

The health hazards of accidental exposure to nanoparticles

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The 4 universes of nanoparticle exposure

combustion-derived
nanoparticles



bulk manufactured
nanoparticles

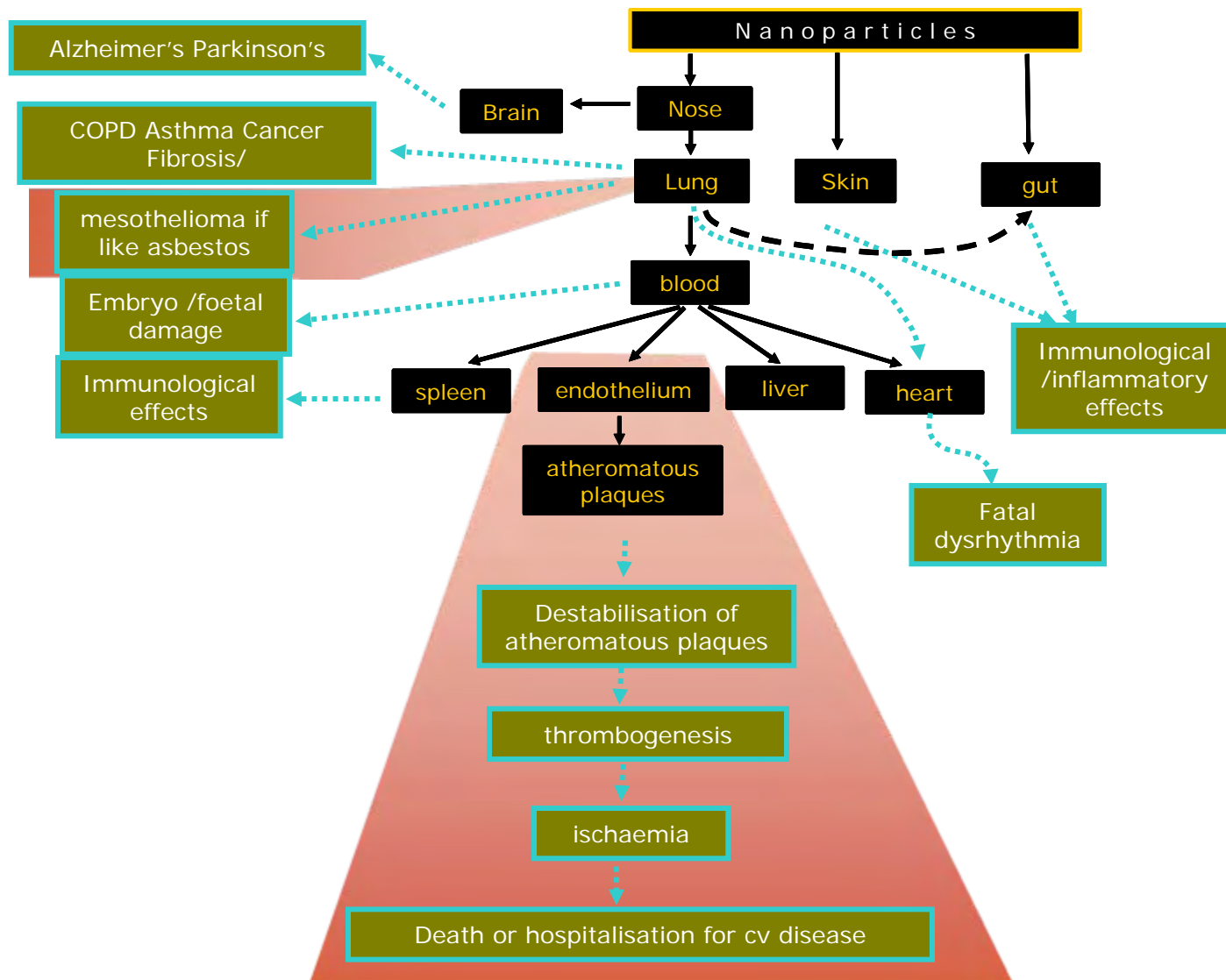


engineered
manufactured
nanoparticles



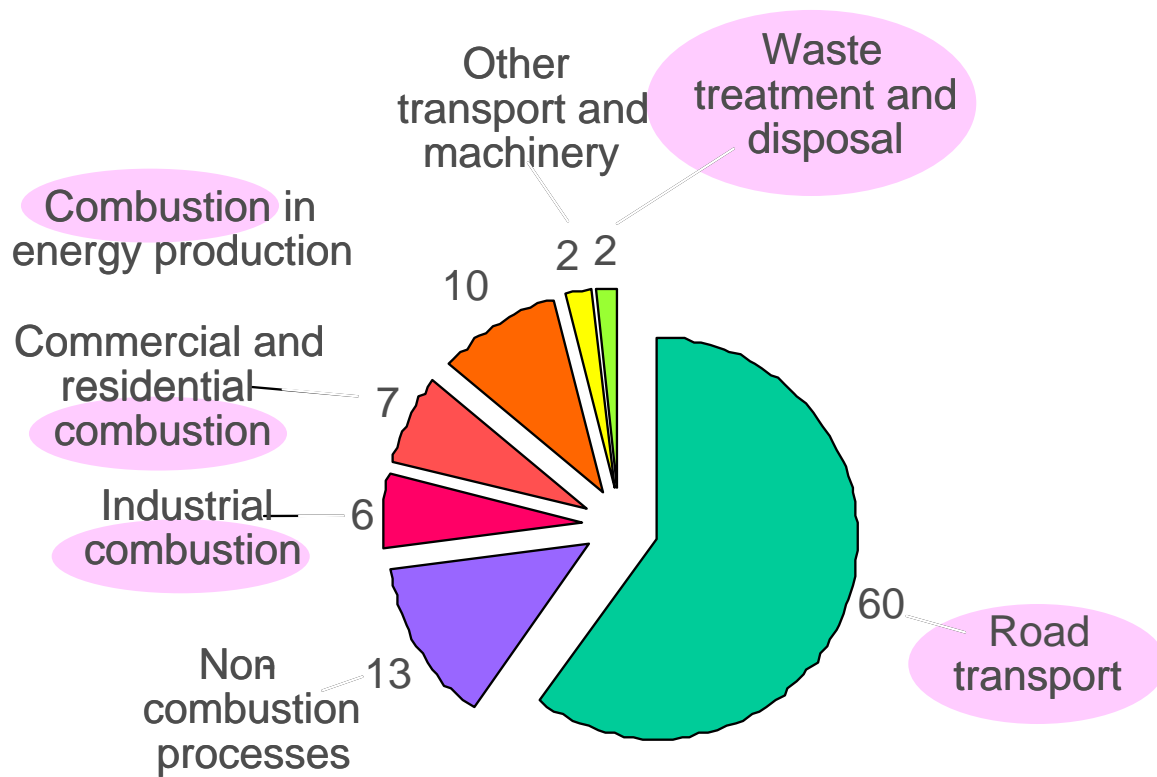
medical
nanoparticles

Primary and secondary targets and potential outcomes from exposure to nanoparticles

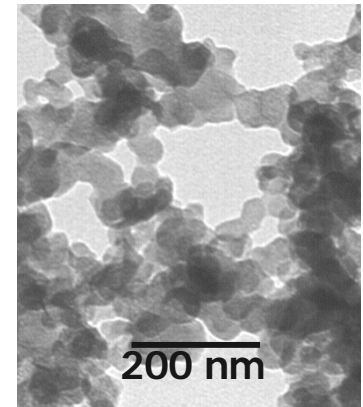
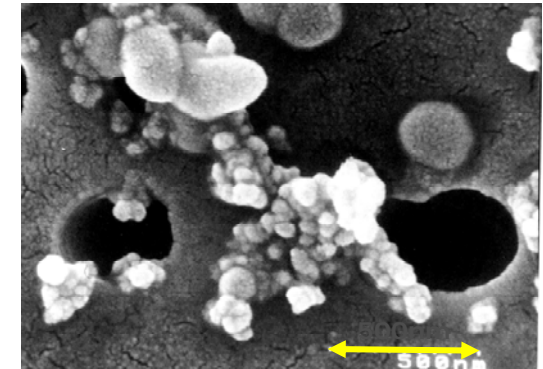


Most NP hazard identification is based on high exposure to a few manufactured NP types plus assumptions from other studies in animals and combustion-derived NP

Origins of environmental nanoparticles

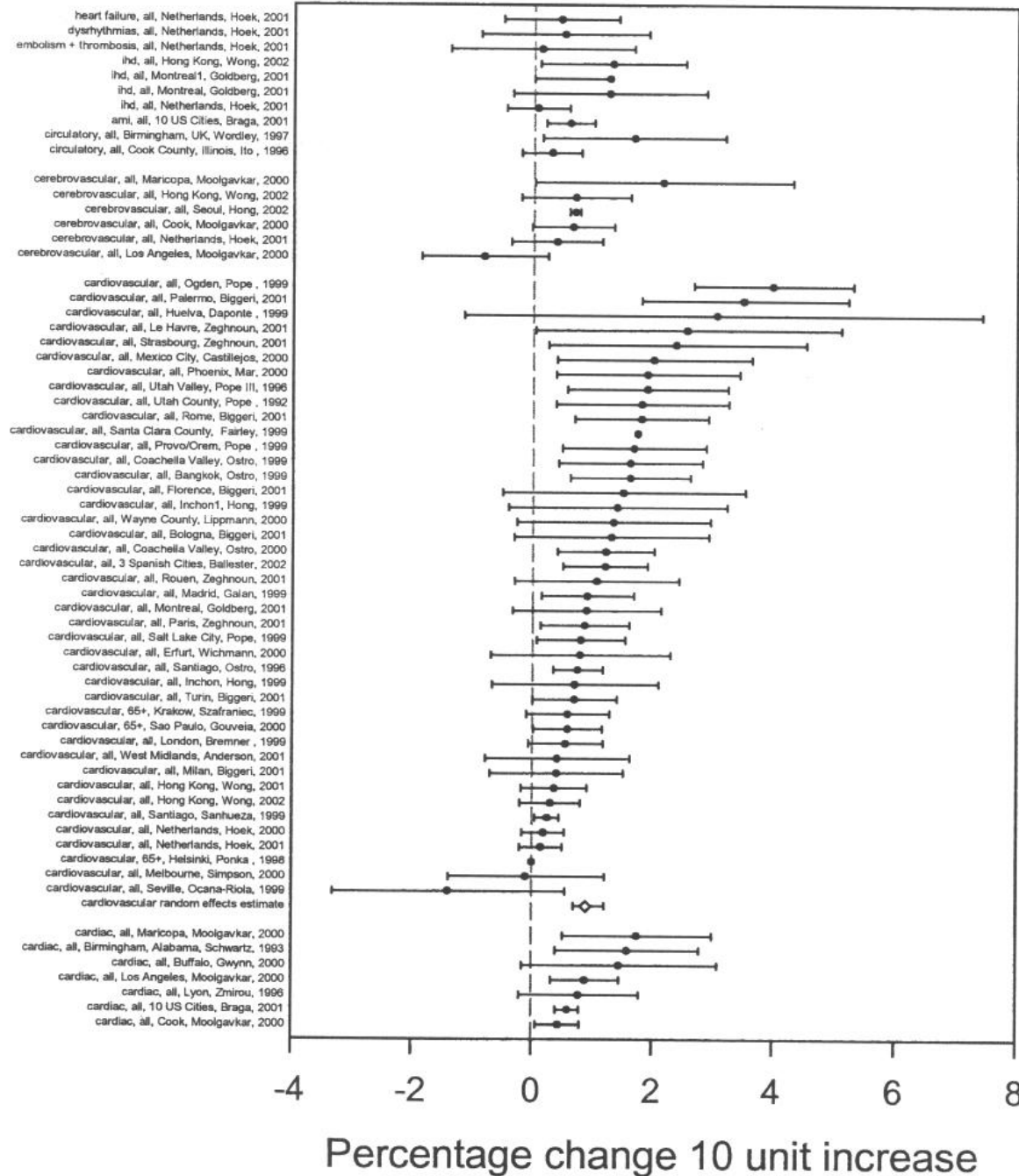


EM images of
traffic
nanoparticles



Deaths and hospitalisations for COPD, asthma, cardiovascular disease with increases of $10\mu\text{g}/\text{m}^3$

- There is a considerable weight of epidemiology evidence that increases in PM₁₀ are associated with cv mortality
- These effects of PM₁₀ are dominated by the traffic effect
- The main pollutant from traffic is CDNP
- i.e. these cv effects are likely driven by the CDNP



Endothelial dysfunction after diesel exhaust inhalation

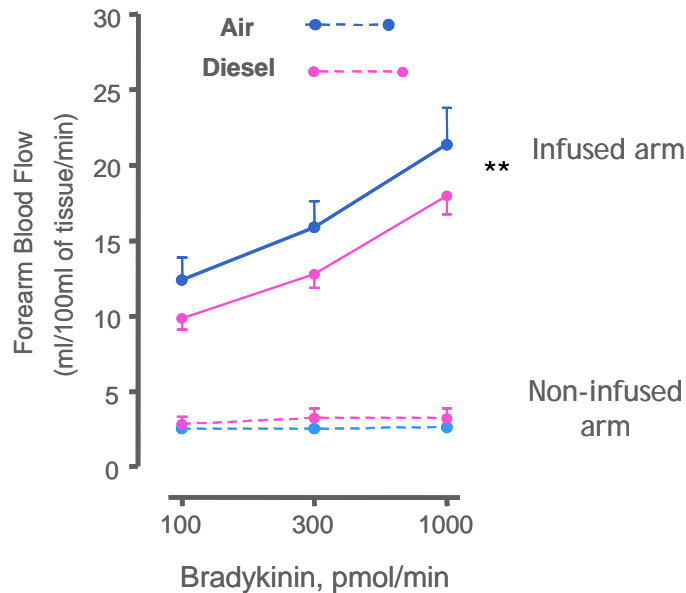


Diesel exhaust nanoparticles ($300\mu\text{g}/\text{m}^3$ for 1 hour)

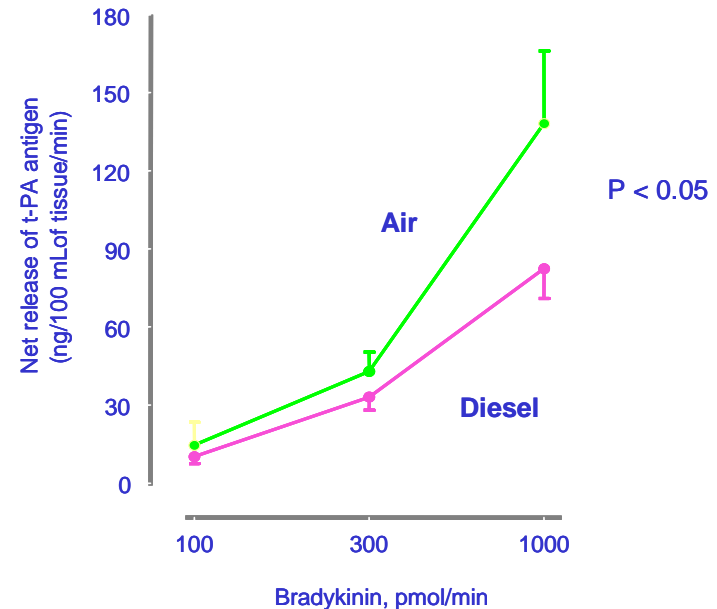
Mills, N. L., H. Tornqvist, S. D. Robinson, M. Gonzalez, K. Darnley, W. MacNee, N. A. Boon, K. Donaldson, A. Blomberg, T. Sandstrom, and D. E. Newby. 2005. Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis *Circulation* 112:3930-3936.

Inhaling diesel nanoparticles impairs the cardiovascular system

Vasomotor response



Ability to dissolve clots

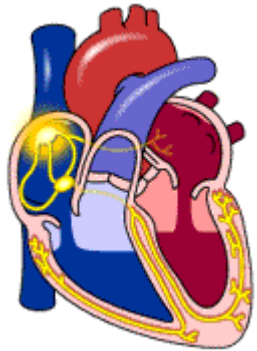


For more details see

Mills, N. L., H. Tornqvist, S. D. Robinson, M. Gonzalez, K. Darnley, W. MacNee, N. A. Boon, K. Donaldson, A. Blomberg, T. Sandstrom, and D. E. Newby. 2005. Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis *Circulation* 112:3930-3936.

The sequential electrical activation of the heart

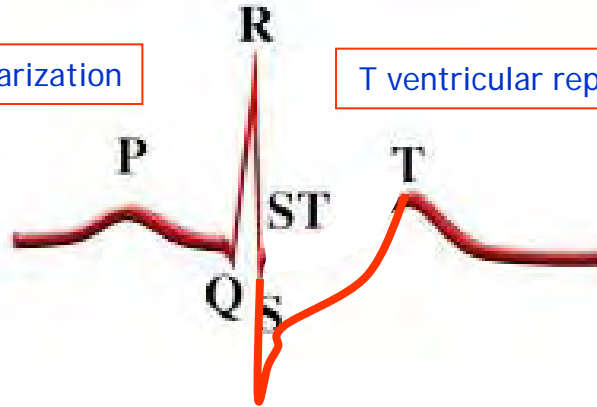
P-, QRS- and T-waves in the ECG.



P atrial depolarization

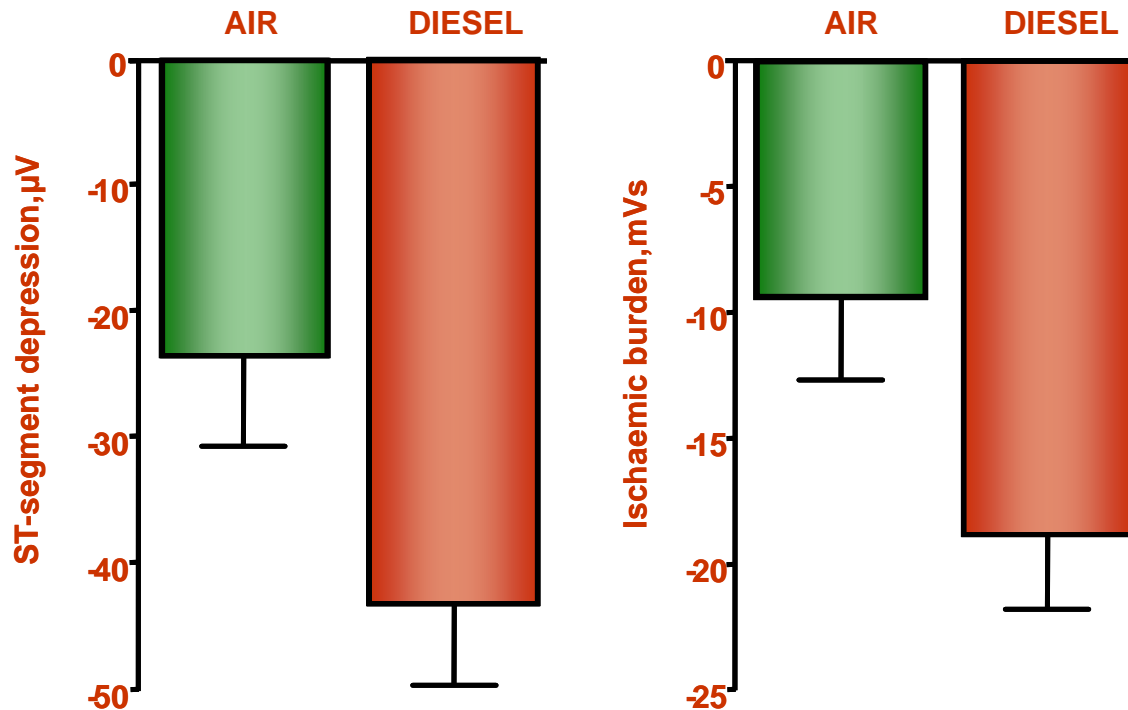
QRS ventricular depolarization

T ventricular repolarization.



- ST usually slanted slightly upward
- In coronary artery disease the blood flow to the heart is compromised.
- If oxygen delivery is not sufficient, ischemia results in the ventricular myocardium.
- The ischemic tissue cannot maintain the membrane potential.
- This is seen as displacement of ST segment downwards
- The larger the ischemic area, the greater this deviation.

S-T segment depression in patients with stable Coronary Heart Disease exercising in air or dilute diesel exhaust

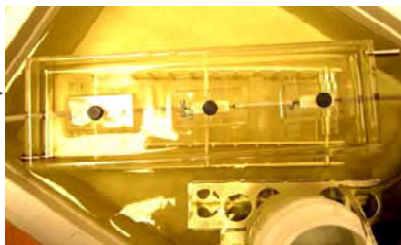


Ischaemic burden = Duration of exercise x change in ST segment depression

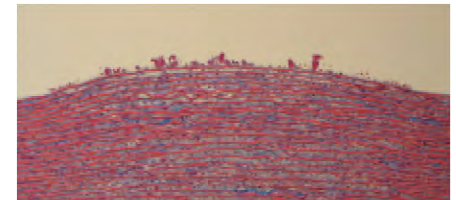
Studying thrombosis in humans after diesel exhaust inhalation The Badimon Chamber



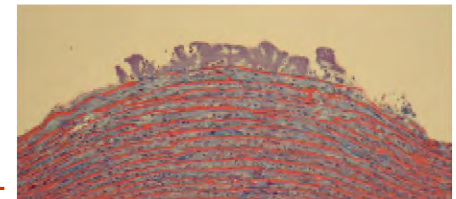
Expose to Diesel exhaust nanoparticles
(300ug/m³ for 1 hour)



AIR



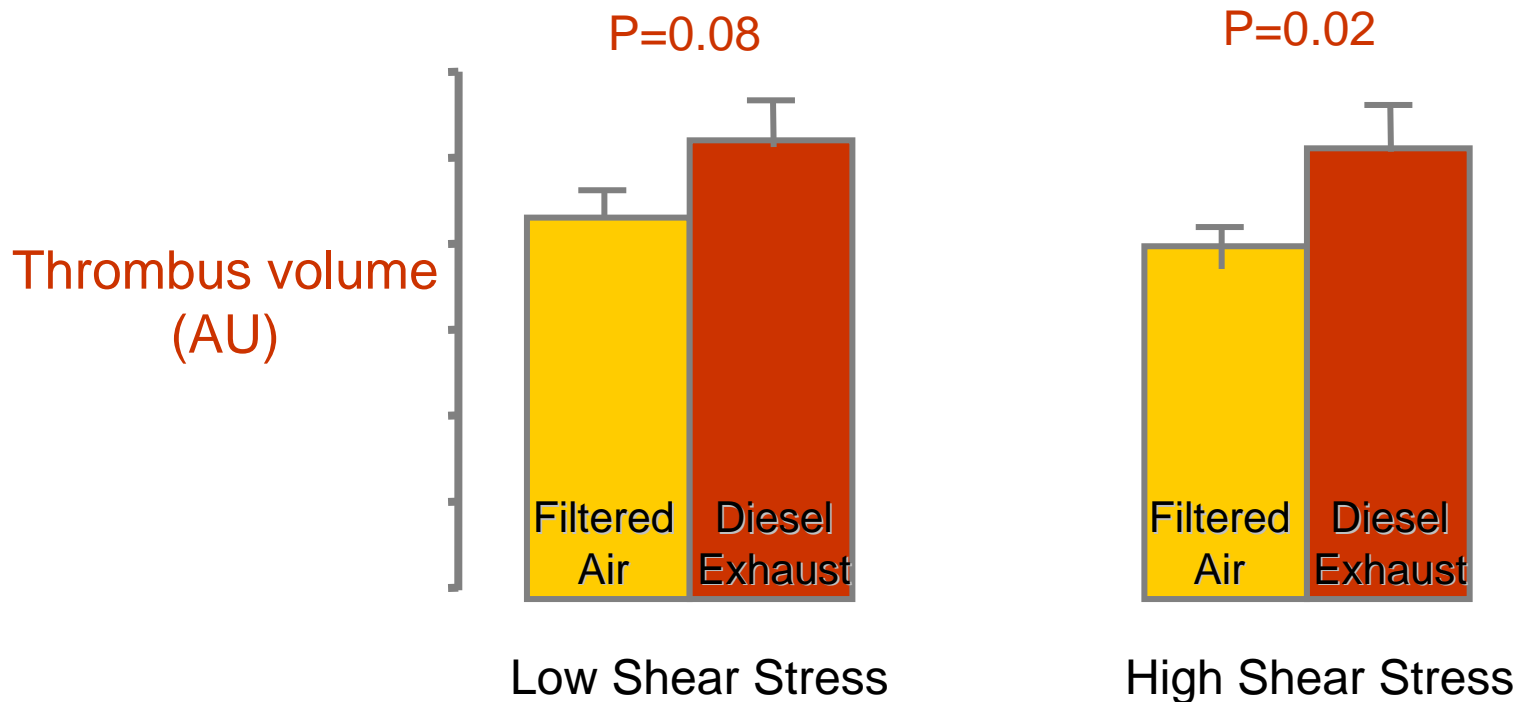
DIESEL



Courtesy of Dr Andy Lucking

Effect of Diesel Exhaust on Thrombus Formation in the Badimon Chamber

Diesel exhaust nanoparticles (300ug/m³ for 1 hour)



Lucking *et al.* submitted

Courtesy of Dr Andy Lucking

Data are mean + SEM (n=7)

Combustion-derived nanoparticles (diesel soot) enhance the development of atherosclerotic plaques in ApoE mice

Dr Mark Miller, Dr Katy Shaw, Dr Rodger Duffin,
Professor David Newby,

ApoE mice instilled with



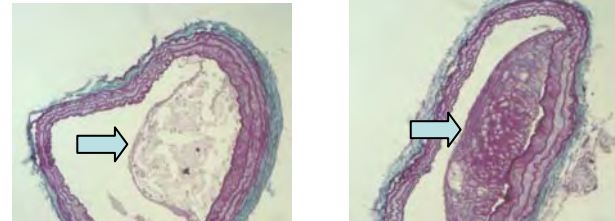
Saline

Diesel

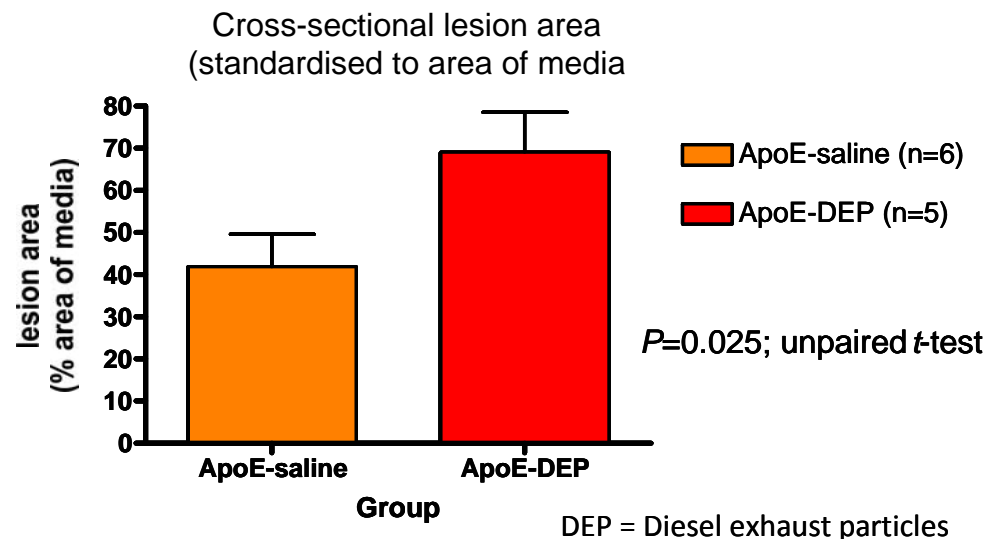


Sudan staining for lipid (red)

Examples of atherosclerotic lesions (arrows) in ApoE mice



Conclusion Exposure to dilute diesel exhaust particles enhances the development and instability of atheromatous plaques which are the cause of cardiovascular mortality and morbidity



Data courtesy of Dr Mark Miller (In press)

CV system and nanoparticles

Diesel nanoparticle exposure causes:-

- 1) Endothelial dysfunction and fibrinolytic deficit in normal subjects
- 2) Enhanced S-T segment depression in exercising patients with mild coronary artery disease
- 3) Enhanced pro- thrombotic effect in normal subjects
- 4) Instilling diesel soot into mouse lungs enhances atherosclerotic plaque development

These data form a clear mechanistic link between exposure to traffic pollution-derived nanoparticles and acute cv effects



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

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nature

COMMENTARY

Safe handling of nanotechnology

The pursuit of responsible nanotechnologies can be tackled through a series of grand challenges, argue **Andrew D. Maynard** and his co-authors.

When the physicist and Nobel laureate Richard Feynman challenged the science community to think small in his 1959 lecture 'There's Plenty of Room at the Bottom', he planted the seeds of a new era in science and technology. Nanotechnology, which is about controlling matter at near-atomic scales to produce unique or enhanced materials, products and devices, is now maturing rapidly, with more than 300 claimed nanotechnology products already on the market¹. Yet concerns have been raised that the very properties of nanostructured materials that make them so attractive could potentially lead to unforeseen health or environmental hazards².

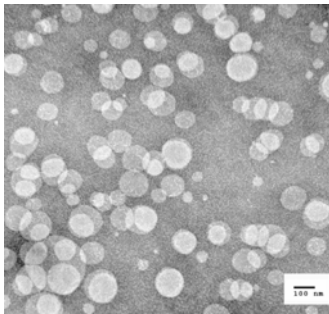
The spectre of possible harm — whether real or imagined — is threatening to slow the development of nanotechnology unless sound, independent and authoritative information is developed on what the risks are, and how to avoid them³. In what may be unprecedented pre-emptive action in the face of a new technology, governments, industries and research



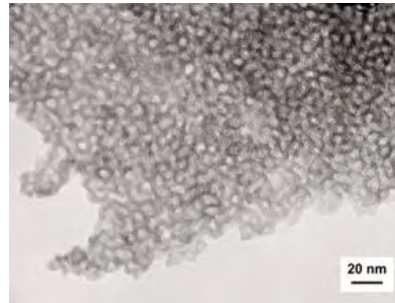
Potential health risks from exposure to engineered nanomaterials must be understood and minimized.

'....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

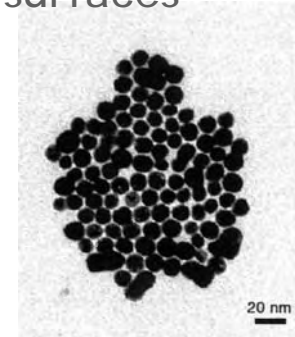
Designed for diverse uses within the food, finish, IT, ink, paint, cosmetics, glass etc industries-
variable compositions and surfaces



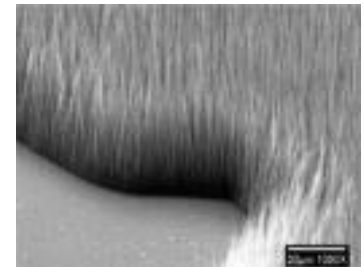
polymer



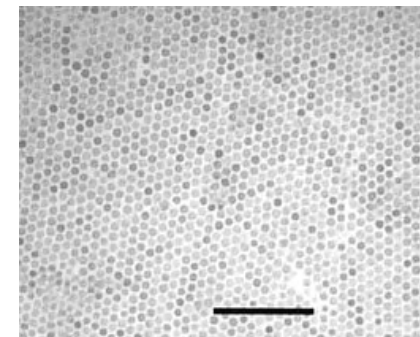
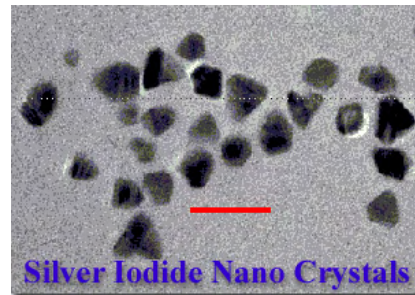
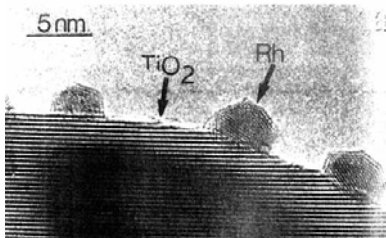
zirconium



gold



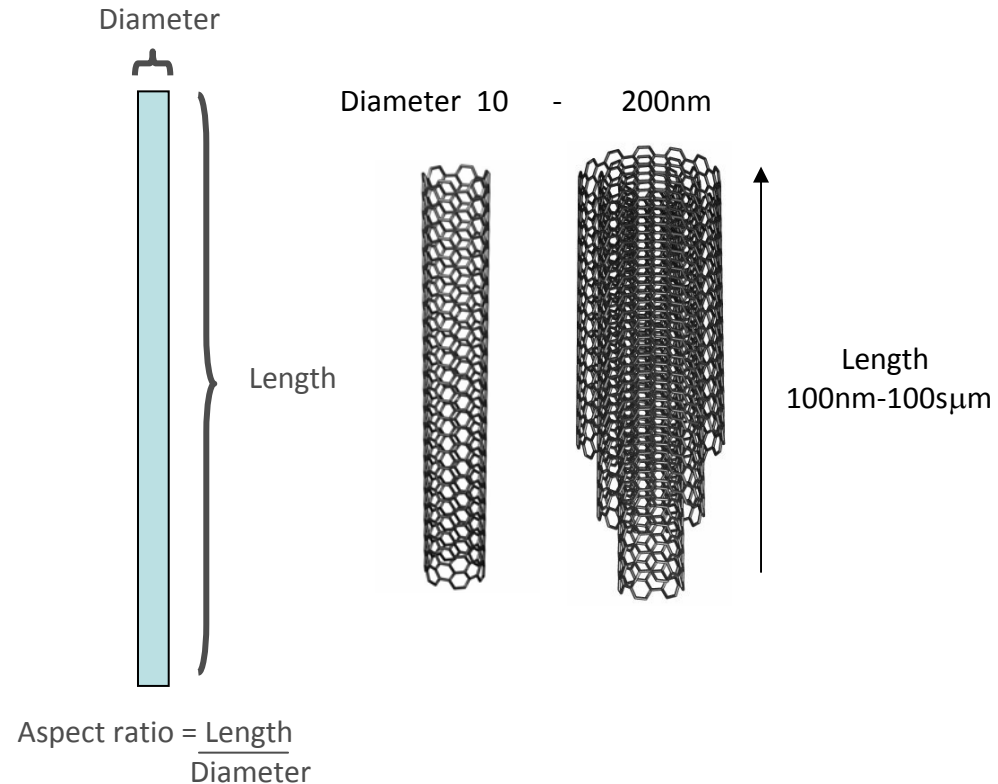
carbon
nanotubes



cobalt

Infinite potential for different chemistry /composition

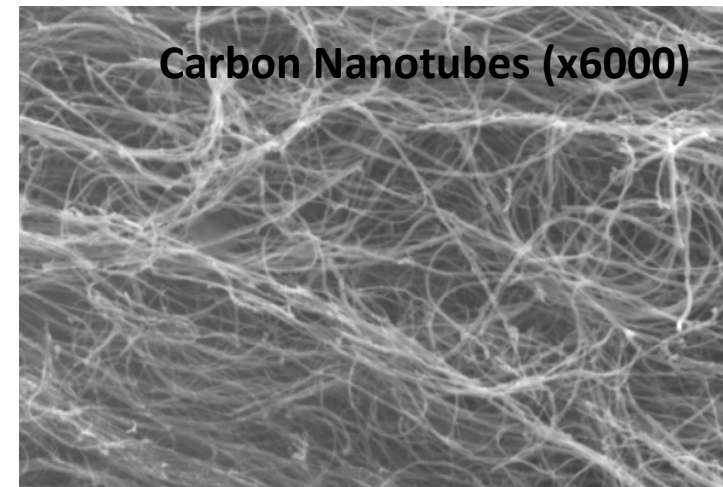
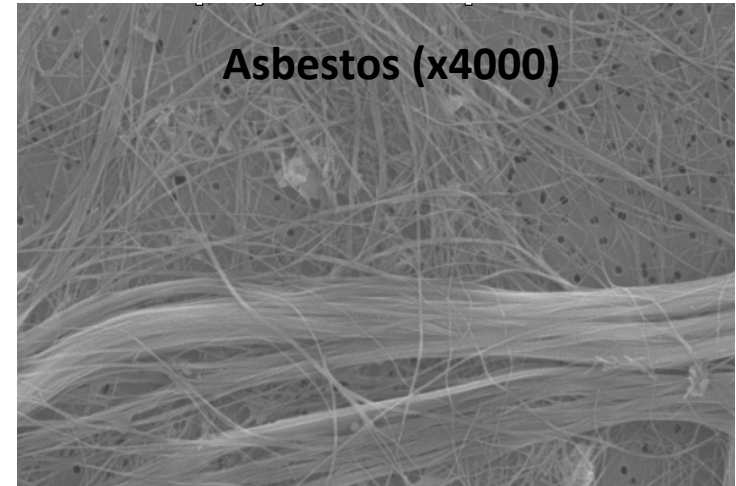
High aspect ratio (or being a fibre) as an 'extra hazard' factor in the toxicity of a particle



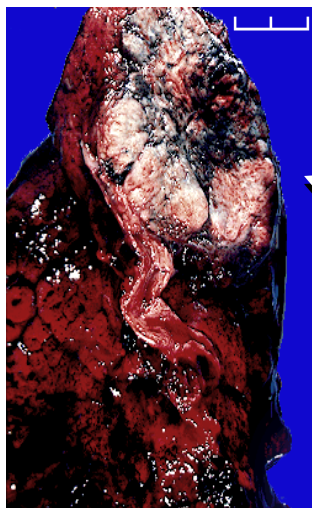
A fibre is any particle longer than 5µm, thinner than 3µm and with an aspect ratio greater than 3:1

WHO definition

and must be regulated as such in workplace air



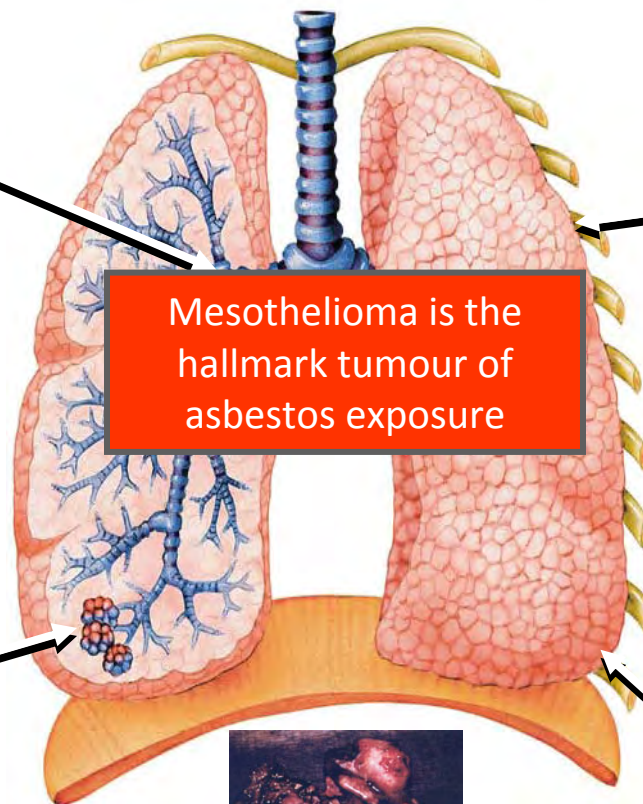
Asbestos-related Lung Disease



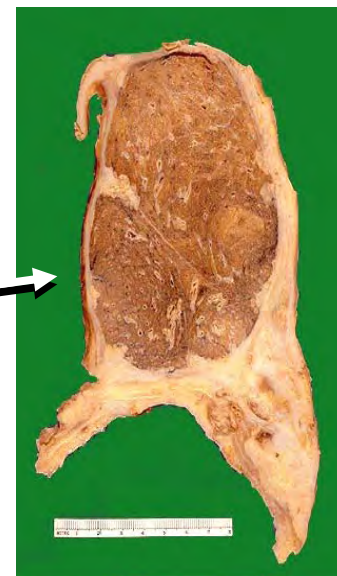
Bronchogenic
carcinoma



Asbestosis
Honeycomb lung



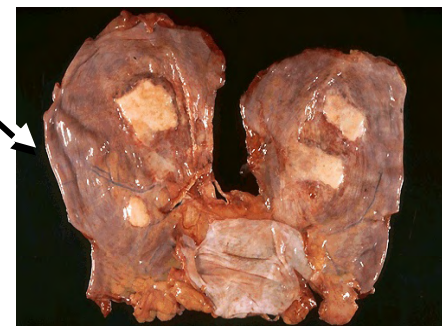
Mesothelioma is the
hallmark tumour of
asbestos exposure



Pleural
mesothelioma



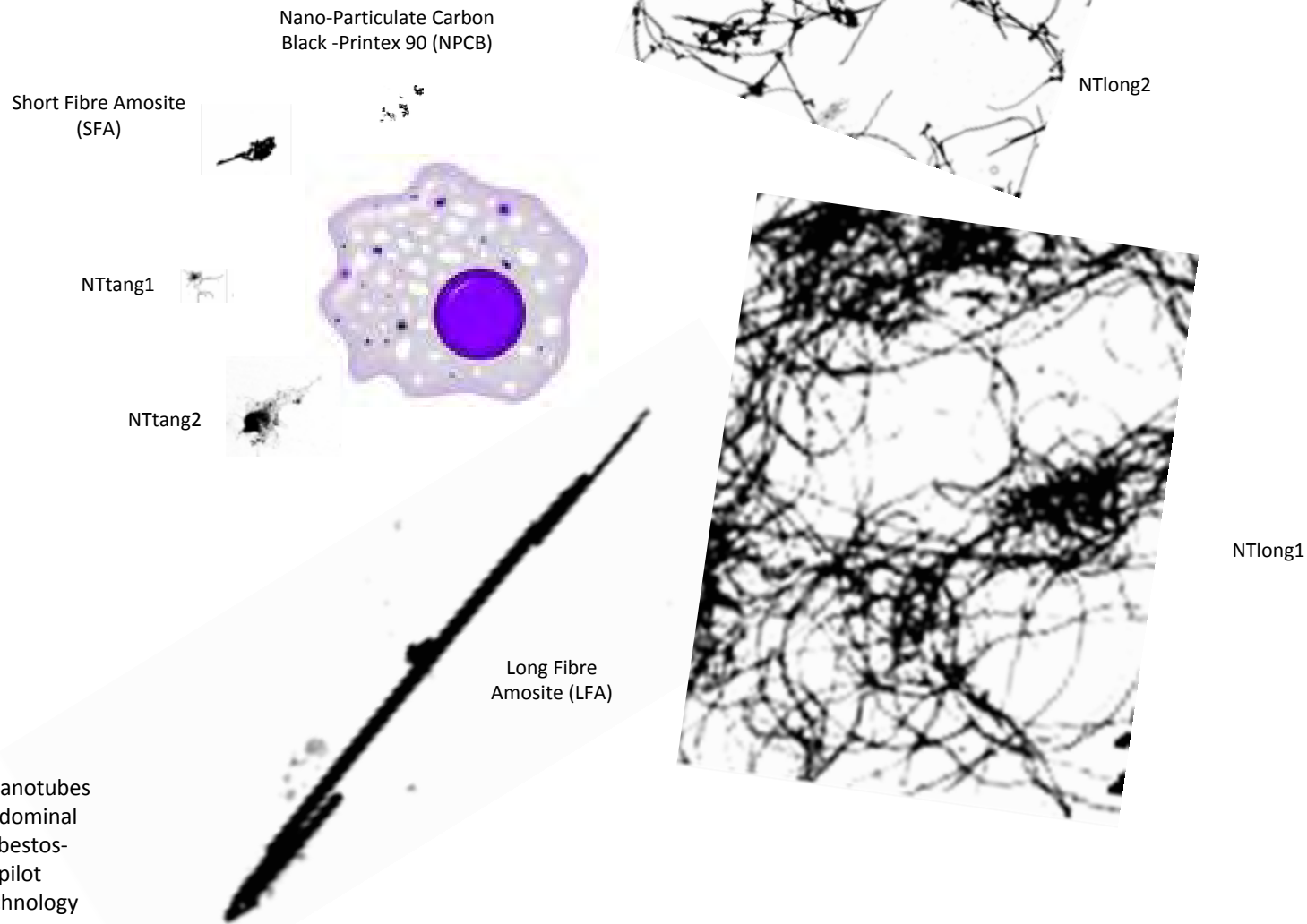
Peritoneal mesothelioma
(5-50%)



Pleural plaque



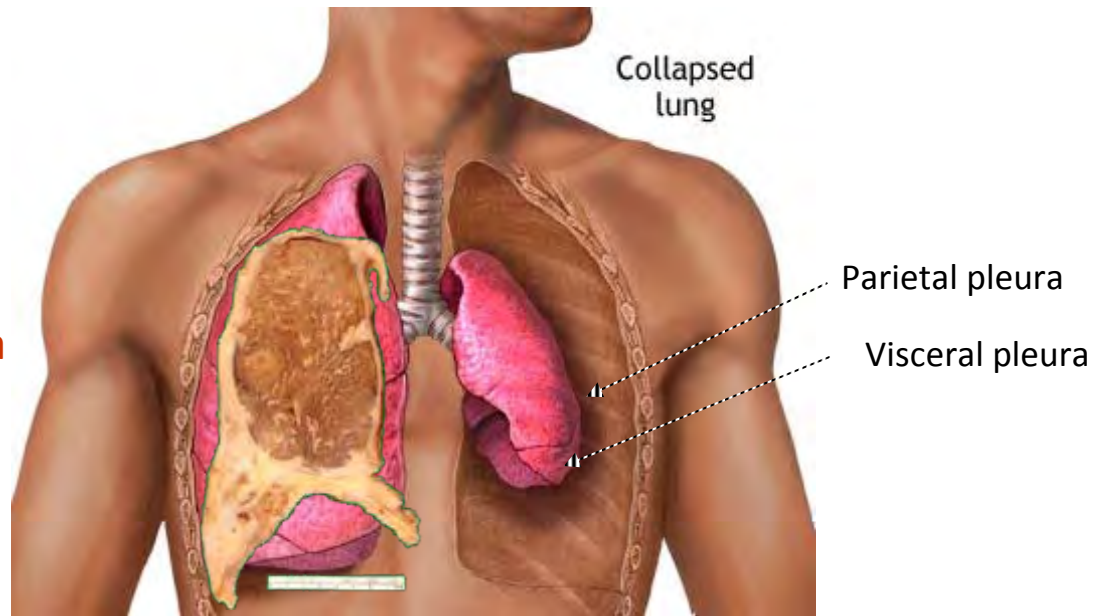
Testing the theory that only long nanotubes, like asbestos would be a mesothelioma risk: Panel of Particles



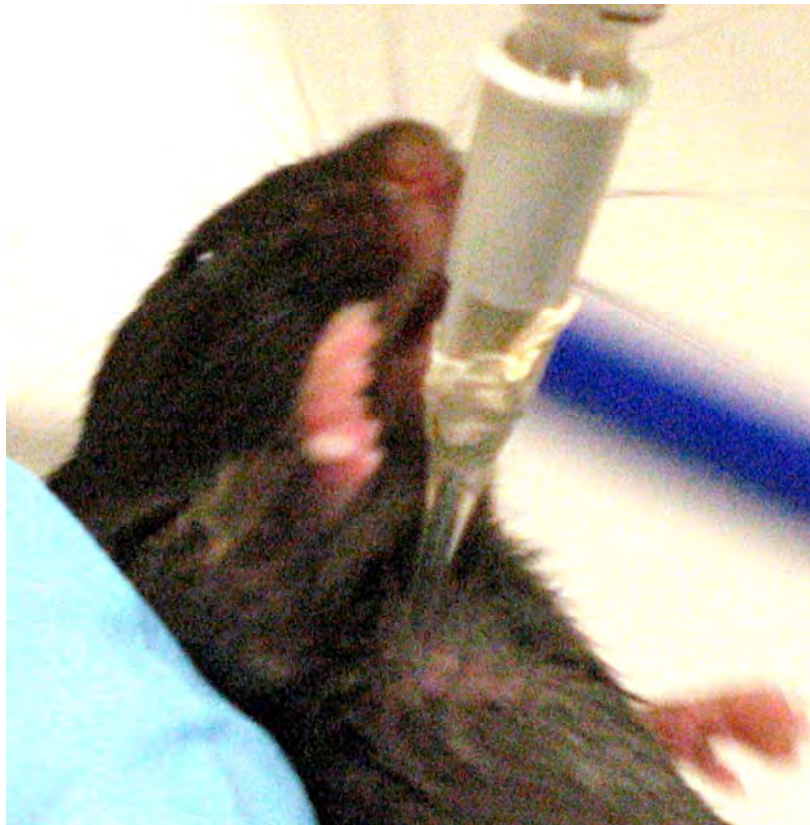
Poland *et al.* Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nature Nanotechnology* 3, 423 - 428 (2008)

The pleural mesothelium and mesothelioma

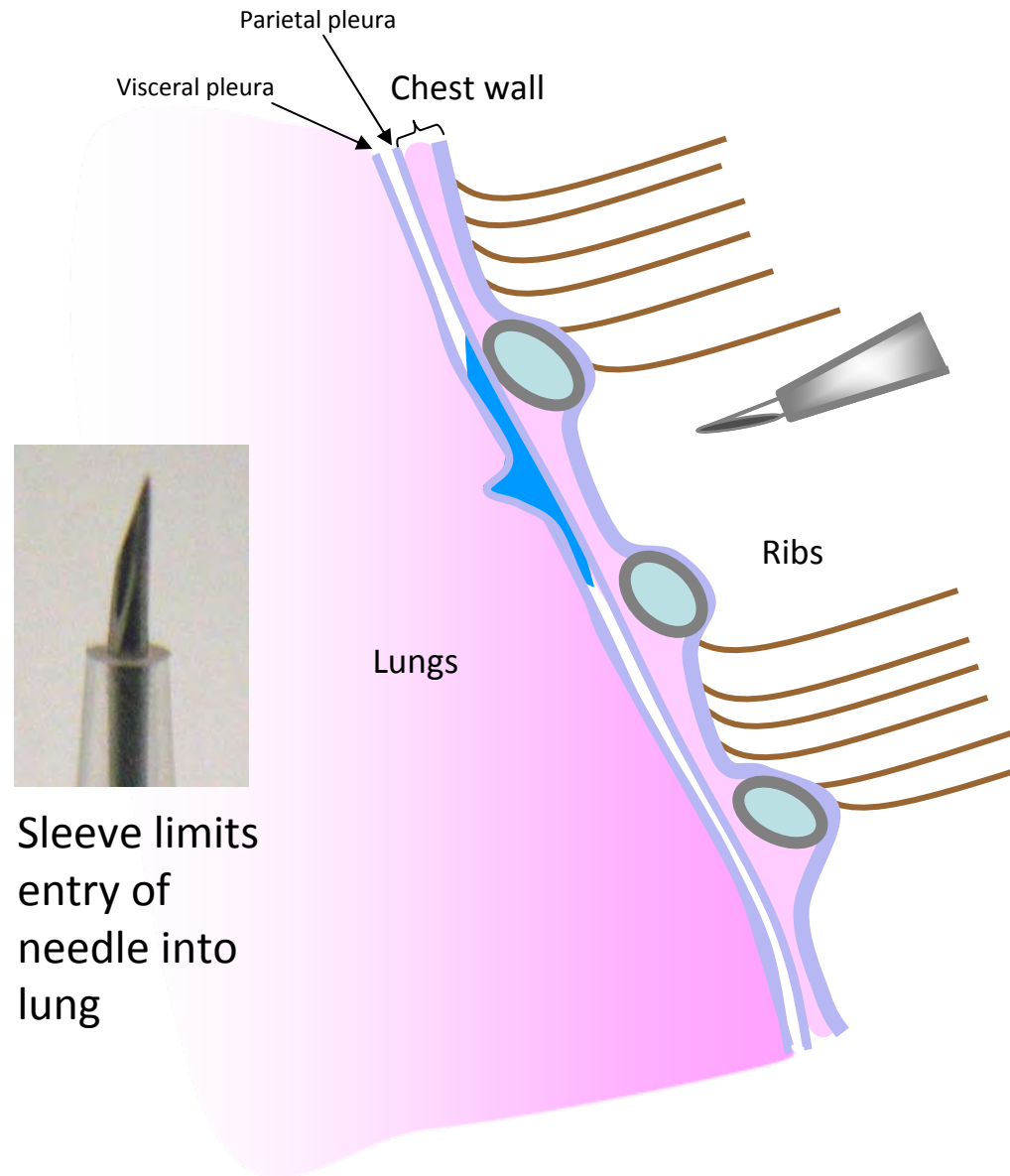
Pleural mesothelioma



Injection of CNT in the pleural space of mice



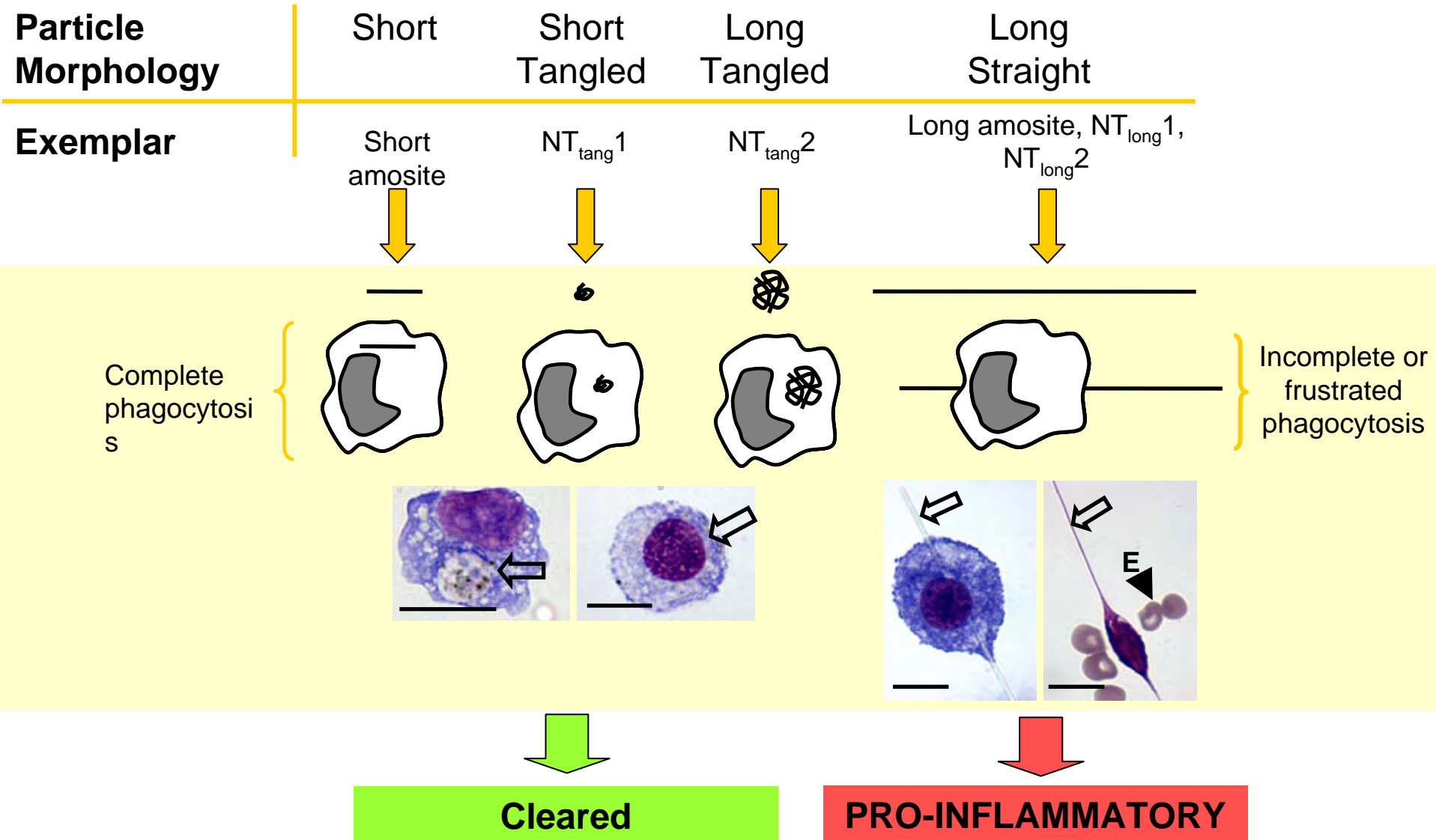
Mouse held to expose ventral surface and 100 μ l injected into right upper quadrant of thorax



The take home message is

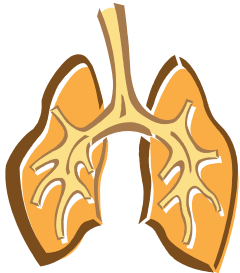
- 1) Not all nanotubes are created equal
- 2) If they are short/tangled then they will not have asbestos-type effects (though they might have particle-type effects)
- 3) If they are long (>15mm) then they may have asbestos-type effects
- 4) Other long thin nanoparticles, if they resist dissolution in the lungs, will likely have asbestos-like effects

Hypothesized Mechanism



Key questions on the risks from nanoparticles

Lungs



What is the exposure?

How do NP exert their inflammatory effects?

How can we screen NP to classify them as more or less hazardous?

Will they impact on the cv system?

Are there long CNT or other HARN in workplace air and will they cause asbestos-like disease?

Do inhaled NP pass to the brain in significant amounts and do they have effects there?

Gut



Is the gut affected by NP?

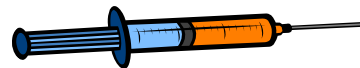
Skin



Do NP in cosmetics and sun-screens pass through the skin?

Do NP have harmful effects on the skin?

Medical nanoparticles



Is it safe to inject medical NP into the blood?

? Ecotoxicological effects

