Hazards and risks from WHO fibres at the workplace

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Natural asbestos minerals: highly potent carcinogens

- appearing in several forms
- physical form (i.e. WHO fibre) determines effect
- induction of lung cancer and mesothelioma
- 10 µg/m³ (0.1 f/ml) equals 4/1000 cancer risk
Physical form determines carcinogenicity

- **Respirability**
  - Thin
    - Small aerodynamic diameter enables deposition beyond the ciliated airways
  - Long
    - Not completely enclosed by macrophages producing frustrated phagocytosis; cannot be effectively cleared

**Biopersistent**
- Retains fibrous shape during residence in the lungs and so long fibre dose accumulates

Figure 1 Diagram illustrating a pathogenic fibre according to the pathogenicity paradigm and the role of particle characteristics.

Rigidity?
Why respirable dust?

upper airways: rapid elimination of dust via cilia

lung alveoli: rather slow elimination of dust by macrophages
Critical fibre dimension: the 'WHO' fibre convention

Fibres are carcinogenic (lung and mesothelia) after inhalation if sufficiently long - thin – biopersistent

- Length > 5 µm
- Diameter < 3 µm
- Aspect ratio > 3:1
Alveolar macrophages and their job:
removal of bacteria and particles

lysis in case particles are not biopersistent

bacteria, particles

pic https://de.wikipedia.org/wiki/Makrophage
Fibres: major mode of toxic action: frustrated phagocytosis

frustrated phagocytosis

=> oxidative stress and chronic inflammation

=> lung cancer

minimum fibre length $\sim 15 \, \mu m$ (Schinwald et al. 2012 Tox Sci 128:461)

pic taken from Donaldson et al 2010 PFT 2010, 7:5
frustrated phagocytosis

$\Rightarrow$ oxidative stress & chronic inflammation

$\Rightarrow$ mesothelial cancer

minimum fibre length $\sim 5 \, \mu m$ (Schinwald et al. 2012 PFT 9:47)
Figure 12 Hypothesised sequence of events leading to pleural responses as a consequence of long fibre retention at the parietal pleural stomatal openings.

- Lung cancer
- Mesothelial cancer
Fibres: additional hypotheses on mode of toxic action:

Evidence low so far

- direct piercing of mesothelial cells
- mechanical interaction with chromosomes
Data on fibre carcinogenicity

**asbestos**

*carcinogenicity proven (lung and mesothelioma):*

*human epidemiology, animal testing*

**other WHO fibres** *(e.g. some man-made mineral fibres)*

*carcinogenicity proven (lung and mesothelioma):*

*animal testing*
Carcinogenicity: fibre testing strategy

**long-term inhalation**
expensive
rat insensitive

**intraperitoneal application, long-term experiment**
simple and inexpensive
rat sensitive
fibres in direct contact to mesothelial tissue
Comparison of the excess tumour risk of asbestos workers with the risk of rats after chronic inhalation

The risk of asbestos workers (dotted line) is derived by linear extrapolation of asbestos-induced death due to lung cancer or mesothelioma in asbestos workers (excluding mining and milling) after 25 years of exposure, when the fibre concentration increases from 1 to 5 fibres per mL air (Doll and Peto, 1985; HEI-AR, 1991). The regression line for the chronic rat inhalation studies is calculated from test results of different authors and different asbestos samples.
Which other fibrous material is acting like asbestos?

in case rigid biodurable fibre of WHO dimension

rigid carbon nanotubes
Additional criterion: rigidity

Figure 2 The frustrated phagocytosis paradigm as it relates to long and short fibres of asbestos (left) and various forms of carbon nanotubes (right). When confronted by short asbestos fibres or tangled, compact carbon nanotube 'particles' the macrophage can enclose them and clear them. However the macrophage cannot extend itself sufficiently to enclose long asbestos or long nanotubes, resulting in incomplete or frustrated phagocytosis, which leads to inflammation.
Fibrous material: acting like asbestos?

- Tangled: acts like granular particle
  low(er) carcinogenic potency

- Rigid: acts like asbestos
  high carcinogenic potency

Hypothesis, 'rigid': diameter > 25-35 nm

Pics BAuA
What do we know on MWCNT carcinogenicity so far?
Rigid MWCNT more potent carcinogens than expected

intraperitoneal application

Rittinghausen et al 2014 PFT 11:59

MWCNT, multi-walled carbon nanotubes
Amosite

MWCNT D:
least potent
least rigid

magnification
MWCNT 10000, 30000
Amosite 2000, 7000
MWCNT: rat lung carcinogen also after inhalation

<table>
<thead>
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<th>mg/m³</th>
<th>0</th>
<th>0.02</th>
<th>0.2</th>
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<tbody>
<tr>
<td>adenoma</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>carcinoma</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>11</td>
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</tbody>
</table>

2-yr study, whole-body inhalation, aerosolized dry MWCNT

Fukushima et al. unpublished
Fibrous MWCNT: **rigid** ones acting like asbestos

**tangled**

**negative ip test**
Muller et al., 2009 \(l=0.7 \mu m\)
Nagai et al., 2011, 2013 \(l=3 \mu m\)

**rigid**

**positive ip test**
Takagi et al. 2008
Nagai et al., 2011, 2013
Rittinghausen et al. 2014

**positive inhalation test**
Fukushima, yet unpublished
Side note: it would be a fatal error…

... to limit the focus on nano (<100 nm diameter) only

Example: Biopersistent respirable fibres: carcinogenic potency and diameter

respirability up to ~1-2 µm median diameter

Pott, ASP 8/77
It is likely not only be restricted to MWCNT…..

CNTs, carbon fibres, nickel wires, silver wires, titanium dioxide fibres….

carbon fibres in use

Arry MWCNT

3.0kV 20.0mm x3 00k SE(L)

10.0µm

titanium dioxide

nickel nanowires
Toxic potency in comparison
reference values/OELs/cancer risk respirable dust (mass concentration)

<table>
<thead>
<tr>
<th>µg/m³</th>
<th>category</th>
<th>critical effect</th>
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<tbody>
<tr>
<td>300¹</td>
<td>micro-GBP</td>
<td>threshold inflammation</td>
</tr>
<tr>
<td>75¹</td>
<td>nano-GBP</td>
<td>threshold inflammation</td>
</tr>
<tr>
<td>~15</td>
<td>quartz</td>
<td>threshold silicosis/lung cancer</td>
</tr>
<tr>
<td>~1</td>
<td>crocidolite</td>
<td>cancer risk $4 \times 10^{-4}$</td>
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<tr>
<td>~0.05</td>
<td>amosite</td>
<td>cancer risk $4 \times 10^{-4}$</td>
</tr>
<tr>
<td>~0.005</td>
<td>MWCNT</td>
<td>cancer risk $4 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

¹ material density =1 g/cm³; GBP, granular biodurable particles not spec. toxic

(assumption similar potency like crocidolite)
Summary

Critical fibres are highly potent carcinogens!

Past exposure and current occupational disease
asbestos

Current and increasing future exposure?
other biodurable fibres of WHO dimension

CNTs, carbon fibres, titanium dioxide fibres…. 

We have to take care now!