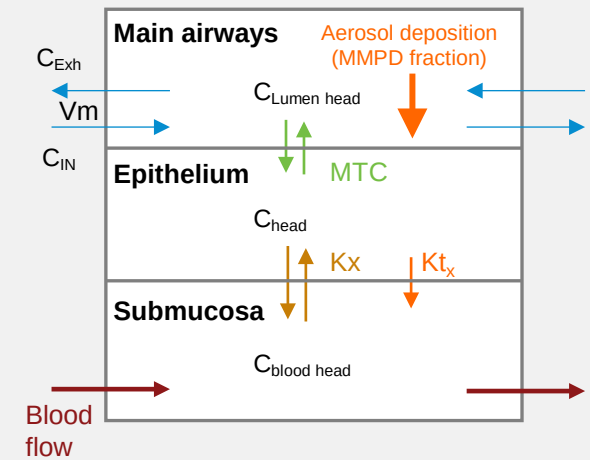
Mass transfer between the lumen, epithelium, and submucosal layer

The PBPK model schematic for nicotine and flavor compounds

A.



B.



Q: blood flow
C: concentration
F: fraction deposited
Vm: minute ventilation
Va: molecular diffusion volume of air
MTC: mass transfer coefficient
Kt: tissue mass transfer for aerosol
Kx: tissue mass transfer for vapor

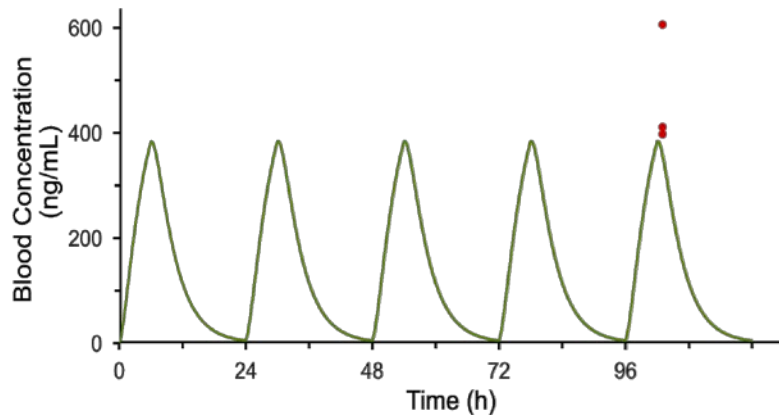


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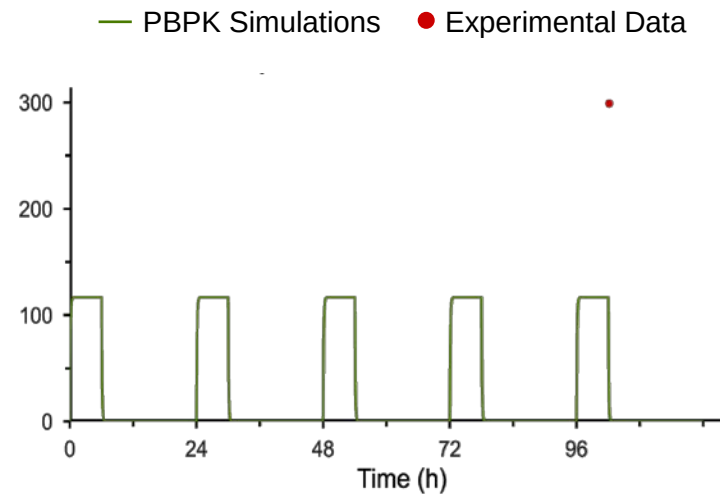
MPPD-PBPK Model: Partial Validation

- The MPPD-PBPK model developed in this study well recapitulated *in vivo* data
- 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

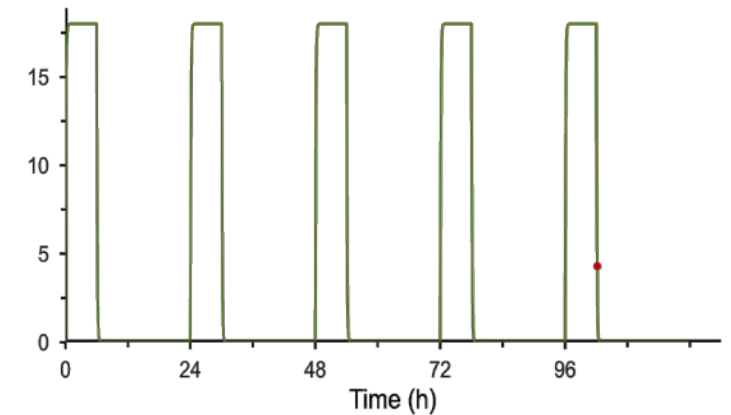
Nicotine Verification



Ethyl Matlol Verification



Methyl Anthranilate Verification



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MPPD Predicted Particle Deposition

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%

For Particle Phase



Mice

URT > Alveolar $\approx$ TB



Humans

Alveolar > > TB > URT



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Flavor Clusters Based on Tissue Concentrations (Mice)

4

high in blood
low in respiratory
tissues
(low liver clearance)

12

low in blood
high in respiratory
tissues (alveolar
region)

20

low in blood
low in respiratory
tissues

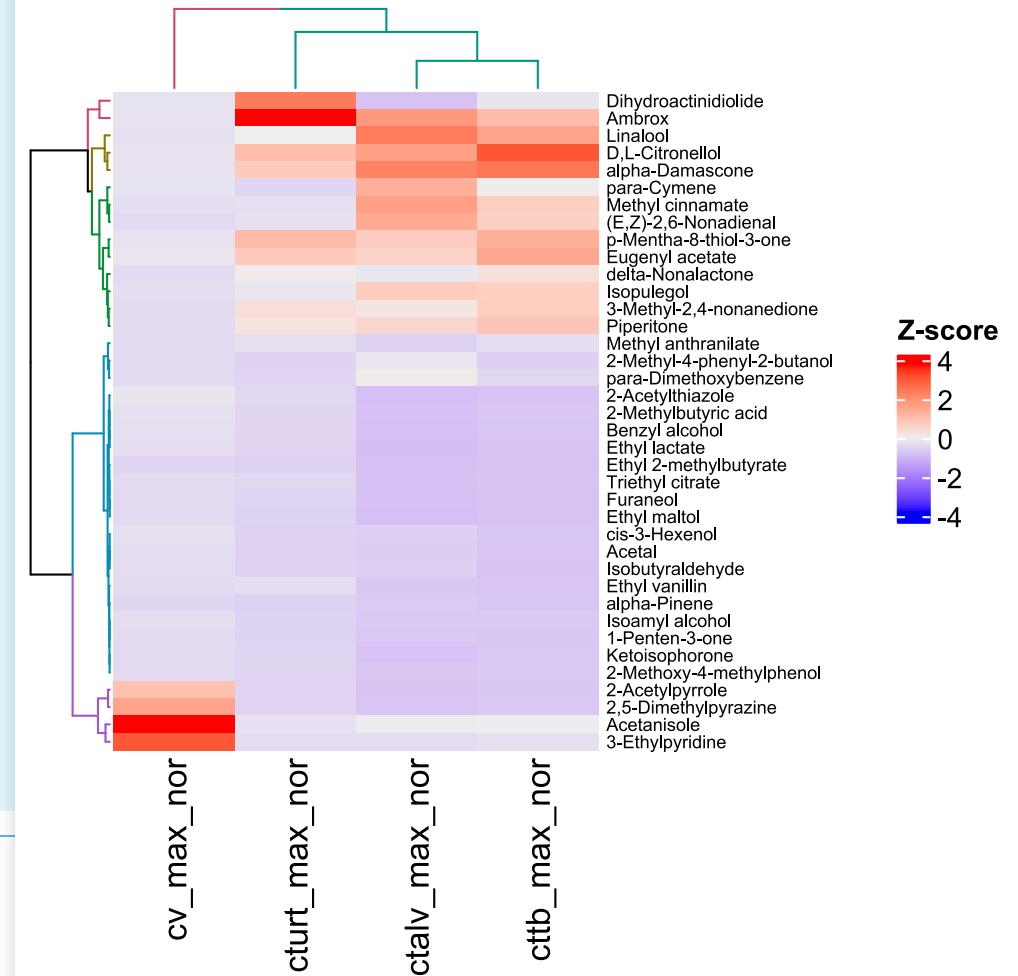
2

low in blood
high in URT region

Tissue concentrations varied
across tissues.

Flavor compounds exhibited
characteristic distribution
profiles that enabled
clustering.

Clustering of tissue concentrations for mice. Steady-state
maximum tissue concentrations were z-score normalized
and analyzed using hierarchical clustering.



Flavor Clusters Based on Tissue Concentrations

Tissue concentrations varied across tissues.

Flavor compounds exhibited characteristic distribution profiles that enabled clustering.

Comparison of the tissue concentrations in mice and humans reveals species divergence.

Clustering of tissue concentrations. Steady-state maximum tissue concentrations were z-score normalized and analyzed using hierarchical clustering. **Human tissue concentrations were merged to mouse chemical clusters.**

Chemical	Z-score mice		Z-score human	
	C_{turt_max}	C_{talv_max}	C_{turt_max}	C_{talv_max}
Dihydroactinidiolide				
Ambrox				
alpha-Damascone				
Linalool				
D,L-Citronellol				
p-Mentha-8-thiol-3-one				
Eugenyl acetate				
para-Cymene				
Methyl cinnamate				
(E,Z)-2,6-Nonadienal				
delta-Nonalactone				
Isopulegol				
3-Methyl-2,4-nonanedione				
Piperitone				
Methyl anthranilate				
2-Methyl-4-phenyl-2-butanol				
para-Dimethoxybenzene				
cis-3-Hexenol				
Acetal				
Isobutyraldehyde				
Benzyl alcohol				
Ethyl lactate				
2-Methylbutyric acid				
2-Acetylthiazole				
Ethyl 2-methylbutyrate				
Triethyl citrate				
Furaneol				
Ethyl maltol				
Ethyl vanillin				
alpha-Pinene				
Isoamyl alcohol				
1-Penten-3-one				
Ketosisophorone				
2-Methoxy-4-methylphenol				
2-Acetylpyrrole				
2,5-Dimethylpyrazine				
Acetanisole				
3-Ethylpyridine				





Correlation Analysis

Tissue concentrations of flavor compounds

Positively correlate to

- Lipophilicity (LogKow) (statistically significant)
- Molecular weight (MW) (weak and indirect)

Do not correlate to

- Vapor pressure (logVP)

Lipophilic compounds (higher LogKow, lower water solubility LogWS) tend to preferentially accumulate in respiratory tissues.

Lipophilic compounds may have longer residence times in respiratory tissues, potentially increasing their local effects.

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)

	 Mouse				 Human	
correlation coefficient	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

Cven: concentration in venous blood

Cturt: concentration in the epithelial layer of URT

Ctalv: concentration in the epithelial layer of alveolar region

Cttb: concentration in the epithelial layer of TB region



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The dosimetry results indicate **species-specific deposition patterns** in humans and in mice.



Tissue doses in mice 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.



Acknowledgement

Please contact me if you have any questions

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THANK YOU!

