Cigarette smoke dose equivalence : human airways versus the *in vitro* air-liquid interface

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Dose is a combination of concentration, location and duration. The fractional and regional deposition of cigarette smoke toxicants in the lungs has implications for the assessment of relative risk arising from smoking cigarettes or using alternative nicotine products. 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 vapour and particle phase fractions of the smoke (Baker & Dixon, 2008, St Charles *et al*, 2013). 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.

A study of volunteer smokers used real-time measurement of puffing, respiration and puffed/exhaled smoke particulate to generate data which were then incorporated into a compartmental model for particle deposition in the human respiratory system. Total deposition and regional deposition of smoke particles from a range of commercial products with different ISO tar yields, formats and filter types, under different smoking regimes was assessed.

Nine volunteers smoked seven different products with their normal puffing regime at three different self-perceived but measured inhalation regimes: mouth hold only, shallow inhalation and normal inhalation.

Measurements of puffing behaviour, respiratory behaviour, and physical and chemical measurements of puffed and exhaled smoke (solanesol content, tar, particle size) were recorded.

Results showed that product type had a significant effect on puffing behaviour but did not have a significant effect on respiratory behaviour. ISO tar yield also had a significant effect on deposition fraction, potentially due to changes occurring to the particles post mouth hold.

There was evidence of coagulation and hygroscopic growth of smoke particles, with mouth hold time having an effect on coagulation, and with product having an effect on hygroscopic growth factor.

For particle phase, data from these deposition studies combined with regional deposition estimates from radiotracer studies (McAughey *et al*, 1997) gives calculated daily tar depositions for smokers of 27–82 $\mu g.cm^{-2}$ (ET: extra-thoracic), 0.6–1.2 $\mu g.cm^{-2}$ (BB/bb: bronchial, bronchiolar) and 0.04–0.08 $\mu g.cm^{-2}$ (AI: alveolar). These data can also be expressed as surface area and number weighted doses, the surface area doses for the BB/bb region being similar to reported pro-inflammatory threshold values of 1-10 $cm^2.cm^{-2}$ (Monteiller *et al*, 2007).

For vapour phase, published model estimates of daily aldehyde exposures in the BB/bb region of smokers suggest daily doses up to 50 $\mu g.cm^{-2}$ (acetaldehyde), 2.0 $\mu g.cm^{-2}$ (acrolein) and 0.2-0.3 $\mu g.cm^{-2}$ (formaldehyde) (Corley *et al*, 2015).

Published data for in vitro exposure systems at the air-liquid interface at various dilutions report particle phase doses of 0.22–25.75 $\mu g.cm^{-2}$ using a quartz crystal microbalance (Adamson *et al,* 2012).

Published data for measured vapour phase carbonyl species suggest ALI exposures up to 75 $\mu g.cm^{-2}$ (acetaldehyde), 2.0 $\mu g.cm^{-2}$ (acrolein) and 1.0 $\mu g.cm^{-2}$ (formaldehyde) can be readily achieved (Majeed *et al*, 2014). The ratio of vapour : particle phase dose is enhanced relative to measured smoke yields (Ishikawa *et al*, 2016) consistent with the deposition mechanisms of diffusion and sedimentation dominating vapour and particle phases respectively.

In conclusion, systems designed for smoke exposure at the air-liquid interface can achieve doses representative of daily dose estimates in smokers for both vapour and particle phases.

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