A model for the respiratory retention of compounds found in cigarette smoke

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Summary

- Data from multiple studies were combined, and measured respiratory retention (RR) was modelled as a function of vapor pressure (VP) (St.Charles *et al.* (2013), *Inhal. Toxicol.* **25**:383-397).
- The average respiratory retention versus the log [VP] at 25°C gave a sigmoidal-type shape with three distinct regions.
- Compounds with VP > 1E-4 Pa had respiratory retentions greater than 90%, and this is generally independent of post-puff inhalation behavior.
- Compounds with VP < 1E-9 Pa better represented the classical non-volatile aerosol with retention dependent on both inhalation volume (depth) and lung residence time.
- A transition region between these ranges includes compounds of toxicological significance such as the tobacco-specific nitrosamines (TSNA) and polycyclic-aromatic hydrocarbons (PAHs).
- The measurement of respiratory retention is typically by difference and should be corrected for endogenous breath VOCs.
- Most experiments used a small number of subjects. The largest source of variability is subject-to-subject.

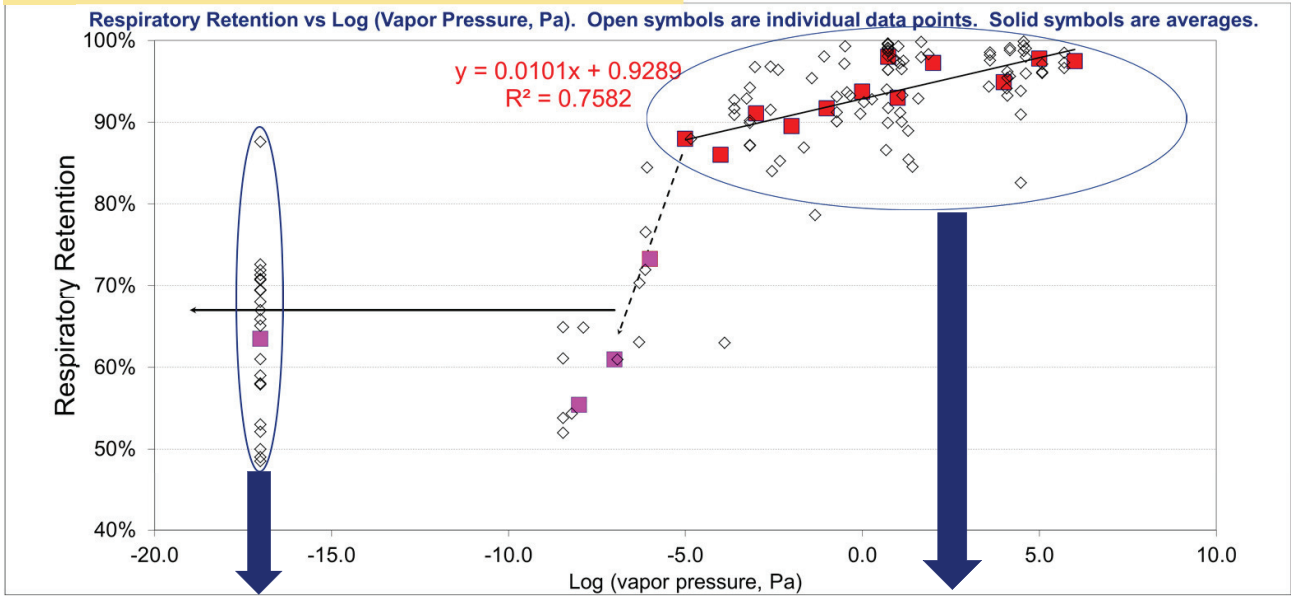
Data Sources

- For respiratory retention, 124 values for 62 compounds from 11 publications were used (cited in St.Charles *et al.* (2013), *Inhal. Toxicol.* **25**:383-397) .
- Solanesol ($C_{45}H_{74}O$), representing particulate retention due to its low VP of 1E-17 to 1E-19 Pa had 22 published results, followed by nicotine with 11 values.
- At least 2 sources of similar online and published values were used for VP data, with calculated values being used to guide selection of differences.
- Solanesol VP was based on calculated values.
- The VP of the pure compound is almost assured to be different than the VP in smoke, but using the log (VP) gives a measure of volatility.

Application

- Application of mouth-spill and respiratory retention models to transform mouth level exposure to dose for acrolein, pyrene and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) both improved correlations with their respective urinary biomarkers and improved estimation of the overall metabolic conversion of a chemical species to its respective biomarker. (St.Charles *et al.* (2013) *Inhal. Toxicol.* **25**:383-397).

Results



SOLANESOL (Non-volatile Particulate) RETENTION

Depends on Inhalation Behavior (Volume and Duration)

- The solanesol retention data are primarily from experiments which controlled inhalation volume (IV) and breath-hold times (BH) over a wide range and therefore show a very wide range of retention. Data from the controlled experiments were used for the multiple regression

% Solanesol retention = A + B x BH (s) + C x IV (mL)

Coefficients were significant (p<1E-4)

A = 45 %, B = 3.26 %/s , and C = 0.0221 %/mL

- The horizontal arrow at 67% represents an 74 subject average IV of 833 mL and BH of 1s from St.Charles *et al.* (2009) *Inhal.Toxicol.* **21**:712-718. This matches, within 1%, the average of the natural inhalation studies by Moldoveanu & Coleman (2008-2009), *Beitr Tabakforsch Int.*

VAPOR PRESSURE ≥ 1E-5 Pa RETENTION

Retention depends primarily on Vapor Pressure

- Average respiratory retention is 86% or greater and decreases slightly as VP decreases over 10 orders of magnitude.
- Compounds associated with particulate phase (as collected on Cambridge filter pads) will also show evaporative behavior in the lung, most significantly for nicotine.
- This implies that retention must depend on vapor transport from particles in addition to particle deposition.
- In practice, solubility of the compound will also influence retention and Henrys Law coefficients may better define behaviour (but are less accessible for predictive purposes).

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Cigarette smoke dosimetry offers a significant challenge given the chemical complexity and physical dynamics of the smoke. Filter studies have often been used to provide estimates of mouth level exposure to compounds in cigarette smoke, but do not account for mouth spill and respiratory retention efficiency. Urinary biomarkers provide the relative uptake of certain compounds when comparing products, but generally do not provide absolute uptake values. Nicotine is an exception since the multiple urinary biomarkers currently measured can account for over 90% of the retained nicotine.

Data from multiple studies have been combined, and measured respiratory retention has been determined as a function of vapor pressure (VP). A plot of the average respiratory retention versus the log (VP) at 20-25°C gives a sigmoid shape with three distinct regions. Compounds with VP > 10^{-4} Pa have respiratory retentions greater than 90%, and this is generally independent of post-puff inhalation behavior. Compounds with VP < 10^{-9} Pa better represent the non-volatile proportion of the aerosol with retention dependent on both inhalation volume (depth) and lung residence time. A transition region lies between these ranges, which includes compounds of toxicological significance such as the tobacco-specific nitrosamines (TSNA) and polycyclic-aromatic hydrocarbons (PAHs).

Application of the mouth-spill and respiratory retention models to modify mouth level exposure to dose for acrolein, pyrene and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) and to correlate these data with their respective urinary biomarkers demonstrated both improved correlations and improved estimation of the overall metabolic conversion of a chemical species to its respective biomarker.

St.Charles, K., McAughey, J., Shepperd, C. (2013) METHODOLOGIES FOR THE QUANTITATIVE ESTIMATION OF TOXICANT DOSE TO CIGARETTE SMOKERS USING PHYSICAL, CHEMICAL AND BIOANALYTICAL DATA. *Inhalation Toxicology* **25**(7):383-397