Carbon nanotubes: Should we worry?

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Various allotropes of carbon exist
All have different arrangements of carbon atoms
Carbon nanotubes

- Discovered in 1991
- Can be pictured as a single layer of carbon atoms rolled to form a cylinder
- Single(A) or Multiwalled(B)
- Diameter of a single walled CNT 1-2nm
- Length typically several micrometers
• 1 nanometer (nm) is one billionth of a meter.
• A nanoparticle must have one dimension less than 100nm ($10^2$ nm)
• Diameter CNT roughly between the size of a glucose molecule and virus depending on whether single or multiwalled
• Width of human hair by comparison 10 000nm ($10^4$ nm)
Nanoparticles

- We are surrounded by billions of nanoparticles
  - Natural nanoparticles
  - Incidental nanoparticles
  - Engineered nanoparticles
- Approximately 20 000/cm³ in a normal room
- Unique properties that differ from their bulk counterparts
Why are CNTs of interest?

- Stronger than steel
- Conductive as copper
- Thinner than hair
- Conducting or semiconducting properties depending on structure
- Can be combined with other material producing a high performance composite material
- In 2010 the estimated global value of nanomaterials stood at $1.8 billion
- By 2014 ten million manufacturing jobs worldwide will involve building products that incorporate nanotechnology
Applications for Carbon Nanotubes?
# Applications for carbon nanotubes

<table>
<thead>
<tr>
<th>Industry</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronics and computing</td>
<td>Nano sized electrical components</td>
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<td></td>
<td>Semiconductors</td>
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<tr>
<td></td>
<td>Data storage</td>
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<td></td>
<td>Batteries</td>
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<tr>
<td>Aerospace industry</td>
<td>Structural parts</td>
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<td>Healthcare</td>
<td>Controlled drug delivery</td>
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<td>Medical imaging</td>
</tr>
<tr>
<td>Environment</td>
<td>Solar storage</td>
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<tr>
<td></td>
<td>Waste recycling</td>
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<tr>
<td>Clothing, health and fitness</td>
<td>Reinforcement of material</td>
</tr>
<tr>
<td></td>
<td>Sports equipment</td>
</tr>
</tbody>
</table>
Production of CNTs

- Produced on a commercial scale using Chemical vapour deposition
- Biggest production plants in Europe are in Germany and Belgium
- These sites can produce 200 and 400 tonnes of CNT per year respectively
- As scale of manufacturing and processing develops Increasing numbers of workers and those involved further down the lifecycle of the product will potentially be at risk of exposure to CNTs
- Some safety concerns as questions have arisen regarding potential toxicity
Properties of concern

1) **Nanoscale size**
   - Respirable particle, able to penetrate into distal airways of the lung
   - Incredibly large surface area.
   - Ability to move to other body systems

2) **Needle like shape**

3) **Poor solubility / biological persistence**

4) **Chemical composition**
   - Metal catalysts used in manufacture may contribute to toxicity

Carbon Nanotube  
Asbestos
Regulation in the UK

• No additional legislation in the UK
• Information sheet regarding CNTs published by HSE in March 2009
  – Highlighted employers responsibilities
  – Recommended a precautionary approach
Aim of the systematic review

- To assess whether respiratory exposure to CNTs is associated with pulmonary toxicity.
Methods

• Articles identified by searching online databases: medline, embase, pubmed, nioshtic-2 and oshline
• Search involved using keywords for CNTs, route of exposure and system of interest
• Included studies that assessed pulmonary toxicity following respiratory exposure to CNTS
• Limited to studies published in English
• Excluded review articles, *in vitro* studies
Methods

Three outcomes evaluated

1) Clinical outcomes
   Death, disturbed respiratory pattern

2) Bronchoalveolar lavage outcomes (BAL)
   Markers of cytotoxocity or inflammation

3) Histopathology outcomes
   Evidence of granulomas or fibrosis
Results

Identified titles / abstracts +/- references reviewed 974

Potentially relevant. Full text obtained 61

Obvious exclusions 913

Exclusions applied 42

Unable to source 1

Additional articles from manual reference search 1

Full text articles fulfilling inclusion and exclusion criteria 18

Articles included in dissertation 19
Characteristics of included articles

• 19 studies identified were all in vivo experimental studies involving rodents
• No human studies published
• Study design involved comparison between groups
• Animals exposed to CNTs and outcomes compared with positive and/or negative controls
• Intratracheal, Oropharyngeal or Inhalational exposure
• Inhalational studies exposure duration varied from 6 hours to 13 weeks. Other studies involved a single bolus exposure.
• Animals sacrificed various time points from 6 hours to 273 days
## Example of study methods

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Type of CNT</th>
<th>Route of exposure</th>
<th>Dose</th>
<th>Exposure</th>
<th>Animals sacrificed (days post treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddy et al. 2010(8)</td>
<td>Rats (Wistar)</td>
<td>MWCNT diameter 60-80nm,</td>
<td>Intratracheal</td>
<td>0.2, 1, 5 mg/kg</td>
<td>Single dose</td>
<td>1, 7, 30, 90</td>
</tr>
<tr>
<td>Mitchell et al. 2007(48)</td>
<td>Mice (C57BL/6)</td>
<td>MWCNT diameter 10-20nm, length 5-15µm</td>
<td>Inhalational</td>
<td>0.3, 1.0, 5.3 mg/m$^3$ (estimate deposited dose 0.2,0.5,2.7mg/kg)</td>
<td>6 hours per day for 7 or 13 consecutive days</td>
<td>7, 14</td>
</tr>
</tbody>
</table>
Number of studies documenting specific characteristics of CNT

![Bar chart showing the number of studies for different characteristics of CNT.](chart.png)
## Results - Clinical Outcomes

<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>Number of studies (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths reported</td>
<td>2</td>
</tr>
<tr>
<td>Exposure significantly disturbed respiratory pattern</td>
<td>2</td>
</tr>
<tr>
<td>Exposure had no significant effect on clinical observations +/- respiratory pattern</td>
<td>6</td>
</tr>
<tr>
<td>Study did not comment on clinical outcomes or only reported no deaths</td>
<td>9</td>
</tr>
</tbody>
</table>
## Results – Brochoalvelar Lavage (BAL)

<table>
<thead>
<tr>
<th>BAL outcomes</th>
<th>Number of studies (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not assessed</td>
<td>5</td>
</tr>
<tr>
<td>No significant difference</td>
<td>3</td>
</tr>
<tr>
<td>Significant increase in GGT</td>
<td>3</td>
</tr>
<tr>
<td>Significant increase in macrophages</td>
<td>4</td>
</tr>
<tr>
<td>Significant increase in ALP</td>
<td>4</td>
</tr>
<tr>
<td>Significant increase in collagen</td>
<td>4</td>
</tr>
<tr>
<td>Significant increase in total cell count</td>
<td>6</td>
</tr>
<tr>
<td>Significant increase in PMNs</td>
<td>6</td>
</tr>
<tr>
<td>Significant increase in proteins</td>
<td>8</td>
</tr>
<tr>
<td>Significant increase in LDH</td>
<td>10</td>
</tr>
</tbody>
</table>
## Results - Histopathology

<table>
<thead>
<tr>
<th>Histopathology outcomes</th>
<th>Number of studies (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not assessed</td>
<td>2</td>
</tr>
<tr>
<td>No significant histopathological lesions</td>
<td>2</td>
</tr>
<tr>
<td>Evidence of fibrosis</td>
<td>7</td>
</tr>
<tr>
<td>Granulomas</td>
<td>11</td>
</tr>
</tbody>
</table>
Discussion

• Findings from this systematic review suggest that CNTs are toxic to the lungs of rodents
  – Association with increased biomarkers of lung injury and inflammation on bronchoalveolar lavage
  – Histological evidence of granulomas and less frequently fibrosis

• New technologies such as CNTs raise huge challenges for regulating authorities and occupational medicine

• Until further information is known then a cautionary approach, reducing exposure using traditional hierarchy of controls measures prudent
What next?

- Hazard characterisation and efforts to identify a dose response and no adverse effect level required.
- Further studies to explore workplace exposure and effectiveness of control measures
- Consider other body systems
- Consider other routes of exposure
- Environmental impact.
Acknowledgements