

Dose equivalence : human cigarette smoking versus *in vitro* at the air-liquid interface

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Introduction

- Cigarette smoke dosimetry offers significant challenges for measurement and modelling given the chemical complexity and physical dynamics of the smoke.
- Published data suggest different deposition mechanisms for vapor and particle phase fractions of the smoke.
- In turn, regional deposition will be influenced by these physical behaviours, but more significantly by the available surface area in each region of the lung, that is, the extra-thoracic (ET), bronchial / bronchiolar (BB/bb) and alveolar-interstitial (AI) regions.
- Further differences will arise from different mechanisms and rates of clearance
- The subsequent challenge is to re-create representative doses at the air-liquid interface (ALI) for *in vitro* exposure systems.

ALI geometries & deposition mechanisms

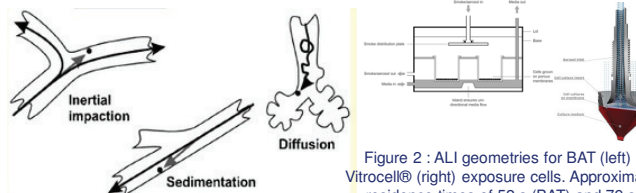


Figure 1 : Principal mechanisms of particle deposition in lung

Figure 2 : ALI geometries for BAT (left) & Vitrocell® (right) exposure cells. Approximate residence times of 52 s (BAT) and 79 s (Vitrocell® @ 5 ml.min⁻¹) support particle deposition by sedimentation and vapor deposition by diffusion

Regional deposition - carbonyls

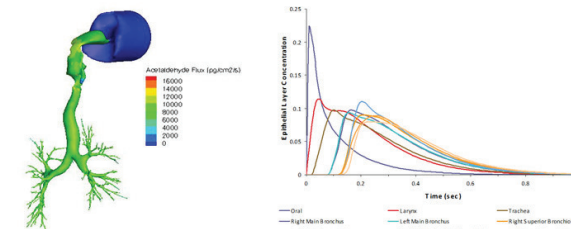


Figure 4 : CFD modelled vapor flux and estimated deposition (Corley *et al*, unpublished communication)

Compound	ET	BB/bb
Acetaldehyde	100-200	50
Formaldehyde	0.4-0.8	0.2-0.3
Acrolein	2-5	2

Table 2 : Estimated daily dose (µg.cm⁻²) calculated from Corley *et al*, 2015 for 20 cigarettes per day smoker

Calculated dose – particle mass

Study	n	ET	BB/bb	AI	Total
Pritchard, 1987	23♂	0.14	0.36	0.24	0.74
McAughey, 1991	14♂	0.05	0.22	0.42	0.69
McAughey, 1991	14♀	0.15	0.19	0.36	0.70
Ishikawa, 2016*	17	0.226	0.224	0.173	0.62

Table 3 : Measured regional deposition fraction for radiolabelled tar or solanesol*

	ET	BB/bb	AI
Mass (µg.cm ⁻²)	27 - 82	0.6 - 1.2	0.04 - 0.08
Surface (cm ² .cm ⁻²)	7.7 - 23	0.18 - 0.33	0.012 - 0.022
Number (cm ²)	9.7 - 29 e+9	2.2 - 4.2 e+8	1.6 - 2.7 e+7

Table 4: Estimated daily tissue dose from particles for historical radiotracer studies assuming average daily tar intake of 260 mg (Mariner *et al*, 2011). Data expressed as mass, surface area and number dose

	Mouth/Throat	Bronchi	Bronchioles	Respiratory bronchioles	Alveoli
ICRP Surface Area (cm ²)	4.5e2	2.9e2	2.4e3	7.5e4	1.4e6
Average retention fraction	0.118	0.035	0.024	0.132	0.194
Daily dose (µg.cm ⁻²)	82	37.2	3.0	0.5	0.04

Table 5 : Estimated daily tissue dose (µg.cm⁻²) based on BAT regional deposition model (accompanying poster) for 20 per day 7 mg ISO tar cigarettes

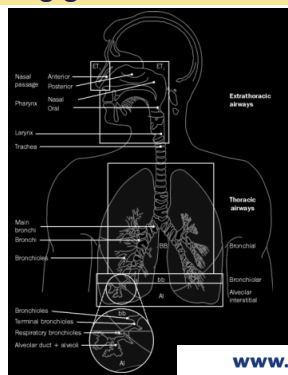
Reported doses at the air-liquid interface

Material	Minimum Dose (µg.cm ⁻²)	Maximum Dose (µg.cm ⁻²)	Notes [Reference]
QCM Mass	0.22	25.75	30 puffs UK 3R4F @ ISO : Adamson <i>et al</i> , 2012
QCM Mass	3.4	180	66 puffs UK 3R4F @ HCl : Majeed <i>et al</i> , 2014
QCM Mass	0.7	5.1	10 puffs UK 3R4F @ HCl : RM20S : Adamson, 2016
QCM Mass	3.6	21.2	10 puffs UK 3R4F @ HCl : VC10 : Adamson, 2016
Solanesol*	0.24	4.1	4 cigs (?44 puffs) UK 3R4F @ HCl : Ishikawa <i>et al</i> , 2016
Nicotine	0.019	0.13	10 puffs UK 3R4F @ HCl : RM20S : Adamson, 2016
Nicotine	0.08	0.73	10 puffs UK 3R4F @ HCl : VC10 : Adamson, 2016
Acetaldehyde	0.5	13.5	4 cigs (?44 puffs) UK 3R4F @ HCl : Ishikawa <i>et al</i> , 2016
Acetaldehyde	4.6	85	66 puffs UK 3R4F @ HCl : Majeed <i>et al</i> , 2014
Formaldehyde	0.12	1.6	66 puffs UK 3R4F @ HCl : Majeed <i>et al</i> , 2014
Acrolein	0.24	2.3	66 puffs UK 3R4F @ HCl : Majeed <i>et al</i> , 2014

* ~34x solanesol mass equivalent to 'QCM mass'

Table 1 : Delivered dose at the ALI per cm² calculated from published studies

Lung geometries



- Lung regions defined by function
- Lung geometries and surface areas derived from Weibel, 1973 within ICRP 66 model, 1994.

Figure 3 : ICRP 66 Lung regions

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Results

- Published data for *in vitro* exposure systems at various dilutions report particle phase doses of 0.22–180 µg.cm⁻² using a quartz crystal microbalance depending on number of cigarettes smoked.
- This compares with calculated daily particle doses for smokers of 27–82 µg.cm⁻² (ET), 0.6–1.2 µg.cm⁻² (BB/bb) and 0.04–0.08 µg.cm⁻² (AI).
- Published data for measured vapor phase carbonyl species suggest ALI doses up to 75 µg.cm⁻² (acetaldehyde), 2.0 µg.cm⁻² (acrolein) and 1.0 µg.cm⁻² (formaldehyde) can be readily achieved.
- Published model estimates of daily aldehyde dose in the BB/bb region of smokers suggest doses up to 50 µg.cm⁻² (acetaldehyde), 2.0 µg.cm⁻² (acrolein) and 0.2-0.3 µg.cm⁻² (formaldehyde).

Conclusions

- Doses representing daily exposures to cigarette smoke particle and vapor constituents appear achievable at the air-liquid interface
- The dose for vapor phase components is proportionately greater than particle phase at the ALI, relative to smoke content, consistent with higher deposition efficiency of the vapor phase by diffusion
- There is a clear need to develop a consistent reporting approach for units of dose to allow comparison of multiple data sets

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The subsequent challenge is to re-create representative doses at the air-liquid interface (ALI) for in vitro exposure systems.

Published data for in vitro exposure systems at various dilutions report particle phase doses of 0.22 – 25.75 $\mu\text{g}\cdot\text{cm}^{-2}$ using a quartz crystal microbalance. This compares with calculated daily depositions for smokers of 27 – 82 $\mu\text{g}\cdot\text{cm}^{-2}$ (ET), 0.6 – 1.2 $\mu\text{g}\cdot\text{cm}^{-2}$ (BB/bb) and 0.04 – 0.08 $\mu\text{g}\cdot\text{cm}^{-2}$ (AI). These data can also be expressed as surface area and number weighted doses, the surface area doses being similar to reported pro-inflammatory threshold values of 1 - 10 $\text{cm}^2\cdot\text{cm}^{-2}$.

Published data for measured vapor phase carbonyl species suggest ALI exposures up to 75 $\mu\text{g}\cdot\text{cm}^{-2}$ (acetaldehyde), 2.0 $\mu\text{g}\cdot\text{cm}^{-2}$ (acrolein) and 1.0 $\mu\text{g}\cdot\text{cm}^{-2}$ (formaldehyde) can be readily achieved. Published model estimates of daily aldehyde dose in the BB/bb region of smokers suggest exposures up to 50 $\mu\text{g}\cdot\text{cm}^{-2}$ (acetaldehyde), 2.0 $\mu\text{g}\cdot\text{cm}^{-2}$ (acrolein) and 0.2 - 0.3 $\mu\text{g}\cdot\text{cm}^{-2}$ (formaldehyde).

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