Oxford University Begbroke Science Park

Nanosafety: The concerns and the actions

Professor Peter J Dobson

Academic Director of the Oxford University Begbroke Science Park

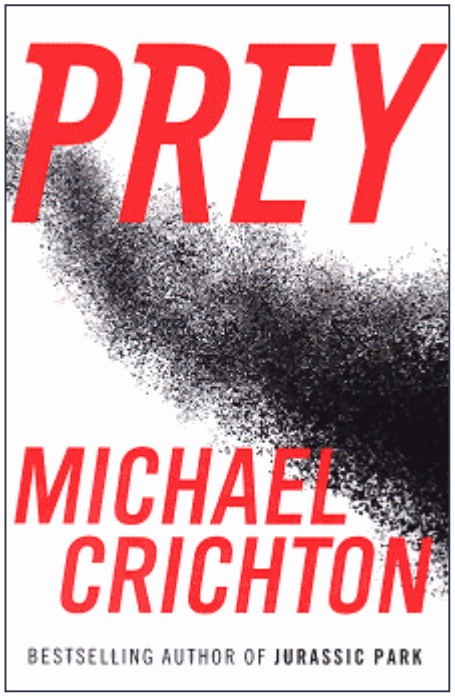
Nanosafety: The concerns and the actions

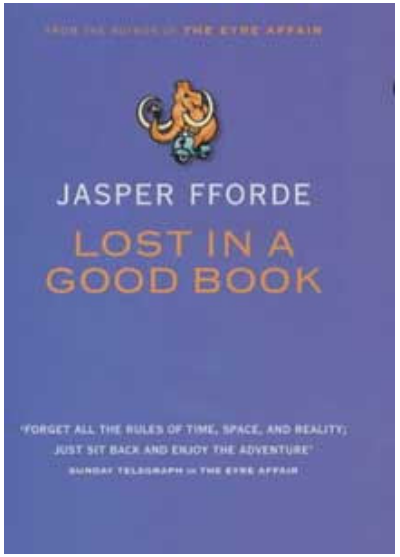
- The Hype factor
- The real concerns and natural vs man-made
- Some of the science issues: settling of particles; agglomeration; interaction with the body and with cells.
- National and International Programmes
- Examples of activity
- Some web-sites and further reading.

Raquel Welch leads the nanotechnology revolution in Medicine !

1960s concept movie about tackling disease at blood cell level

Real or Science Fiction?





Myths and Scares and…..

- Drexler: “Engines of Creation” 1986 created a lot of interest in nanotechnology
- Bill Joy (Sun Microsystems) 2000: warnings “to those involved in advancing new technologies to devote best efforts to head off disaster”- suggestions are unrealistic.
- Grey Goo: science fiction in “Prey” 2002, by Crichton inadvertently publicised by Prince Charles.
- ETC Group “The Big Down” 2003
- Many scientists have “jumped on the bandwagon” to “whistleblow”
- Greenpeace “Future technologies, today’s choices” 2003
- Royal Society and Royal Academy of Engineering report on Nanotechnology, safety 2004
- NANOSAFE 1 report 2004 (EU)
- NANOSAFE 2 programme 2005- (EU)
- NanoSafety Networks (EPSRC funded) 2005-

Prince Charles and Grey Goo

- THE DAILY TELEGRAPH

  Prince Charles asks scientists to look into 'grey goo'
  By Roger Highfield, Science Editor
  (Filed: 05/06/2003)

- Fears by the Prince of Wales that armies of microscopic robots could turn the face of the planet into an uninhabitable wasteland have prompted the nation's top scientists and engineers to launch an inquiry.

  "The nightmare scenario of self-replicating nanobots destroying everything is about as likely to come true as Jurassic Park, another product of Michael Crichton's fertile imagination," said Lord May.

  Fearful of the same polarised debate developing as with GM, Lord May has decided to launch the inquiry, even though many of the risks are "purely imaginary and conjectured".

  Some of the benefits of nanotechnology, such as superior materials and sunscreens, are clear cut "but maybe there are some things we ought to be thinking about".

Prince Charles and Grey Goo

- BBC News 11th July 2004
- Prince Charles says he never used the expression "grey goo", adding: "I do not believe that self-replicating robots, smaller than viruses, will one day multiply uncontrollably and devour our planet.
- "Such beliefs should be left where they belong, in the realms of science fiction."
- The Prince acknowledges nanotechnology is a "triumph of human ingenuity".
- "Some of the work may have fundamental benefits to society, such as enabling the construction of much cheaper fuel-cells, or new ways of combating ill-health," he says.
- But he adds: "How are we going to ensure that proper attention is given to the risks that may... ensue?
- Professor Ken Donaldson, professor of respiratory toxicology at the University of Edinburgh, welcomed the Prince's intervention.
- He said: "I agree that more research needs to be done and that risk assessment must keep pace with commercial development."

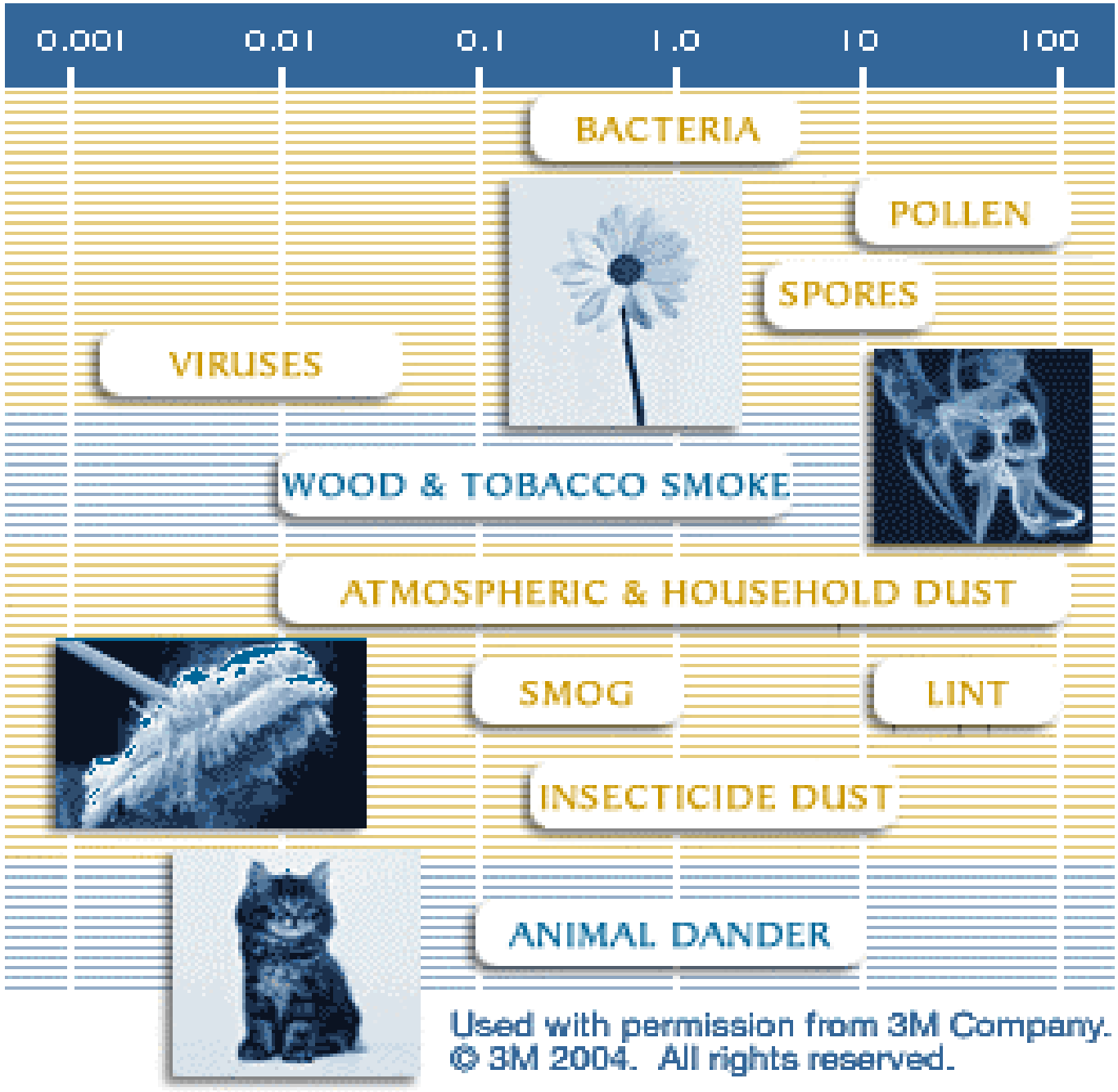
UK Govt. response to the Royal Society/RAE report

- Government commits to regulating nanotechnologies but will it deliver?

  25 Feb 2005
- The Government must commit adequate funding to improve the understanding of any potential risks to human health and the environment from nanotechnologies said the Royal Society and the Royal Academy of Engineering in reaction to the publication today (Friday 25 February 2005) of a Government report into the science of the very small.

- While the report, a response to the two academies study into nanotechnologies, commits the Government to taking forward the regulation of these novel technologies, it does not dedicate any new money for the research which will be essential to support the development of robust regulations. No special funding has been provided in the UK and funding elsewhere is not given high priority

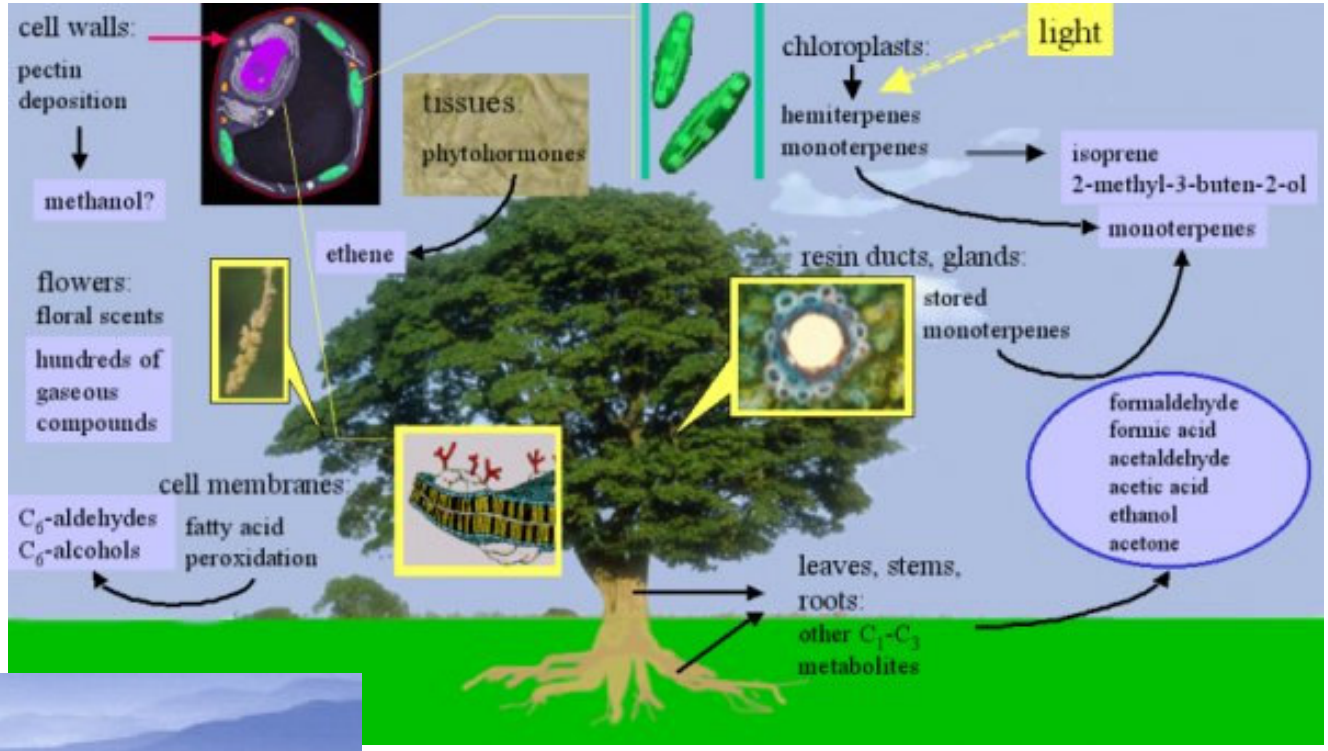
Common particle sizes in microns



Natural Particles in the Air

- These range from clouds and mists to other sources
- Dust from desserts and volcanoes
- Aerosol from the sea (including ocean products)
- Particles produced by plants
- “Natural” combustion.

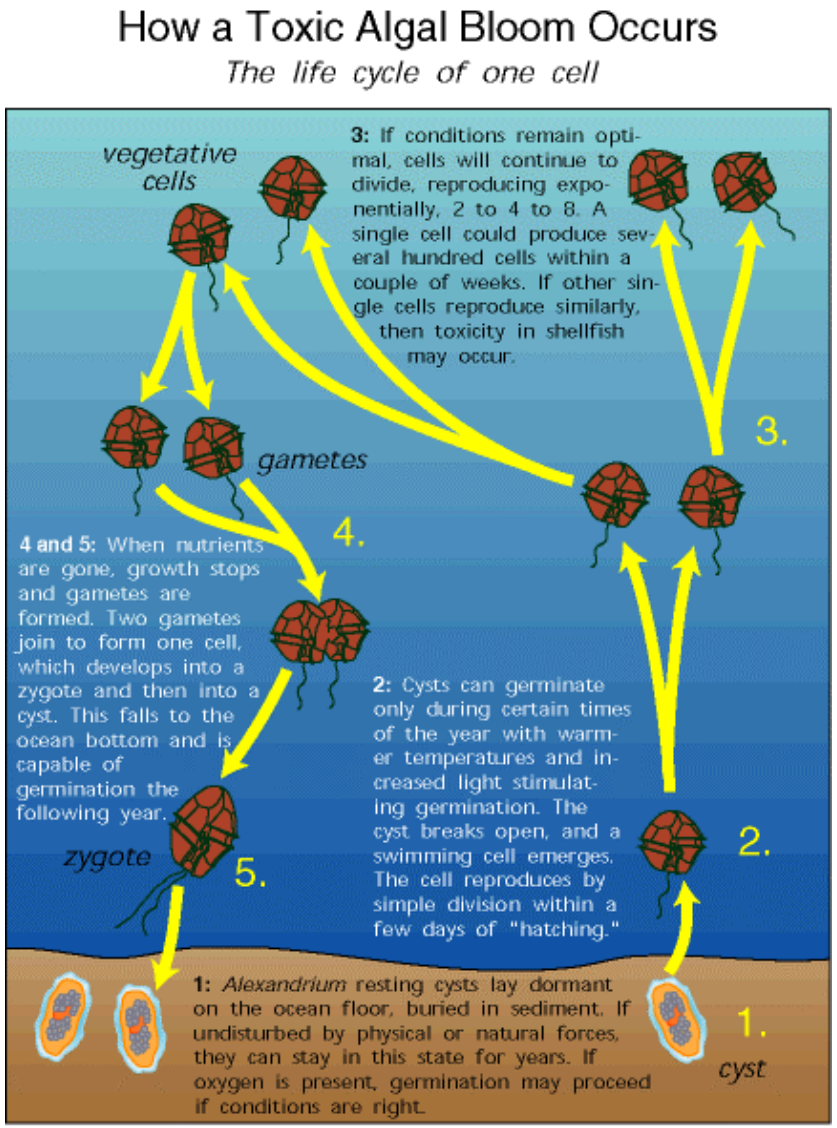
Blue haze aerosol



The terpenes emitted from trees and plants are believed to be responsible for the blue hazes in mountain regions.

These compounds are powerful antioxidants.

“Red tide” aerosol



Algae blooms can produce toxins that restrict their own population and harm other species

Toxins in this bloom can be transferred to an aerosol by waves, bubbles etc at the sea surface

The sea aerosol is a major contributor to the particles in the atmosphere.

Particle distributions

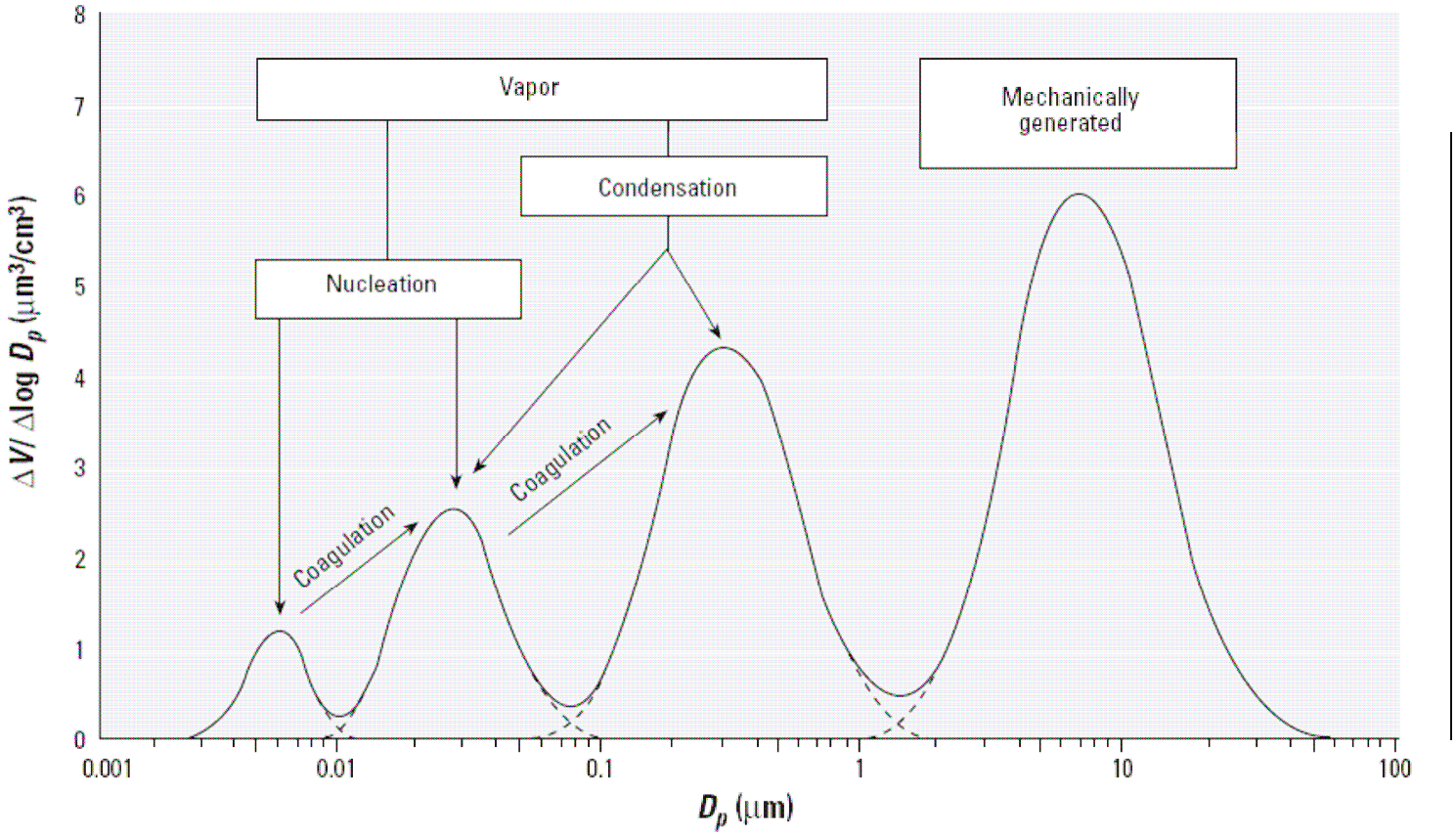


Figure 1. Idealized size distribution of traffic-related particulate matter (U.S. EPA 2004). D_p, particle diameter. The four polydisperse modes of traffic-related ambient particulate matter span approximately four orders of magnitude from < 1 nm to > 10 µm. Nucleation- and Aitken-mode particles are defined as UFPs (< approximately 100 nm). Source-dependent chemical composition is not well controlled and varies considerably. In contrast, NPs (1–100 nm) have well-controlled chemistry and are generally monodispersed.

Airborne particles

Small particles settle slowly, so they stay airborne.

Note 5nm particles have a similar “molecular weight” to enzyme and protein molecules. Viruses are slightly bigger.

Stoke’s Law settling velocity

$$v = \frac{g d^2 (\rho_1 - \rho_2)}{18\eta} \quad \text{m/s}$$

ρ_1 is particle density (kg/m$^{3)}$

ρ_2 is air density (kg/m$^{3)}$

g = 0.981 m s^{-2}

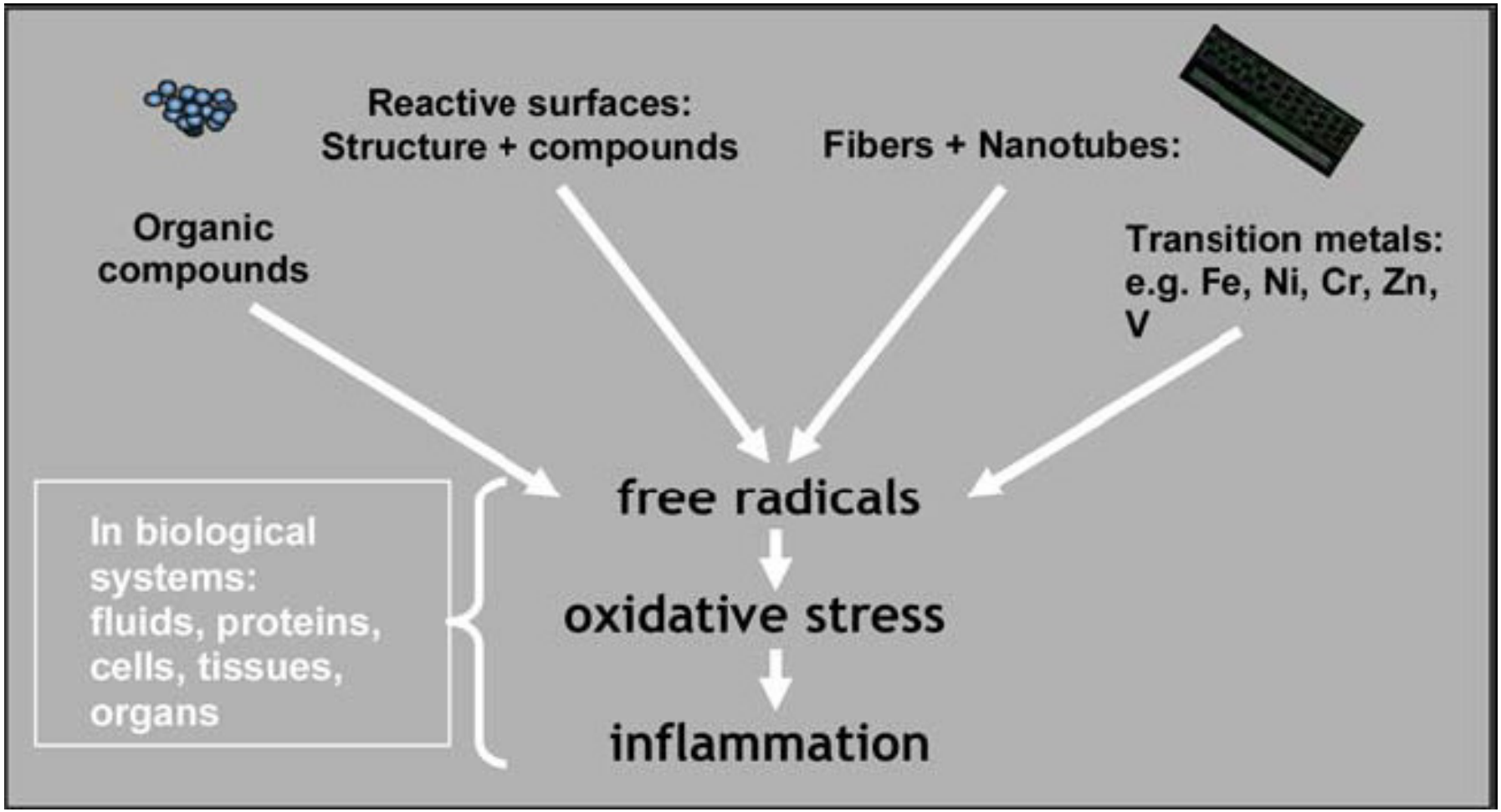
d is particle diameter (m)

η is air viscosity (Pa s)

10nm particles settle at 0.07 μm/s and diffuse thermally at ~ 330 μm/s

100nm particles settle at 0.88 μm/s and diffuse thermally at ~37 μm/s

Important parameters of ultrafine particles



Kreyling et al: J Nanoparticle Research **8**, 543-562 (2006)

Penetration issues

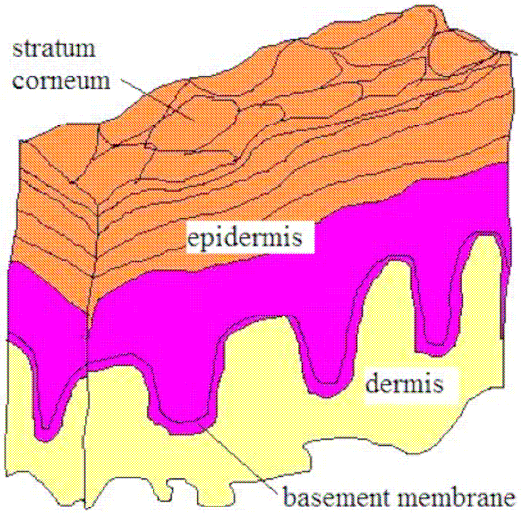


Figure 1
schematic representation of human skin; Stratum corneum is the top of the five layers making epidermis, it is composed of keratinised dead cells glued by lipids. It is shed off and replaced every two weeks. Depending on the part of the body its thickness varies from 0.05 mm to 1.5 mm.

Other parts of respiratory system may be more effective

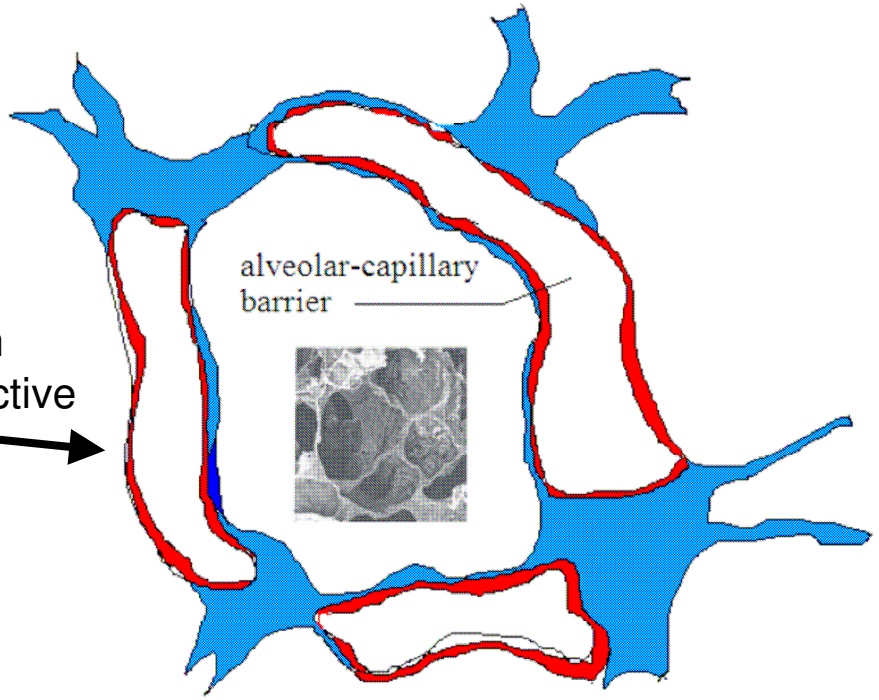


Figure 2
Cross-section of alveoli; Schematic cross-section of alveoli showing a very thin (500 nm) separation between blood and air. An SEM image of the alveoli is shown in the inset.

Very little evidence for skin penetration so far

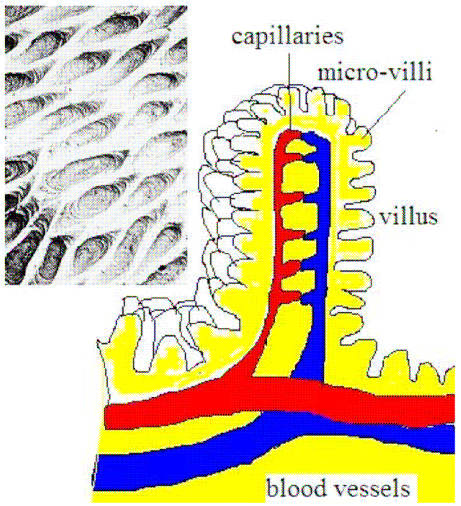


Figure 3
Villi in small intestine; A surface structure of villi covered with micro-villi is dramatically multiplies the area of gastero-intestine tract to 200 m^2. Inset shows an SEM image of villi.

Three critical situations in the body for nanoparticle interaction

Hoet et al: J Nanobiotechnology **2**:12 doi 10.1186/1477-3155-2-12

http://www.jnanobiotechnology.com/content/2/1/12

Industrial release of nanoparticles

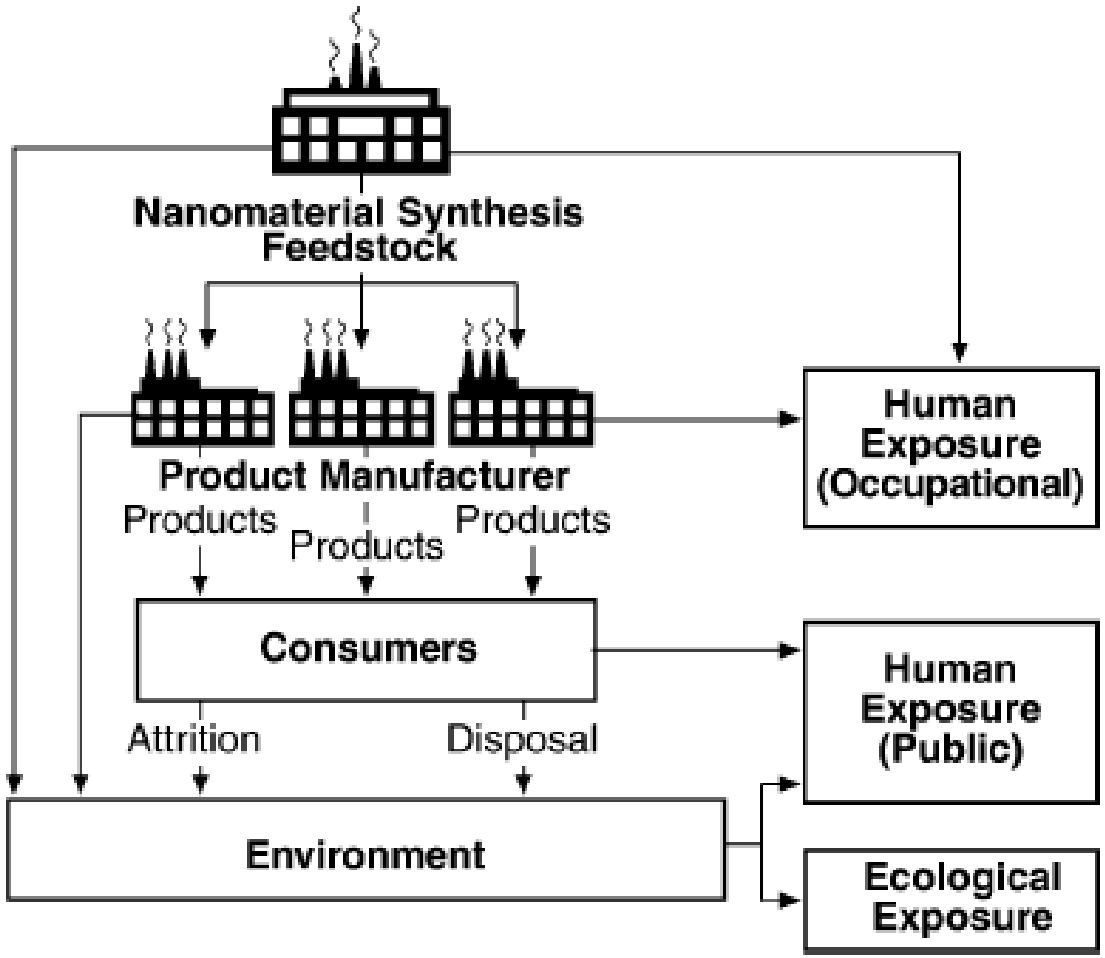
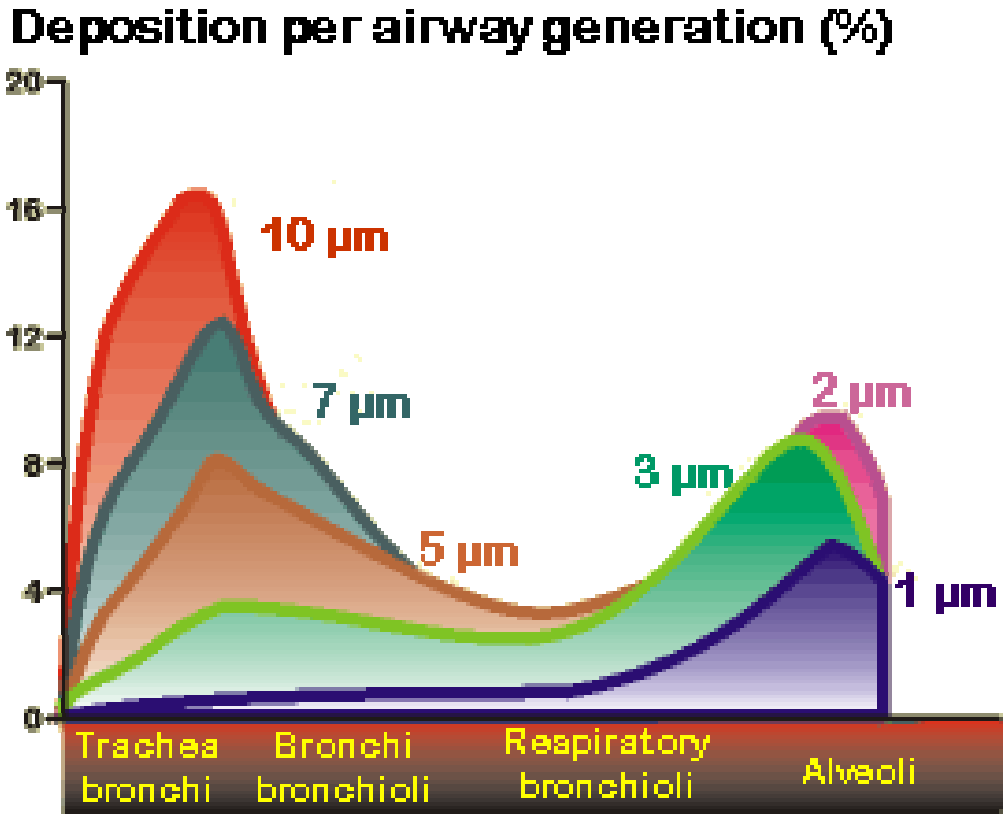
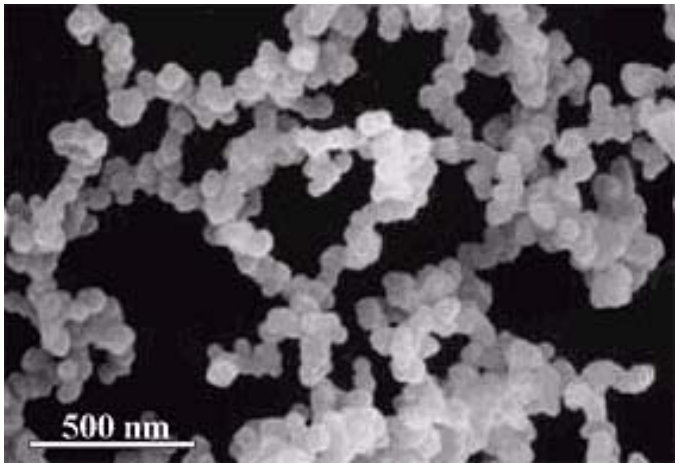


FIG. 5. Potential for release and exposure to nanoscale substances.

Tsuji et al: Toxicological Sciences **89**, 42-50 (2006)

Particle deposition in the airways

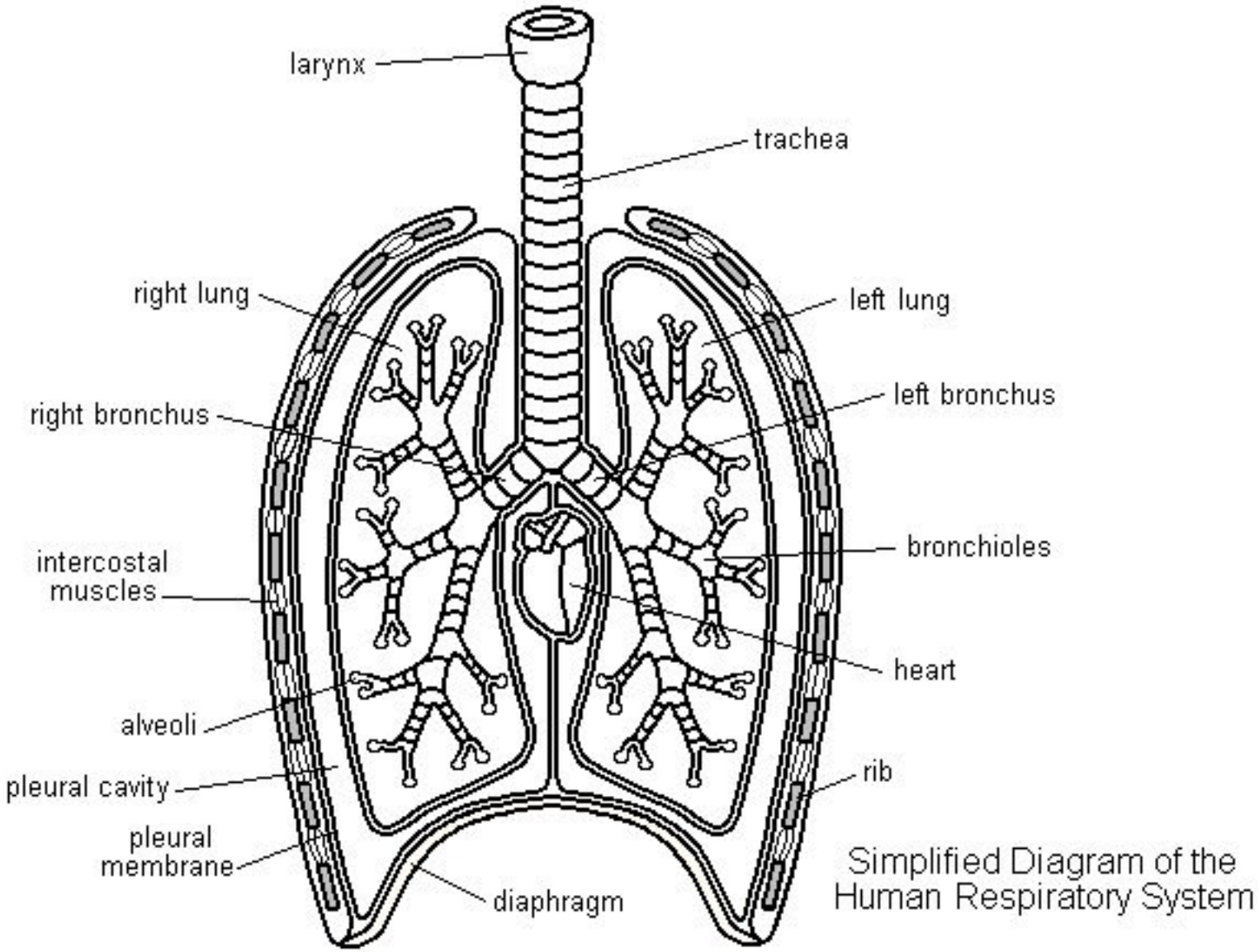




Example of some carbonaceous nanoparticles from a diesel engine

This can be harmful but it points a way to deliver drugs
We will first examine how to reduce diesel particulates.

Structure of the Lungs and Thoracic Cage



Simplified Diagram of the Human Respiratory System

Deposition in the airways

This also has important implications for inhaled drug delivery

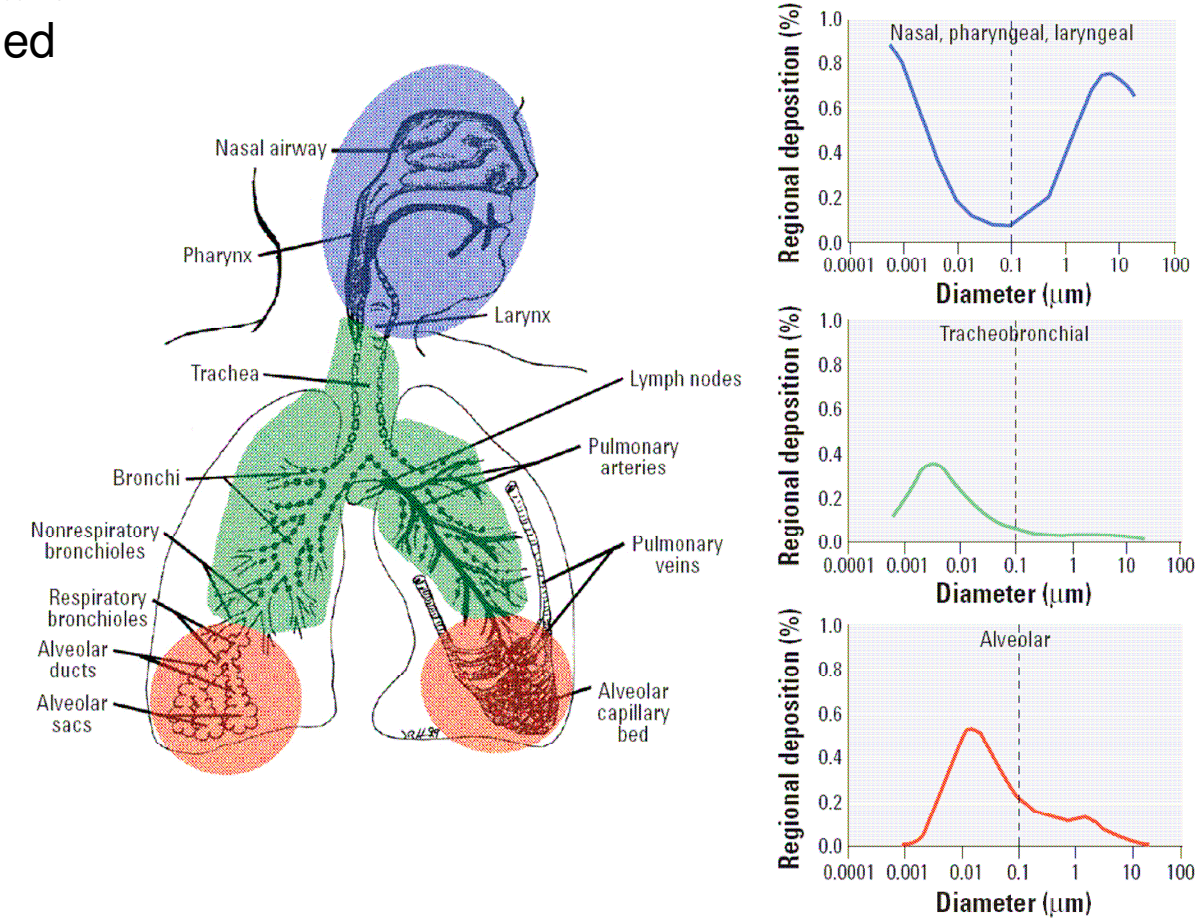


Figure 8. Predicted fractional deposition of inhaled particles in the nasopharyngeal, tracheobronchial, and alveolar region of the human respiratory tract during nose breathing. Based on data from the International Commission on Radiological Protection (1994). Drawing courtesy of J. Harkema.

Clearance mechanisms

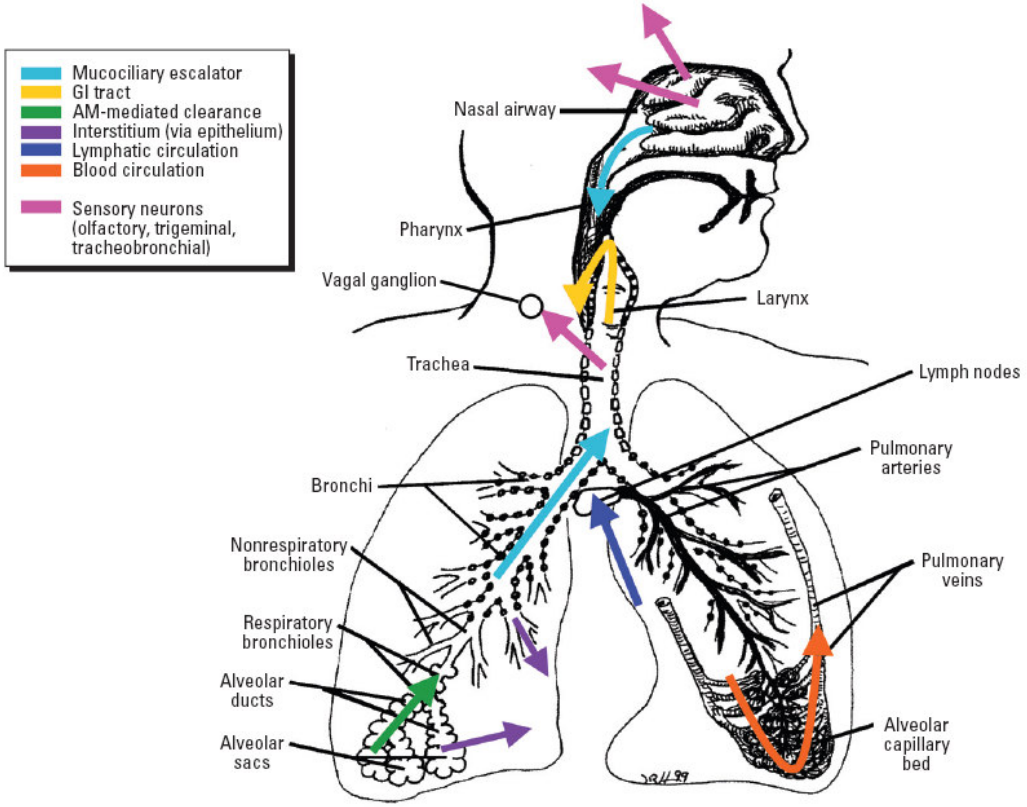
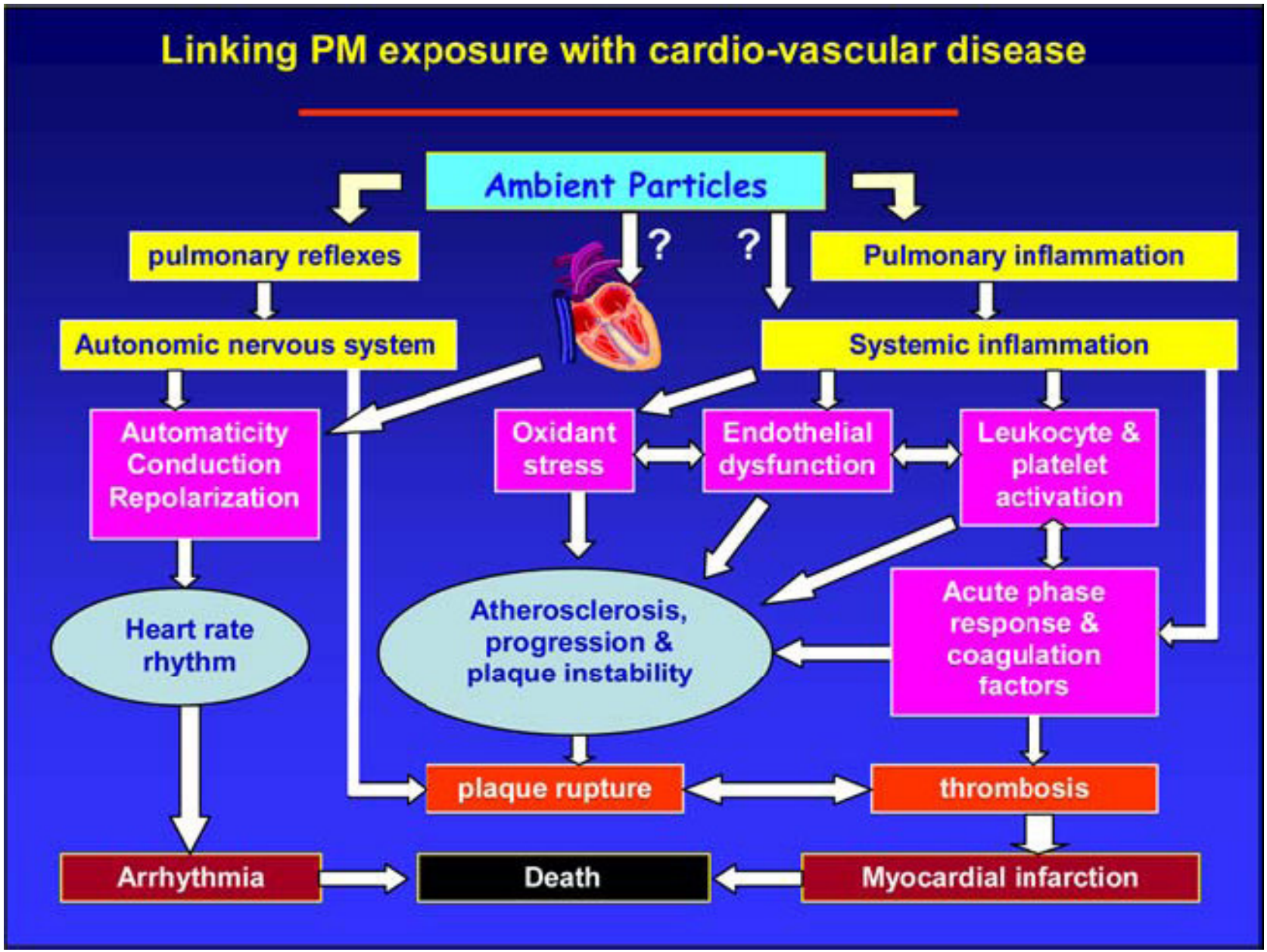


Figure 9. Pathways of particle clearance (disposition) in and out of the respiratory tract. There are significant differences between NSPs and larger particles for some of these pathways (see "Disposition of NSPs in the respiratory tract"). Drawing courtesy of J. Harkema.



Kreyling et al: J Nanoparticle Research **8**, 543-562 (2006)

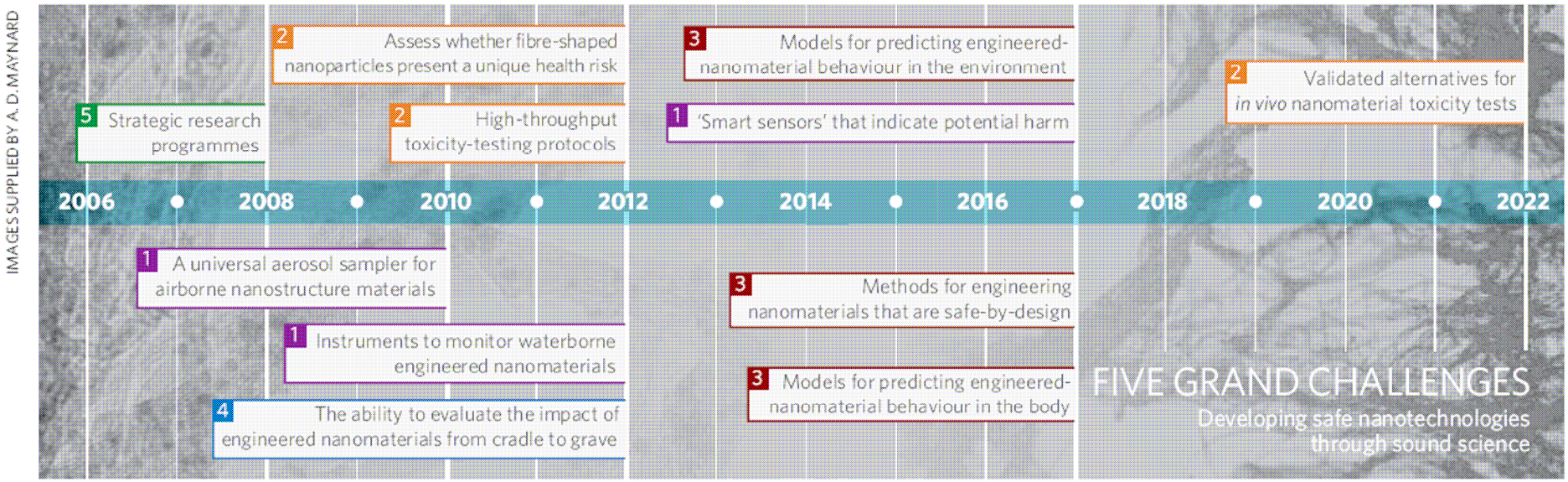
Nanotechnology Safety Challenges

Maynard et al Nature vol 444, p267 (2006)

- Develop strategic programmes that enable relevant risk-focused research (1 year)
- Instruments to assess exposure to engineered nanomaterials in air and water (3-10 years)
- Validate methods to evaluate toxicity of engineered nanoparticles (5-15 years)
- Robust systems to evaluate health and environmental impact of engineered nanoparticles over their life cycle (5 years)
- Models to predict potential impact of engineered nanoparticles on health and environment (10 years)

These are similar to NANOSAFE2 which has a 4 year horizon

The Grand Challenge Timelines



Maynard et al Nature vol 444, p267 (2006)

Strategic Programmes

- DEFRA has introduced a voluntary reporting scheme
- DTI (MNT) (in the UK) has funded Safenano.org
- Several programmes in the US.
- All emphasise: collaboration, communication and coordination

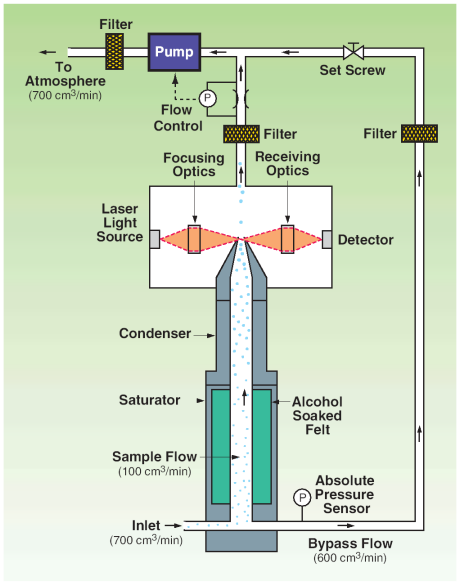
New Instrumentation

Requirements: size, shape and mass/number concentration, surface charge and chemistry

- Air sampling varies from complex condensation counters to simple smoke detectors.
- Liquid sampling methods based on photon correlation spectroscopy, Brownian motion and zeta potential measurement
- New particle collection methods are being developed for both air and liquid. Some of these collect the particles by charge separation.

Particle size instrumentation (from TSI)

Portable condensation counters



TO Order

Hand-held Condensation Particle Counter

Specify	*Description*
3007	CPC and accessories: spare wicks (2), battery holder, alkaline batteries (6 AA), AC adapter, alcohol fill capsule with storage cap, alcohol cartridge, 30-ml bottles reagent-grade isopropyl alcohol, zero filters (2), carrying case, software on CD-ROM, computer cable, operation and service manual, calibration certificate, and one-year warranty

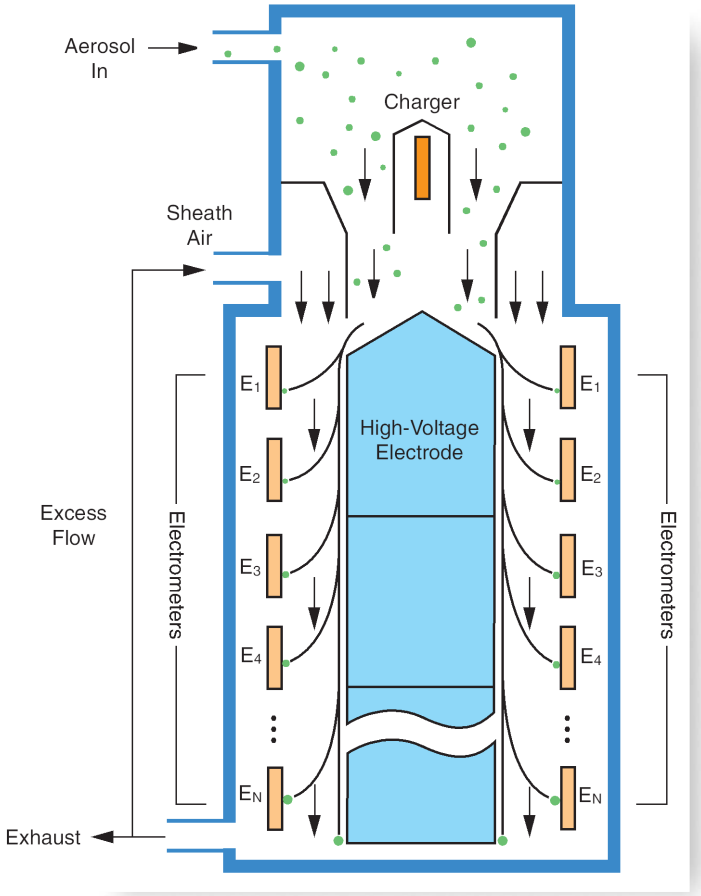


Figure 2. EEPS flow schematic

Differential mobility analyser

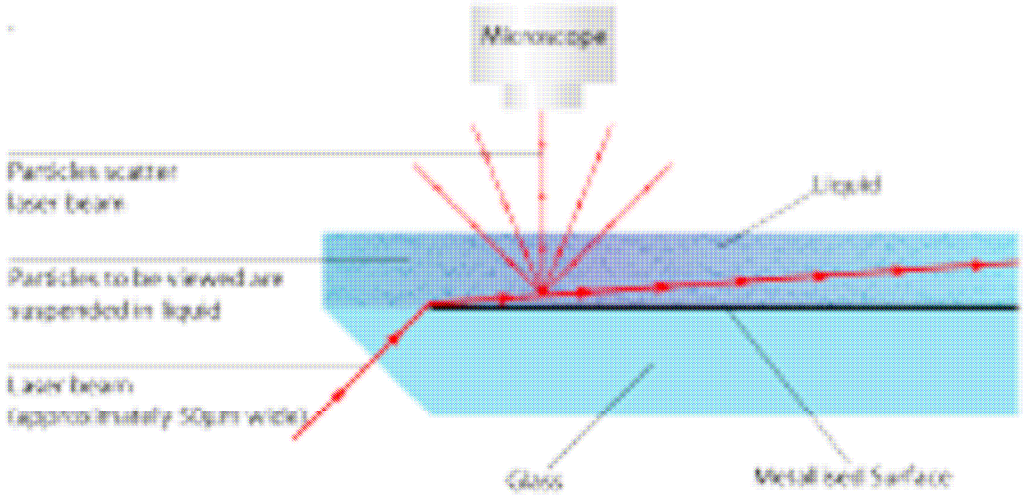
Particle Sizers (Malvern Instruments Zetasizer Nano ZS)

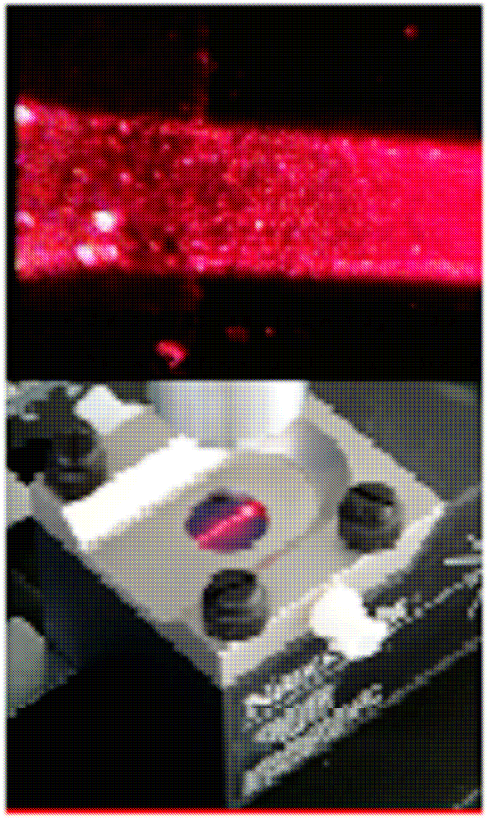
This instrument has a large size range (0.6nm upwards) and it measures zeta potential for particles from 3nm to 10 microns

It uses velocity measurement and light scattering.

Nanoparticle Tracking Technology

Uses Brownian motion velocity analysis to determine hydrodynamic diameter





Poly-ion deposition to create a charged collection surface

(Decher Science vol 277, 1232 (1997))

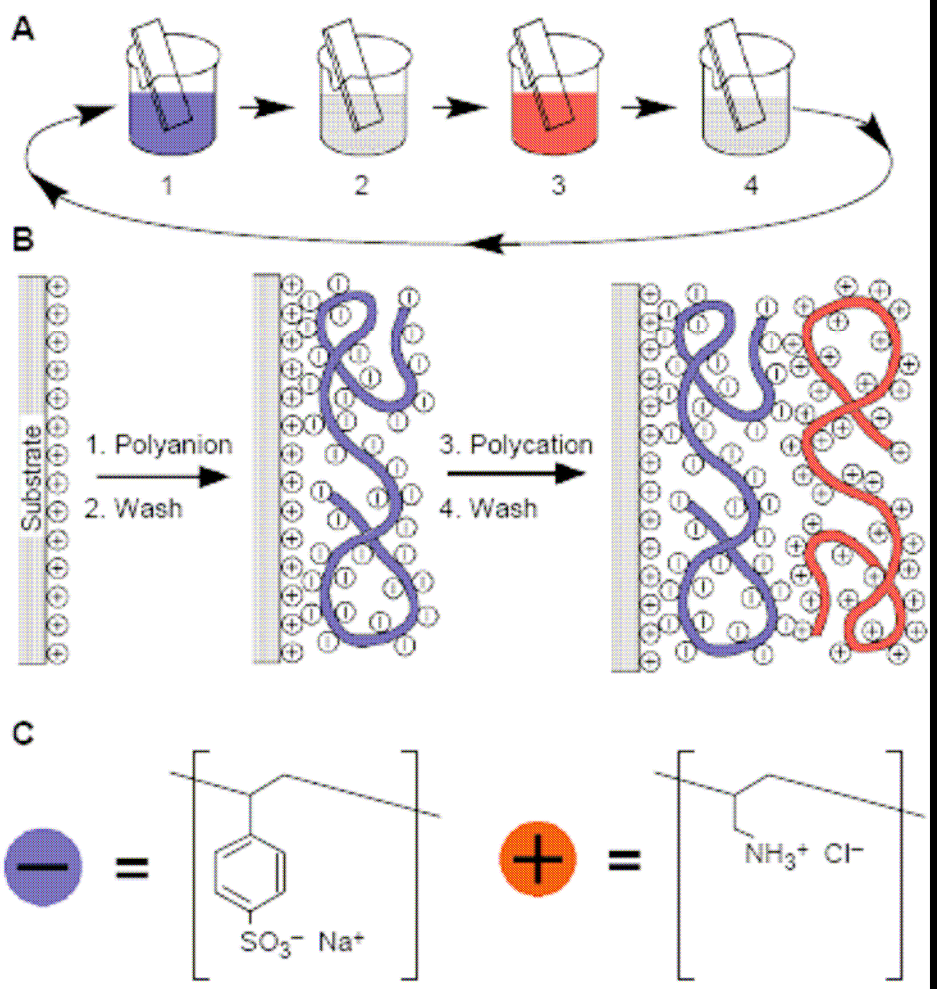
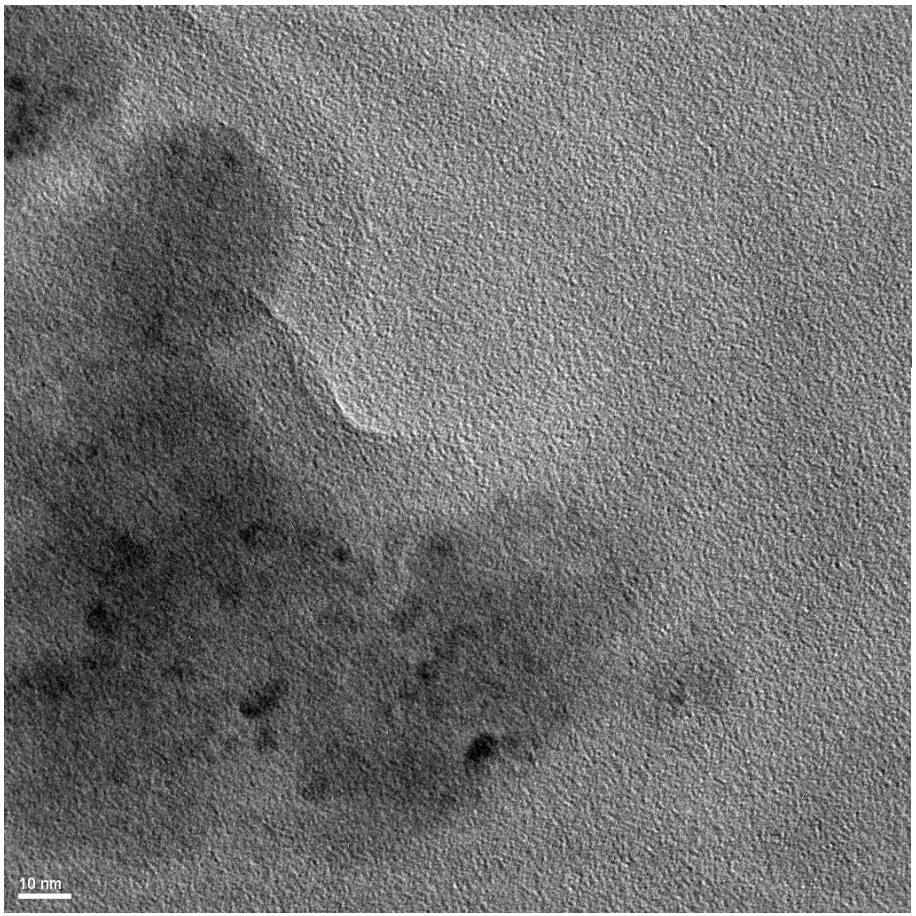


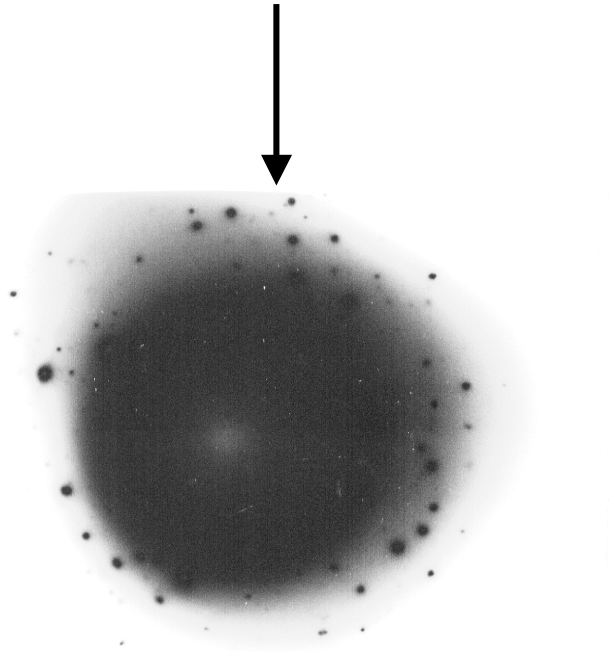
Fig. 1. (**A**) Schematic of the film deposition process using slides and beakers. Steps 1 and 3 represent the adsorption of a polyanion and polycation, respectively, and steps 2 and 4 are washing steps. The four steps are the basic buildup sequence for the simplest film architecture, $(A/B)_n$. The construction of more complex film architectures requires only additional beakers and a different deposition sequence. (**B**) Simplified molecular picture of the first two adsorption steps, depicting film deposition starting with a positively charged substrate. Counterions are omitted for clarity. The polyion conformation and layer interpenetration are an idealization of the surface charge reversal with each adsorption step. (**C**) Chemical structures of two typical polyions, the sodium salt of poly(styrene sulfonate) and poly(allylamine hydrochloride).

Particles from tap water

Ordinary tap water contains a lot of particles!



Diffraction pattern, seems to indicate calcite and other compounds?



Monica Ratoi 2007

Methods for Toxicology

- Animal tests are controversial and may not be good indicators for humans
- Need to develop high throughput in vitro tests on different cell types
- Preliminary indications are that it is difficult to test with nanoparticles because they agglomerate so readily.
- Dispersion of nanoparticles raises other issues: “does the dispersant change the particles’ toxicity?” “are dispersants safe?”

Assessment of nano-titania using dye photo-degradation

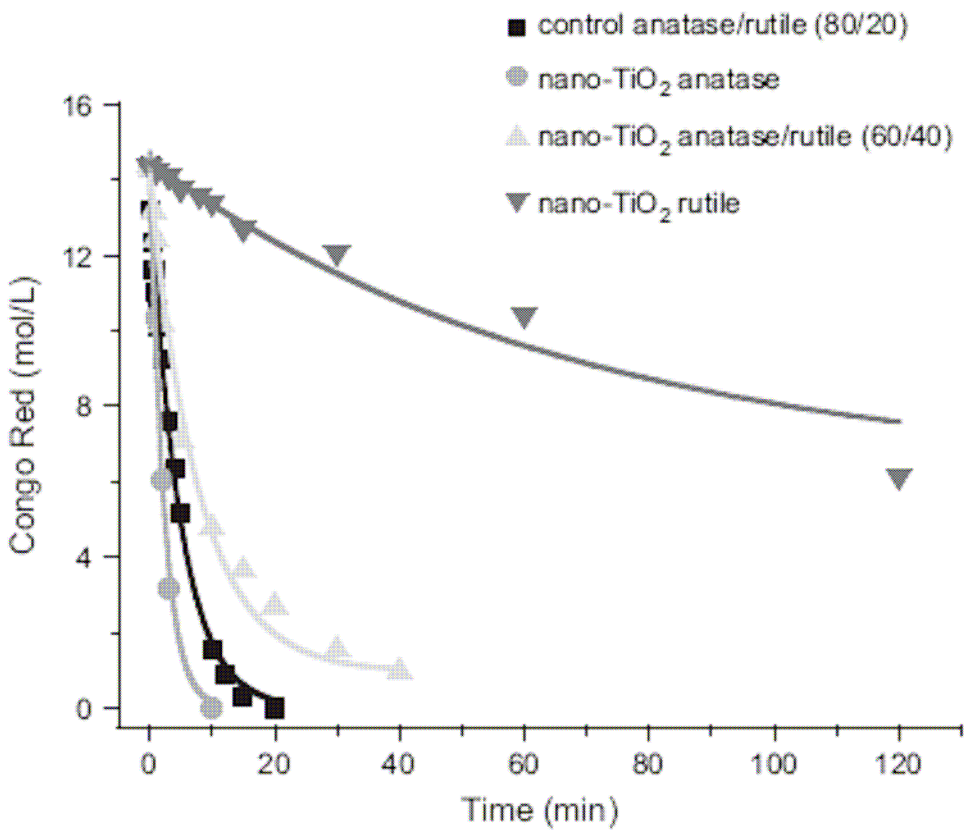


FIG. 8. Photodegradation of aqueous Congo red (10 mg/l, 14 μmol/l) in the presence of various nano-TiO_2 catalysts (1 g/l). Based on this plot, the per gram efficiencies of the TiO_2 powders increased in the order nano-TiO_2 rutile particles < nano-TiO_2 anatase/rutile particles < control anatase/rutile < nano-TiO_2 anatase particles.

We would expect Mn doped rutile to show further improvement

Sayes et al: Toxicological Sciences **92**, 174-185 (2006)

Further nano-titania studies showing superiority of rutile for reduced photo-activity

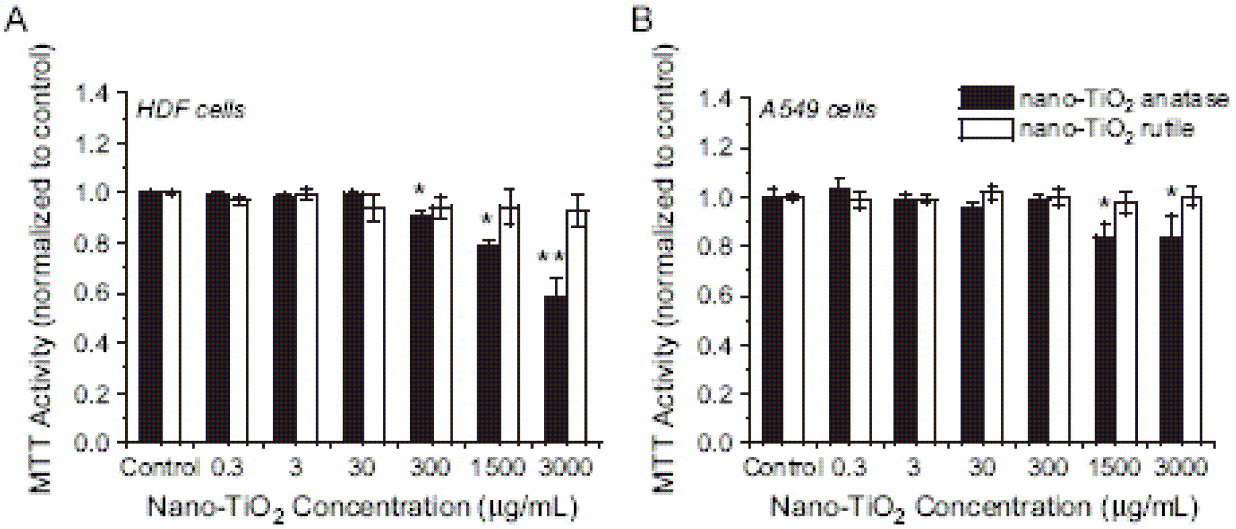
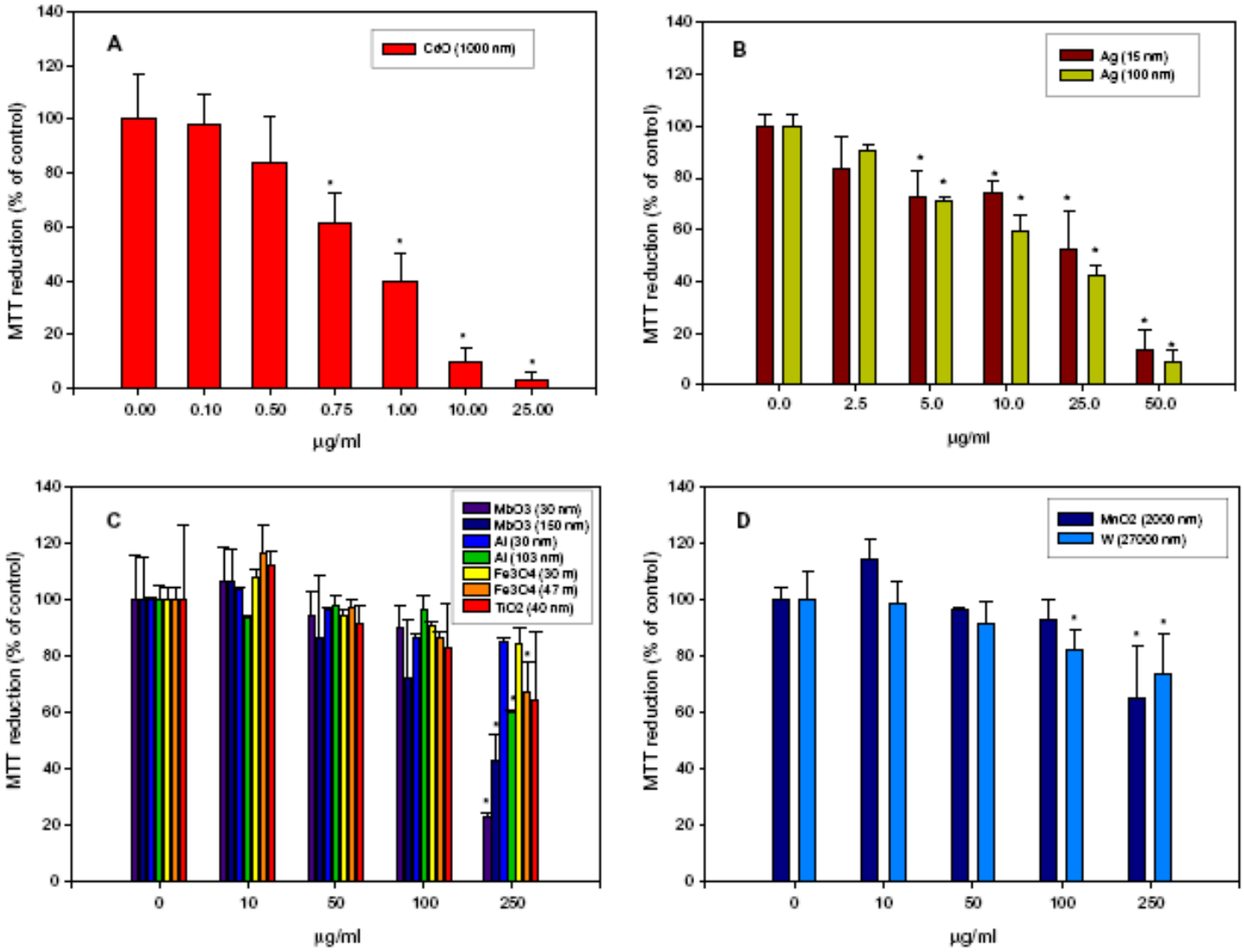


FIG. 5. The mitochondrial activity (MTT activity) of (A) HDF and (B) A549 cells after 48 h exposure to nanoscale TiO_2 anatase and rutile phases. Results are combined from three independent exposures. Groups significantly different from the control group (by ANOVA $p_{HDF} < 0.00231$ and $p_{A549} < 0.00197$ followed by Dunnett's test) are shown by $*p < 0.05$ or $**p < 0.01$).

Sayes et al: Toxicological Sciences **92**, 174-185 (2006)

Nanoparticle effect on mitochondrial function of rat cells



All types of np show harmful effects, but oxides are better than most.

Hussain et al: Toxicology in vitro **19**, 975-983 (2005)

Oxidative stress paradigm

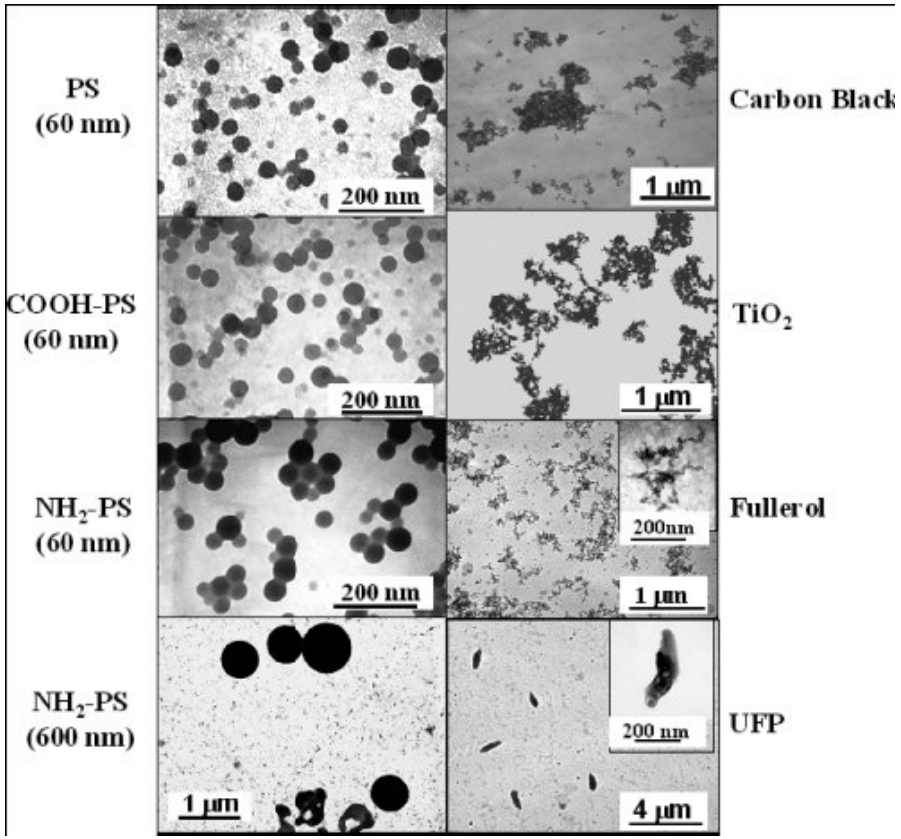


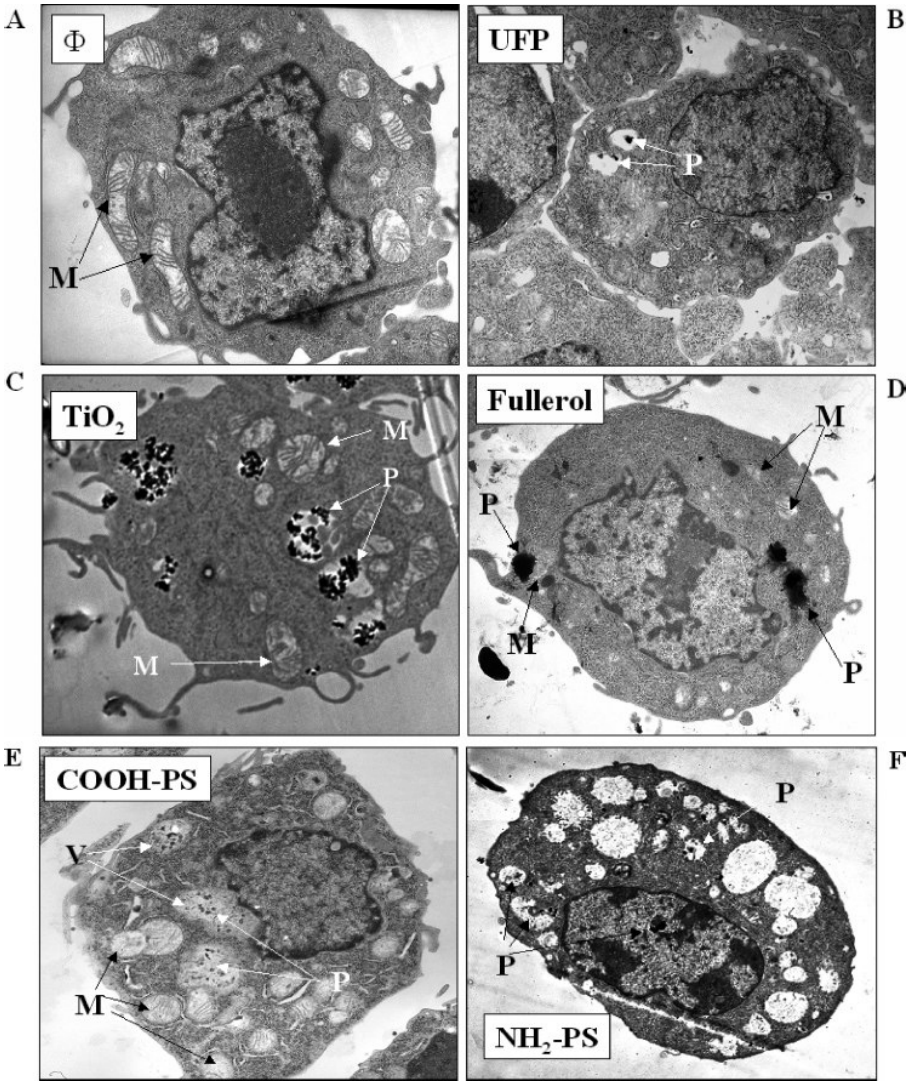
Table 1. Physical Characterization of Nanoparticles[a]

particle	av diameter (nm)	PDI	electrophoretic mobility U (μm cm/(V s))	zeta potential ζ (mV)	MATH (%)
		In Aqueous Media			
UFP	1034	1.0	−2.28	−29.1	8.2
PS	68	0.041	−2.85	−36.4	2.7
NH_2-$PS_{60\ nm}$	65	0.055	3.15	40.3	5.3
NH_2-$PS_{600\ nm}$	648	0.096	3.58	45.8	4.2
COOH-PS	56	0.063	−2.15	−27.6	0.0
TiO_2	364	0.466	−1.28	−16.4	1.6
carbon black	245	0.251	−4.26	−54.6	7.1
fullerol	218	0.388	−1.76	−22.6	0.6
		In Cell Culture Medium			
UFP	1778	0.379	−0.86	−11.0	
PS	90	0.200	−1.00	−12.7	
NH_2-$PS_{60\ nm}$	527	0.339	−0.87	−11.1	
NH_2-$PS_{600\ nm}$	1913	1.0	−0.96	−12.2	
COOH-PS	82	0.191	−0.85	−10.9	
TiO_2	175	0.877	−0.97	−12.4	
carbon black	154	0.278	−1.06	−13.5	
fullerol	106	0.700	−0.97	−12.4	

[a] The reported mean particle size (average diameter) is calculated based on an intensity weighted average; PDI = polydispersity index; MATH = microbial adhesion to hydrocarbon test.

Xia et al: Nano Letters **6**, 1794-1807 (2006)

Up-take of NPs in Cells



This is an important area, and it is important to see the effect the cell has on the NP

Xia et al: Nano Letters **6**, 1794-1807 (2006)

Impact over life cycle

- Evaluate hazards and risks in production and manufacture
- Evaluate hazards and risks during use of product
- End-of-life aspects: recycling, incineration, landfill?

A good example of this is vehicle tyres: they are composed of very fine carbon black and silica, with many chemical additives.

Fine particles are shed through use, and recycling is very difficult in terms of recovery of safe useful products.

Predictive models

- Can we use the data collected on engineered nanoparticles to predict their impact?
- Can we predict the transport and fate of particles released into the environment?
- Can we predict the effect of nanoparticles introduced into the body? (eg: also for drug release)
- Does the environment modify nanoparticles?

Some references to follow up

http://www.greenpeace.org.uk/MultimediaFiles/Live/FullReport/5886.pdf
http://www.etcgroup.org/en/materials/publications.html?pub_id=171
http://www.nanosafe.org/
http://www.safenano.org/
http://www.nanotechproject.org/
http://www.royalsoc.ac.uk/landing.asp?id=1210
http://www.nano.org.uk/
http://es.epa.gov/ncer/nano/
http://nihroadmap.nih.gov/nanomedicine/
http://circ.ahajournals.org/cgi/content/full/circulationaha;105/4/411
http://transaq.ce.gatech.edu/epatac/documents/kittelsn.pdf

And the references on the slides!