Modelling of Accumulating Inhaled Particles and the Potential for Associated Lung Toxicity

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• What happens to poorly soluble particles delivered to the lung?
• Current literature evidence and understanding
• Example: Inhaled PF-`X` 
• Estimating Lung Burden in an inhaled TK study
• Basic principles and PK equations
• Accumulation observed for PF-`X` and potential link to histopathology
• Impact of species differences in alveolar macrophage clearance rates
• Conclusions
What happens to poorly soluble particles in the lung?

• 3 mechanisms of clearance of deposited material in the lung

  a) **Mucociliary clearance** of particles in conducting airways (within hours)

  b) **Slow dissolution** followed by absorption through the lung into systemic circulation (within hours)

  c) **Alveolar macrophage (AM) clearance** of particles in the alveoli, transport particles to mucociliary elevator and the lymph nodes (days)

• Therefore the mass of material in the lung depends on:

  Rate delivered to the lung → frequency (e.g. daily dosing) and mass delivered

  Rate out of the lung → the summation of mucociliary clearance, dissolution and AM clearance
Literature data on particulates

2000 - Inhalation of poorly soluble particles. II Influence of particle surface area on inflammation and clearance Tran et al, Inh. tox,
1996 - Modelling retention of inhaled particles in rat lungs including tox and overloading effects – Gradon et al, J.Aer. Sci
1997 – Inhaln of high concns of low toxicity dusts in rats results in impaired pulmonary clearance mechanisms and persistent inflammation Warheit et al, Tox. And Applied Pharm.
1995 - Model of particle-alveolar macrophage relationships during the alveolar clearance of a low lung burden of instilled particles Bernadin & Lehnert, J.aer. Sci,
1992 - Pulmonary and thoracic macrophage subpopulations and clearance of particles from the lung Lehnert B.E, Env. Health Persp.
1989 - Retention patterns for inhaled particles in the lung: Comparisons between lab animals and humans for chronic cases Snipes et al, Health Phys.
1986 – Pulmonary Response to impaired lung clearance in rats following excessive TiO2 dust deposition Lee et al, Envir. Research
1985 - Comparative deposition of inhaled aerosols in experimental animals and humans: A review Schlesinger R.B, J. Tox. & Env.Health,

Key theme is the focus on completely insoluble molecules
• Increasing non-dissolved material in the lung stimulates excessive macrophage localisation which can appear foamy and can lead to tissue damage = adverse findings in inhaled toxicity studies

• Threshold values have been proposed by several authors for these findings (Warheit, 1997 and Lee 1986)

0.1- 1mg/g lung – non-adverse adaptive changes i.e ↑ macrophages
>1mg/g lung – associated with adverse changes i.e additional inflammation, tissue degeneration

Q. How do the lung thresholds relate to our rat studies with inhaled molecules?

Q. Are we above 1mg/g when we observe adverse changes in the lung?
Example: Inhaled `PF-X`

- Inhaled molecule for the treatment of asthma
- MW ~600, LogD pH\textsubscript{7.4} = ~2.0
- Low solubility ~20ug/ml @ pH\textsubscript{6.5} in phosphate buffer

### 28 Day Rat Inhaled Toxicology

<table>
<thead>
<tr>
<th>Dose (ug/kg/day)</th>
<th>Est. Lung Dose (ug/kg/day) \textsuperscript{*assum10%deposn}</th>
<th>Lung Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>633</td>
<td>63</td>
<td>No treatment related changes</td>
</tr>
<tr>
<td>5128</td>
<td>513</td>
<td>Adverse changes consistent with insoluble particles</td>
</tr>
<tr>
<td>67425</td>
<td>6743</td>
<td>Adverse changes consistent with insoluble particles</td>
</tr>
</tbody>
</table>

\textsuperscript{* Anjilvel & Asgharian 1995}

- Are these adverse changes due to the mass of particulates in the alveoli?
- If so have we reached steady state?
- Could longer term tox studies provide adverse effects at lower doses?
Estimating Lung Burden in a TK Study

Estimate pulmonary deposition based on multiple path modelling (~10% in rat, Anjilvel & Asgharian 1995)

- Using PK principles we can estimate the input and outputs from the lung

- Therefore we can estimate the lung burden on any day and at steady state

Mass delivered to the lung / day

Accumulation of undissolved particles

Mass absorbed through the lung into the circulation

Mass cleared by macrophages

Literature information available on AM T1/2's

Calculate using the TK systemic exposure data
Equation 1. Estimating the lung Ka from the observed systemic TK accumulation
- Where systemic IV PK half life is <12h systemic TK accumulation is driven by lung absorption rate

\[
\text{Systemic accumulation on day `n`} = \frac{1 - e^{-Ka.t.n}}{1 - e^{-Ka.t}}
\]

\(Ka =\) lung absorption rate constant
\(t =\) dosing interval
\(n =\) number of doses

(Rowland & Tozer 2006)

Equation 2. Estimating the alveolar macrophage clearance rate

\[Kam = \frac{0.693}{\text{AM particle clearance half life}}\]

In the rat undissolved particulates are removed by AMs with \(\sim 100\text{day half life} = 0.007\text{day}^{-1}\) (Oberdorster et al 1992), Human Kam = 200days = 0.0035day\(^{-1}\) (Bailey et al 1985)

Equation 3. Estimating alveolar lung particulate burden

\[
\text{Lung Burden on day `n`} = \text{Dose} \times \frac{1 - e^{-(Ka+Kam)t.(n+1)}}{1 - e^{-(Ka+Kam)t}} - \text{Dose}
\]
Inhaled PF-`X` Accumulation

<table>
<thead>
<tr>
<th>TK Data</th>
<th>Dose (µg/kg/day)</th>
<th>Lung Dose (ug/kg/day)</th>
<th>Lung Dose (ug/g lung)</th>
<th>Systemic Accumulation</th>
<th>Lung Ka (day-1)</th>
<th>Lung burden (ug/g lung)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 Day</td>
<td>633</td>
<td>63</td>
<td>11</td>
<td>4.1</td>
<td>0.28</td>
<td>33</td>
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<tr>
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<td>85</td>
<td>4.5</td>
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<tr>
<td></td>
<td>67425</td>
<td>6743</td>
<td>1124</td>
<td>6.4</td>
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<td>5764</td>
</tr>
</tbody>
</table>

- Modelling indicates undissolved mass in the lung has reached steady state
- Estimated lung burdens are at levels ~ consistent with literature thresholds

Expect adverse changes i.e additional inflammation, tissue degeneration

Non adverse adaptive changes i.e ↑ macrophages

10% deposition 250g rat 1.5g lung per rat
### Further examples

<table>
<thead>
<tr>
<th>Compound</th>
<th>TK Data</th>
<th>Est. Lung Dose (ug/kg/day)</th>
<th>Est. Lung Burden (ug/g)</th>
<th>Lung Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>28 Day</td>
<td>51</td>
<td>0</td>
<td>No treatment related changes</td>
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<tr>
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<td>182</td>
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<td>No treatment related changes</td>
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<td>1470</td>
<td>856</td>
<td>Increased macrophages consistent with insoluble particles but not adverse</td>
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<td>28 Day</td>
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<td>&lt;1</td>
<td>No treatment related changes</td>
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<td>No treatment related changes</td>
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<tr>
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<td>1094</td>
<td>714</td>
<td>Increased macrophages consistent with insoluble particles but not adverse</td>
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<td>91 Day</td>
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<td>29</td>
<td>No treatment related changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>61</td>
<td>74</td>
<td>No treatment related changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1064</td>
<td>1426</td>
<td>Adverse changes consistent with insoluble particles</td>
</tr>
</tbody>
</table>

Data in line with proposed thresholds….

**0.1- 1mg/g lung** – non-adverse adaptive changes i.e. ↑ macrophages

**>1mg/g lung** – associated with adverse changes i.e additional inflammation, tissue degeneration

**Note**: increased foamy macrophages can also be caused by the pharmacology of the inhaled molecule
Differences in AM clearance

- Human AM Cl rate is slower than Rat (~200 vs 100 days)
- Often stated that species differences in particle clearance rates provide differences in lung burden (Snipes 1989, Brown 2005)
- True for completely insoluble molecules but not for slowly absorbed drugs (e.g. with >10% absorption per day, Lung Ka >0.1)

Impact of AM Cl differences across species is negligible

Due to the very small amount removed by AMs per day for rat (~0.7%) and human (~0.35%)

vs >10% absorbed into the systemic circulation

Accumulation of particulates in the rat lung following 10ug/g daily dosing (Ka of 0.1 used for poorly soluble illustration)
Conclusions

- Provides a method to estimate lung burdens achieved which can aid the interpretation of the histopathology findings
- Lung burden data is broadly consistent with published data on pathology associated with corresponding lung burdens of inert material
- Enables an assessment of the extent of accumulation that has occurred and if steady state is reached

- Potentially aid dose selection and likely observations in longer term toxicology studies
- Similar approach can be applied to human using the anticipated clinical dose using an estimated lung Ka
- Provide confidence that lung burdens in human will remain <<threshold for adverse findings on chronic dosing
Questions