

# High Aspect Ratio Nanoparticles (HARN)

Length-Dependent Pathogenic Behaviour mimics that of asbestos in a mesothelial response model

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# Warnings About Carbon Nanotubes Potential for Harm

‘...Given previous experience with asbestos, we believe that nanotubes deserve special toxicological attention...’ 2004

COMMENTARY

## Safe handling of nanotechnology

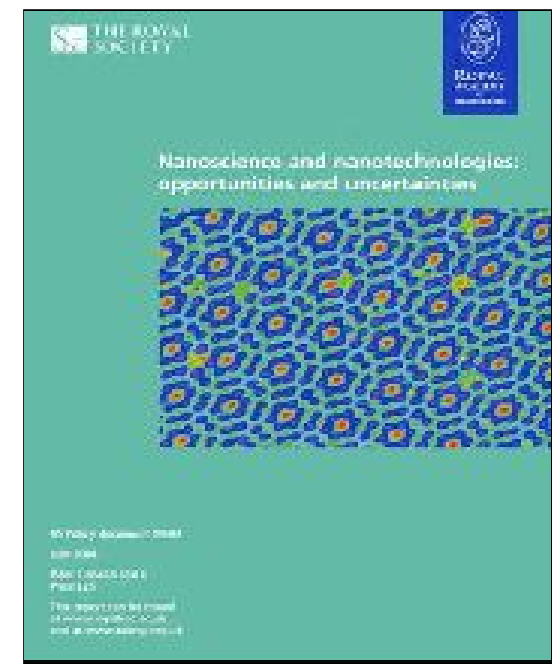
The potential for nanotechnology to be used in a way that poses a health hazard is a possibility that should be taken seriously.

**By Andrew D. Maynard and Nicholas Lescault**



When the first carbon nanotubes were discovered in 1991, they were hailed as a new material with extraordinary properties. They have since found applications in a wide range of fields, from electronics to medicine. However, the potential for nanotechnology to be used in a way that poses a health hazard is a possibility that should be taken seriously.

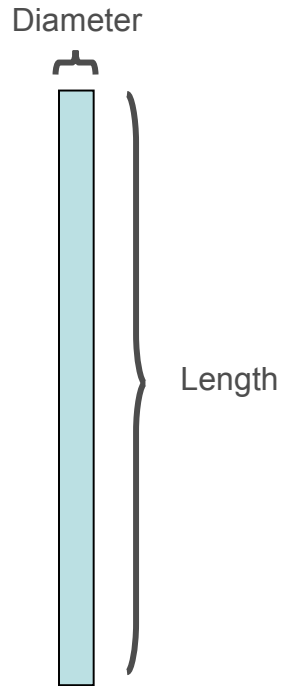
The potential for nanotechnology to be used in a way that poses a health hazard is a possibility that should be taken seriously. The potential for nanotechnology to be used in a way that poses a health hazard is a possibility that should be taken seriously.



‘...Fibre-shaped nanomaterials possibly represent a unique inhalation hazard, and their pulmonary toxicity should be evaluated as a matter of urgency..... failure to pick up asbestos-like behaviour as early as possible would be potentially devastating to the health of exposed people and to the future of the nanotechnology industry...’ 2006

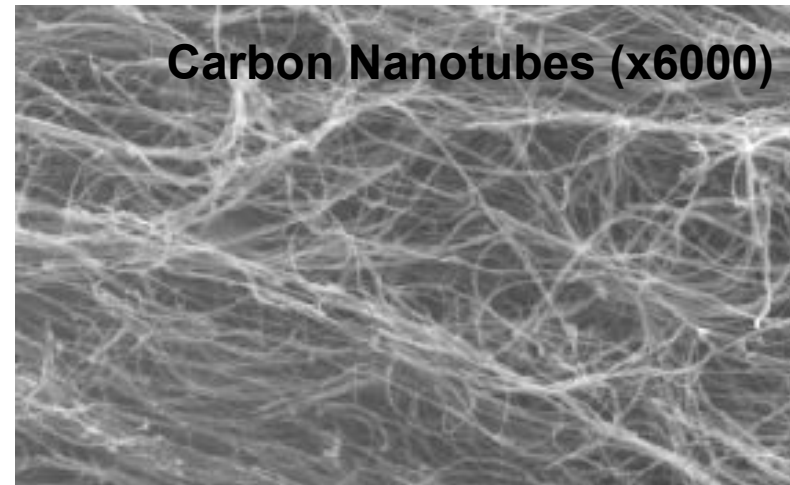
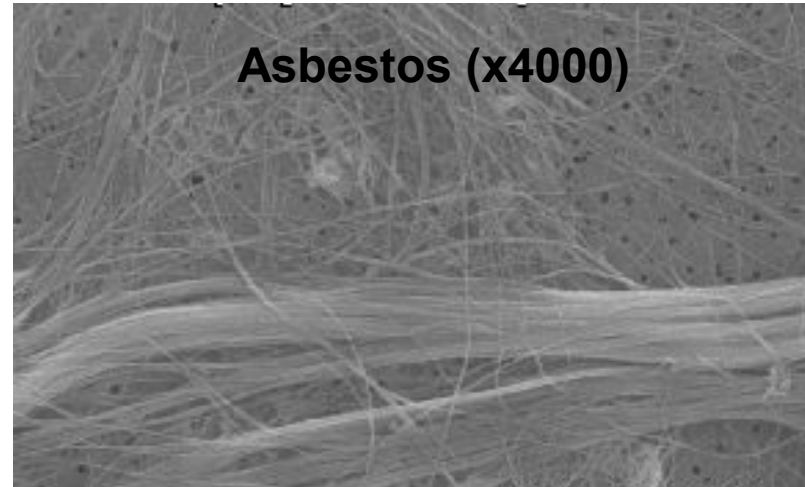


# High aspect ratio (or being a fibre) as an 'extra hazard' factor in the the toxicity of a particle



$$\text{Aspect ratio} = \frac{\text{Length}}{\text{Diameter}}$$

or 'fibre'

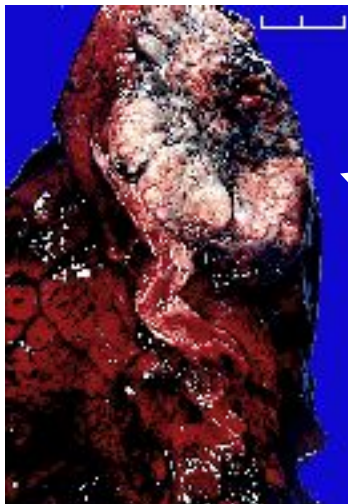




# Diseases caused by particles and fibres

Caused by particles and fibres at high dose

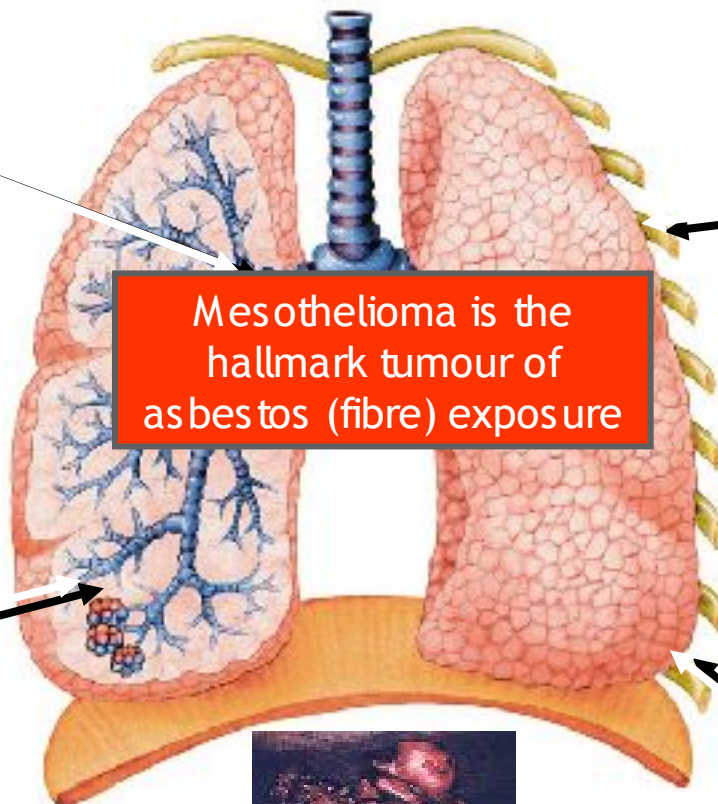
Caused by fibres at low dose



Bronchogenic carcinoma



Fibrosis



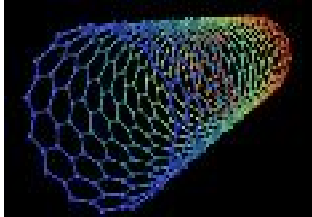
Mesothelioma is the hallmark tumour of asbestos (fibre) exposure



Pleural mesothelioma



Pleural plaque



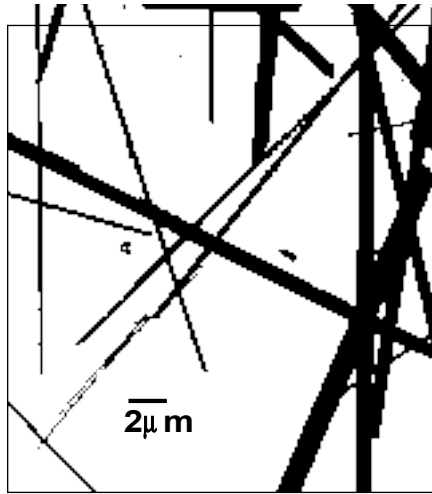
# HARN: Carbon Nanotubes, nanowires and nanorods

- Hexagonal arrangement of carbon atoms built up to form a fibre
  - Diameter in nanometre range
  - Length nanometres to hundreds of microns
- Useful physicochemical characteristics
  - Exceptional strength, electrical and thermal conductance
- Global market for carbon nanotubes is predicted to grow to over \$1 billion by 2014\*
- Assumed that carbon nanotubes are no more harmful than graphite
- Nanowires
  - Metallic (Ni, Pt, Au),
  - Semiconducting (Si, InP, GaN, etc.),
  - Insulating ( $\text{SiO}_2$ ,  $\text{TiO}_2$ ).
- Nanorods
  - Gold
  - Diamond
  - Aluminium

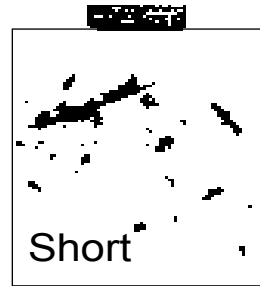
\* Source: Thayer, A. M. Carbon nanotubes by the metric ton: Anticipating new commercial applications, producers increase capacity. Chem. Eng. News 85, 29-38 (2007)



# The importance of fibre length in fibre toxicity : the 1986 Davis study



Long amosite



2 μm

Short amosite

	% animals with		
	Extent of Fibrosis (asbestosis)	Ca Cancer	Mesothelioma (peritoneal instillation)
Control	0.5	0	0
Short amosite	0.15	0	3
<b>Long amosite</b>	<b>11.0</b>	<b>27.5</b>	<b>95</b>



# Testing the hypothesis that nanotubes had the same length –dependent pathogenicity as asbestos

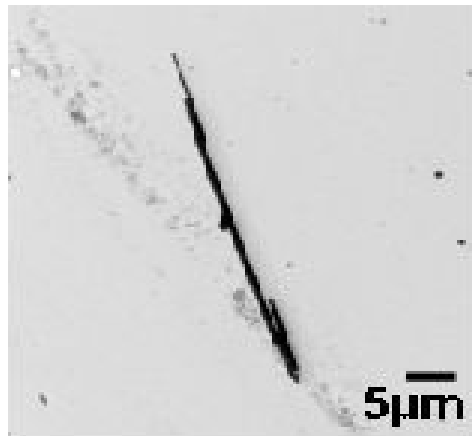


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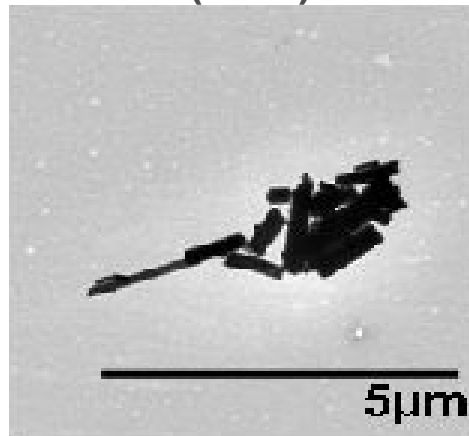
## Panel of Particles Used in The Study

### Controls

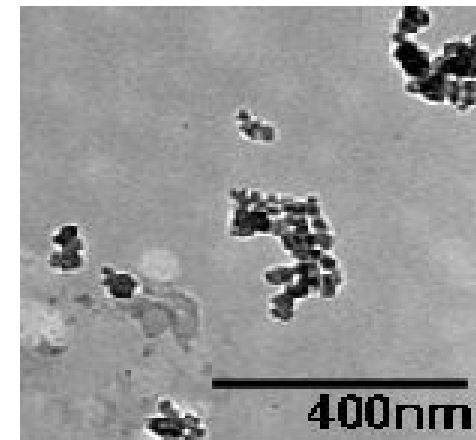
**Long fibre amosite (LFA)**



**Short fibre amosite (SFA)**



**Nano-Particulate carbon black (NPCB)**



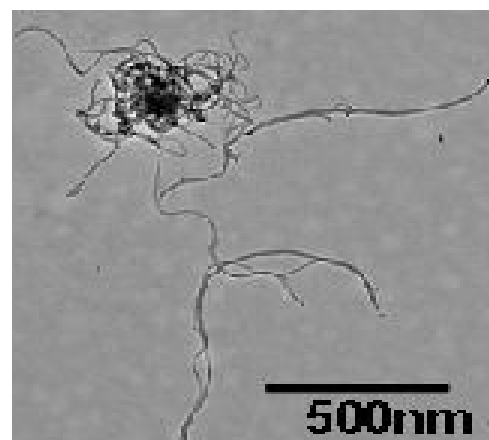
*Note scale bars*



# Panel of Particles Used in The Study

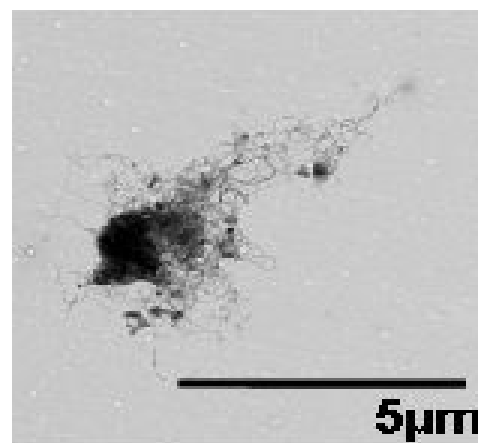
## Short/ Tangled Nanotubes

NT<sub>tang</sub>1



NT<sub>tang</sub>1

NT<sub>tang</sub>2



NT<sub>tang</sub>2

*Note scale bars*

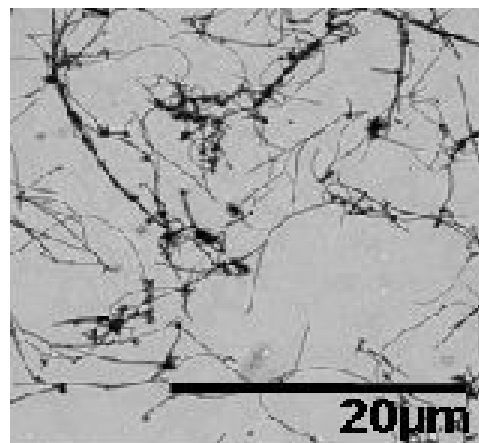




# Panel of Particles Used in The Study

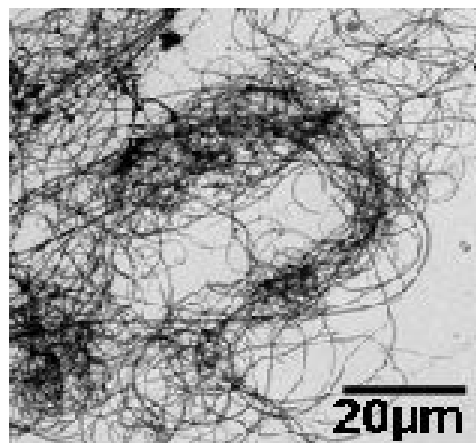
## Long Straight Nanotubes

NT<sub>long1</sub>



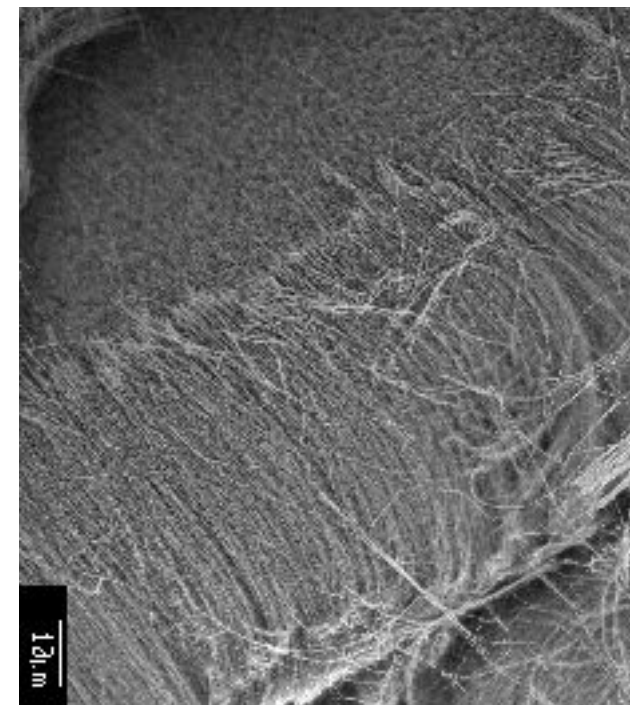
NT<sub>long1</sub>

NT<sub>long2</sub>



NT<sub>long2</sub>

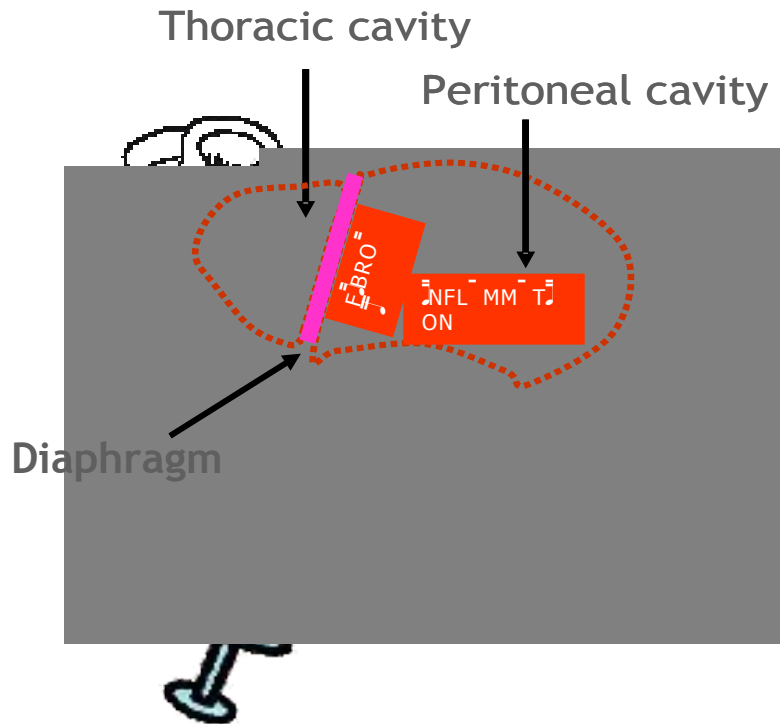
NT<sub>long2</sub>



*Note scale bars*



# Determining whether MWCNT show length dependent pathogenic behaviour in a model of direct mesothelial exposure



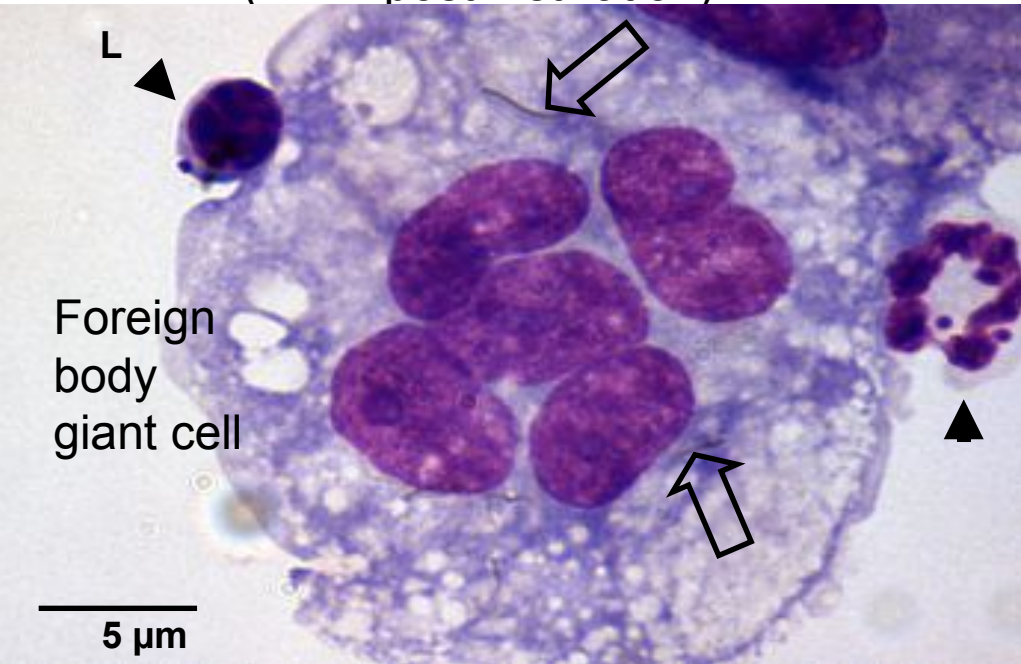
- Inject 50  $\mu\text{g}$  of particles into the peritoneal cavity and directly expose the mesothelium
- Measure inflammation in washings from the peritoneal cavity
- Measure early fibrosis on the diaphragm

In previous studies long asbestos caused inflammation and fibrosis and short asbestos did not

## Assessing the Acute and Chronic Inflammatory Response

### Acute Inflammatory Response

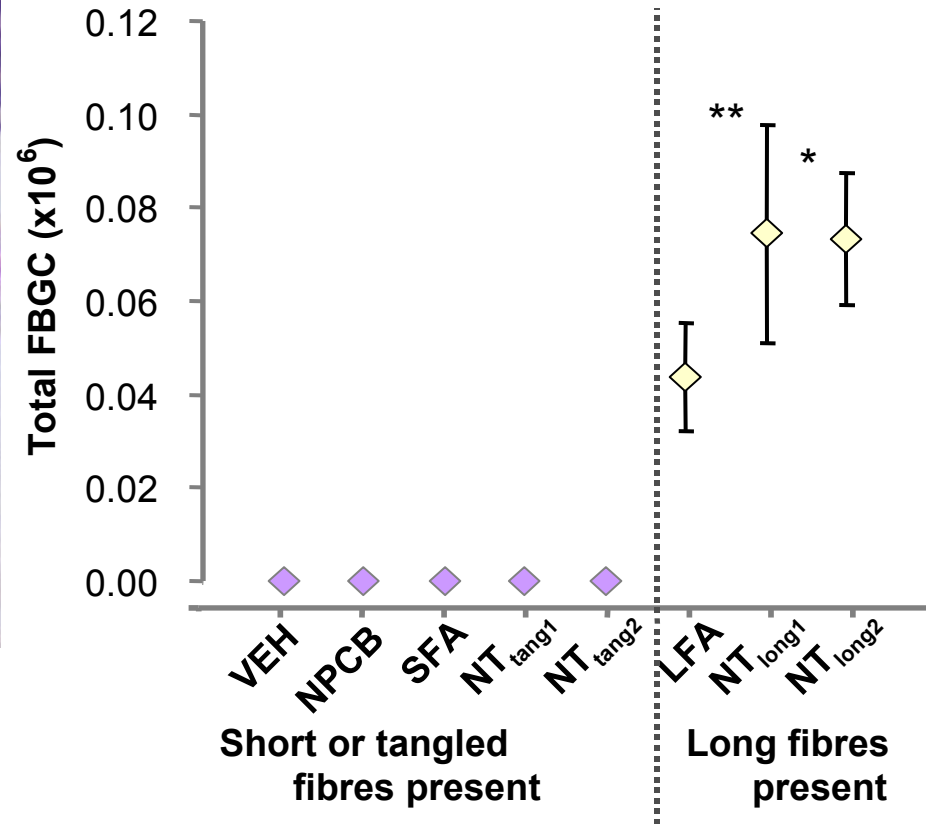
(24-hr post instillation)



VEH	NPCB	SFA	NT <sub>tang1</sub>	NT <sub>tang2</sub>	LFA	NT <sub>long1</sub>	NT <sub>long2</sub>
Short or tangled fibres present					Long fibres present		

### Chronic Inflammatory Response

(7-days post instillation)

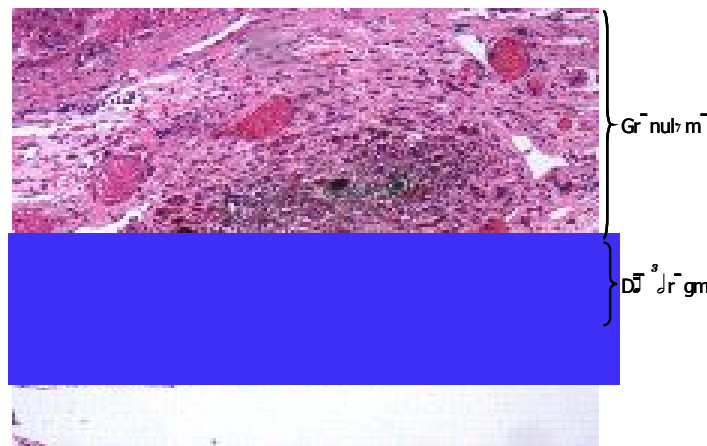
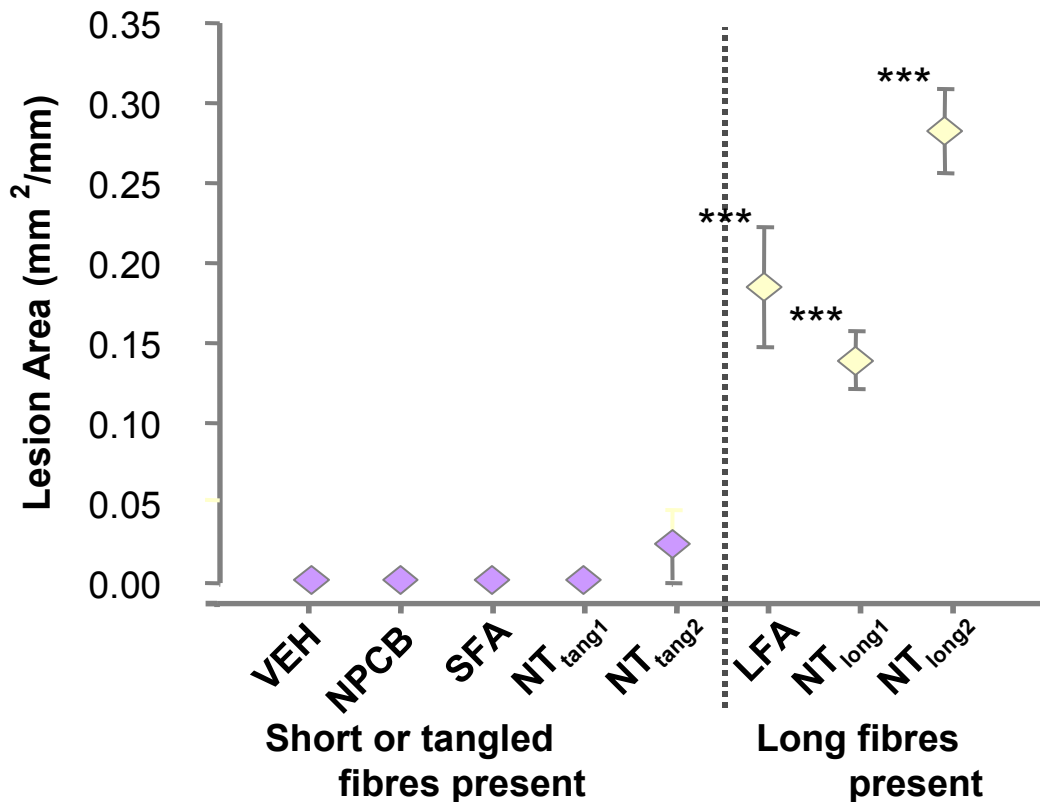


\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  vs. vehicle control



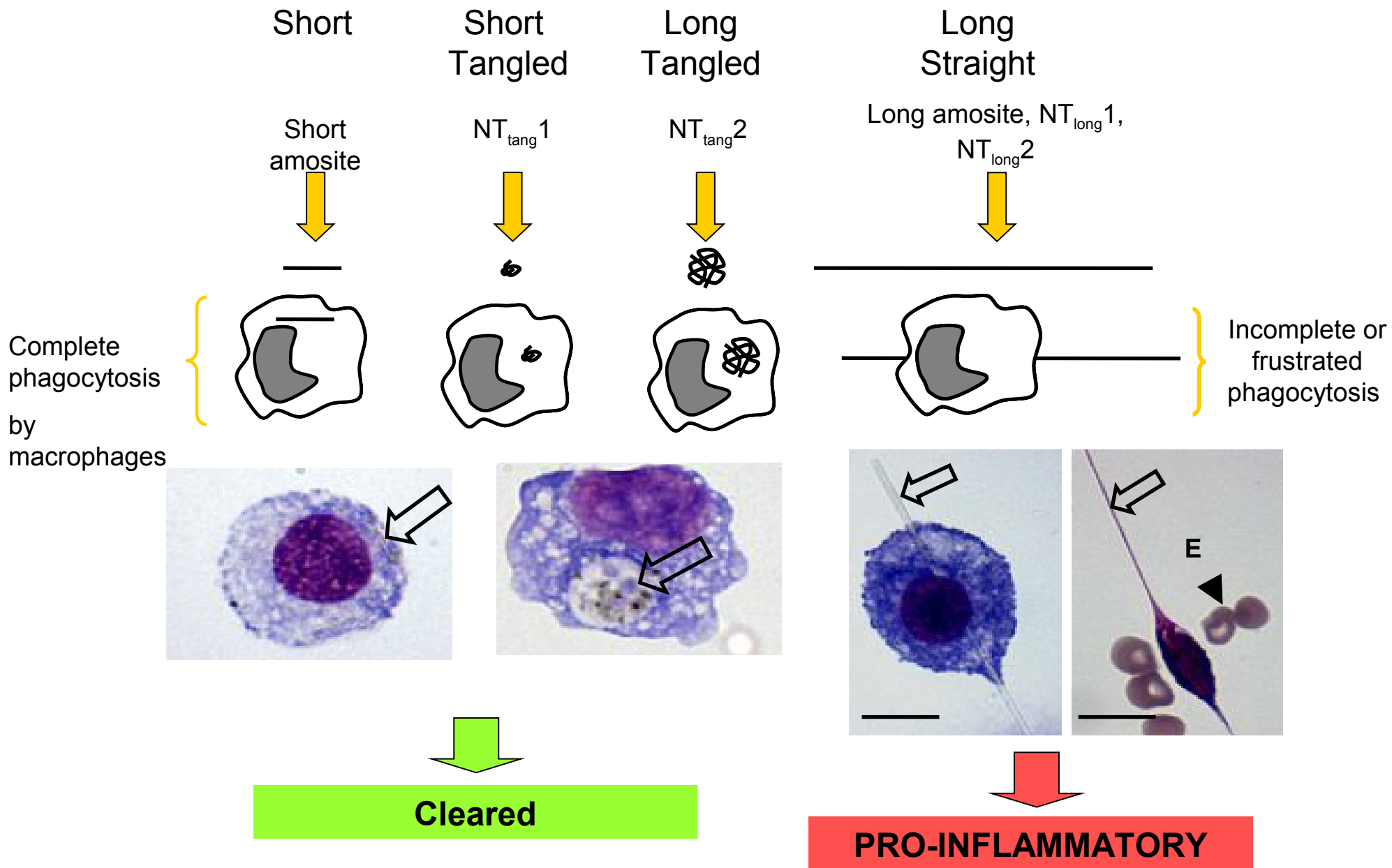
# Long and short nanotubes

## Assessing the ability to cause granulomas (scar/fibrosis)



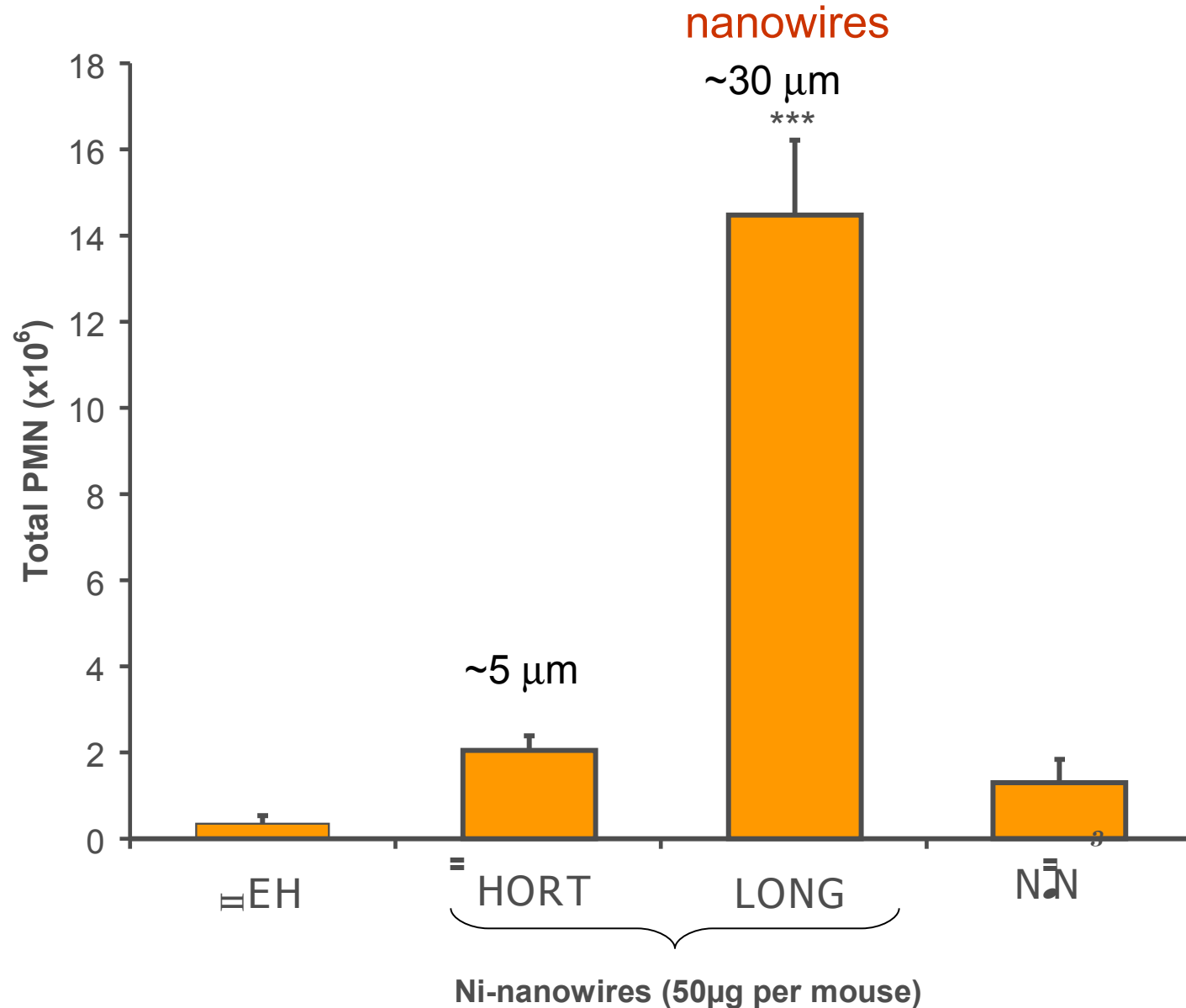
\*\*\* $P < 0.001$  vs. vehicle control

# Hypothesized Mechanism





# Does a completely different HARN show length-dependent pathogenic behaviour: preliminary results for Long and short Nickel-nanowires



Ni nanowires made by Dr Adriele Prina Mello, Trinity College, Dublin

\*\*\* $P < 0.001$  vs. NiNW extract



HARN, probably of any biopersistent (insoluble) material can probably behave like long asbestos if long enough (>about 20 $\mu$ m)

i.e. they show rapid inflammatory and fibrogenic effects in a model of direct mesothelial exposure

In a previous study i.p. long but not short amosite caused mesothelioma in rodents

the longer, straighter and more fibre-like a HARN sample, the more pathogenic it is likely to be

**HARN look like they conform to the general fibre paradigm that determines carcinogenicity of asbestos, glass fibre etc**

## Caveats of this work

To be a true risk for mesothelioma any HARN would need to:-

- Get airborne in the workplace as long fibres in sufficient quantity
- Be biopersistent
- Be able to migrate from the lung airspaces to the pleura
- Produce mesothelioma at the pleura after they reach it
- More studies are urgently needed especially assessment of exposure to long fibres in workplaces that handle HARN
- All the above applies only to CNT as fibres, they may well have adverse effects as particles



The screenshot shows a web browser window displaying the NanoAmor website. The browser's address bar shows the URL <http://www.nanoamor.com/>. The website header features the NanoAmor logo and the tagline "Nanostructured & Amorphous Materials Inc.". A navigation menu includes links for Home, Products, About Us, Our Technology, Research, Order Information, Links, and Contact Us. The main content area is dominated by a large promotional banner for carbon nanotubes. The banner includes a "PRODUCT HIGHLIGHT" tag, the headline "CARBON NANOTUBE PRICES SLASHED BY 50% OR MORE!", and a detailed description of the product offerings: "We have reduced our prices on all carbon nanotubes: high purity; single-, double- or multi-walled; various diameter and length options; surface functionalizations possible." A call to action "Click to find out more" is also present. The browser's taskbar at the bottom shows the Internet Explorer icon and the system clock.

NanoAmor  
Nanostructured & Amorphous Materials Inc.

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[Click to find out more.](#)





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