Modeling particulate lung burden to aid the interpretation of adverse lung findings

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Overview

- Accumulation of particles in the lung
- Literature data available
- A simple methodology for estimating undissolved particulates
- Case study with PF-X
- Future Direction
Aiding inhaled tox design and interpretation

Repeat delivery of particulates to the lung have the potential to build up in the lung if... delivery rate in > disappearance rate from the lung

Complexity of multiple processes
- Delivery rate
- Dissolution rate
- Absorption rate into the lung/blood
- Mucociliary clearance
- Alveolar Macrophage clearance

Impacted by dose size, deposition pattern, pharmacology, disease state, compound properties (lipophilicity, solubility etc)

Widely accepted that a build up of undissolved particulates in the lung can cause adverse lung findings (increase in macrophages, additional inflammation and tissue degeneration)
Literature data on particulates

2011 - Poorly soluble particulates: Searching for a unifying denominator of nanoparticles and fine particles for DNEL estimation – Pauluhn. Toxicology
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 persistant inflammation Warheit et al, Tox. And Applied Pharm.
1996 -Significance of particle parameters in the evaluation of exposure dose response relationships of inhaled particles Ober dorster I.Tox.
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
.....not the same as poorly soluble drugs
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)

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

**Q1.** Can we predict when inhaled particulates are likely to drive adverse lung findings?
- Aid interpretation, help set tox doses, evaluate potential safety risks

**Q2.** Are we able to estimate lung burdens in our inhaled tox studies?
- are they in agreement with the proposed thresholds?
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
**PK Principles and equations used**

**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

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

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

*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 ~100day half life = 0.007day\(^{-1}\) (Oberdorster et al 1992), Human Kam = 200days = 0.0035day\(^{-1}\) (Bailey et al 1985)

**Equation 3. Estimating alveolar lung particulate burden**

\[
\text{Lung Burden on day } n = \left( \frac{\text{Dose} \times \frac{1 - e^{-(Ka+Kam)t.(n+1)}}{1 - e^{-(Ka+Kam)t}}}{1 - e^{-(Ka+Kam)t}} \right) - \text{Dose}
\]

\(Ka = \text{lung absorption rate constant}\)
\(Kam = \text{alveolar macrophage clearance rate}\)
\(t = \text{dosing interval}\)
\(n = \text{number of doses}\)
Case study: PF- `X`

Inhaled molecule for the treatment of asthma
MW ~600, LogDpH7.4= ~2.0
Low solubility ~20ug/ml in phosphate buffer

28 Day Rat Inhaled Toxicology

<table>
<thead>
<tr>
<th>Dose (ug/kg/day)</th>
<th>Est. Lung Dose (ug/kg/day) *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>

* 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?
**Inhaled PF- `X`**

<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>5128</td>
<td>513</td>
<td>85</td>
<td>4.5</td>
<td>0.25</td>
<td>290</td>
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<tr>
<td></td>
<td>67425</td>
<td>6743</td>
<td>1124</td>
<td>6.4</td>
<td>0.17</td>
<td>5764</td>
</tr>
</tbody>
</table>

10% deposition
250g rat
1.5g lung per rat

- **Expect adverse changes** i.e. additional inflammation, tissue degeneration
- **Non adverse adaptive changes** i.e. ↑macrophages

- **Modelling indicates undissolved mass in the lung has reached steady state**
- **Estimated lung burdens are at levels ~consistent with literature thresholds**
## 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>
</tr>
<tr>
<td></td>
<td></td>
<td>182</td>
<td>0</td>
<td>No treatment related changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1470</td>
<td>856</td>
<td>Increased macrophages consistent with insoluble particles but not adverse</td>
</tr>
<tr>
<td>Z</td>
<td>28 Day</td>
<td>5.7</td>
<td>&lt;1</td>
<td>No treatment related changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>64</td>
<td>35</td>
<td>No treatment related changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1094</td>
<td>714</td>
<td>Increased macrophages consistent with insoluble particles but not adverse</td>
</tr>
<tr>
<td>Z</td>
<td>91 Day</td>
<td>26</td>
<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.
Conclusions

Simple approach provides a method to estimate particulate lung burden to 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.
Future Direction

Difficult to collate a rich data set as design principles steer away from physicochemistry that are likely to cause the accumulation of particulates in the lung (learning from the past = fewer molecules with accumulation)

Lung TK not routinely measured, propose lung TK is measured where accumulation is likely to occur to aid validation of these estimates and improve understanding

Potential opportunity to share non confidential lung TK data to expand the examples available and build this area of science based on measured data from inhaled toxicology studies (previous cross pharma collaborations have struggled to get going)

Across the industry we may have enough data collectively to aid everyone’s understanding and build on improving/validating approaches to estimate lung burden thresholds
Questions