OHSI 26th Annual Conference
"Made to Measure"

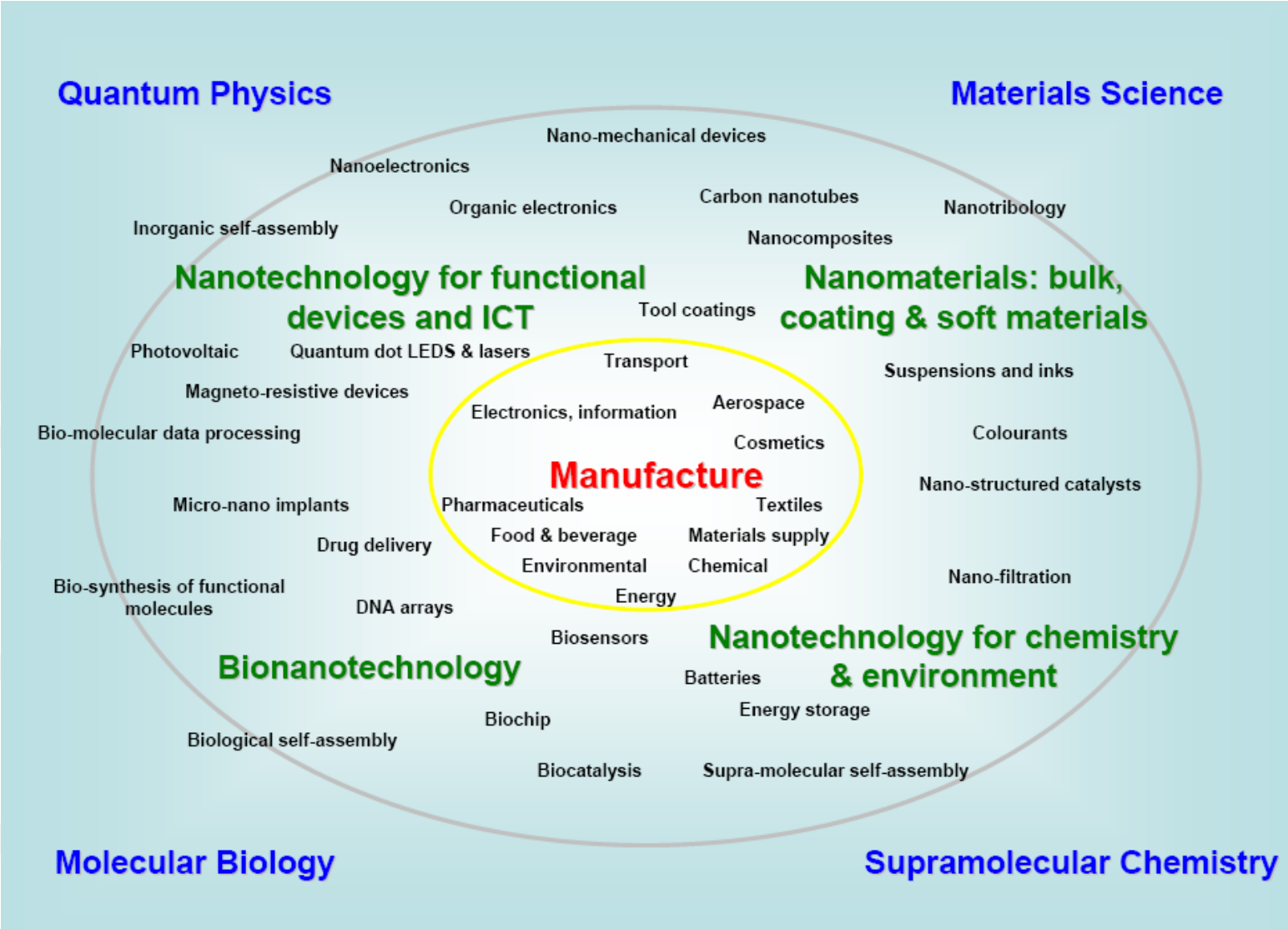
IOM
WORKING FOR A HEALTHIER FUTURE

A Primer on Nanotechnology, Nanoparticles and their Measurement

Dr Steve Hankin

SAFENANO

Nanotechnology as an *enabling* science



Nanotechnology & Nanoparticles

Nanotechnology is the application of scientific knowledge to manipulate and control matter in the *nanoscale* in order to make use of size- and structure-dependent properties and phenomena, as distinct from those associated with individual atoms or molecules or with bulk materials.

Nanoscale = size range from approximately 1nm to 100nm

Nanoparticle = nano-object with all three external dimensions in the nanoscale

Nano-object = material with one, two or three external dimensions in the nanoscale

ISO/TS 80004-1:2010 Nanotechnologies – Vocabulary - Part 1: Core terms

Mitigating risk is needed to ensure the sustainability of nanotechnology

IOM

commentary

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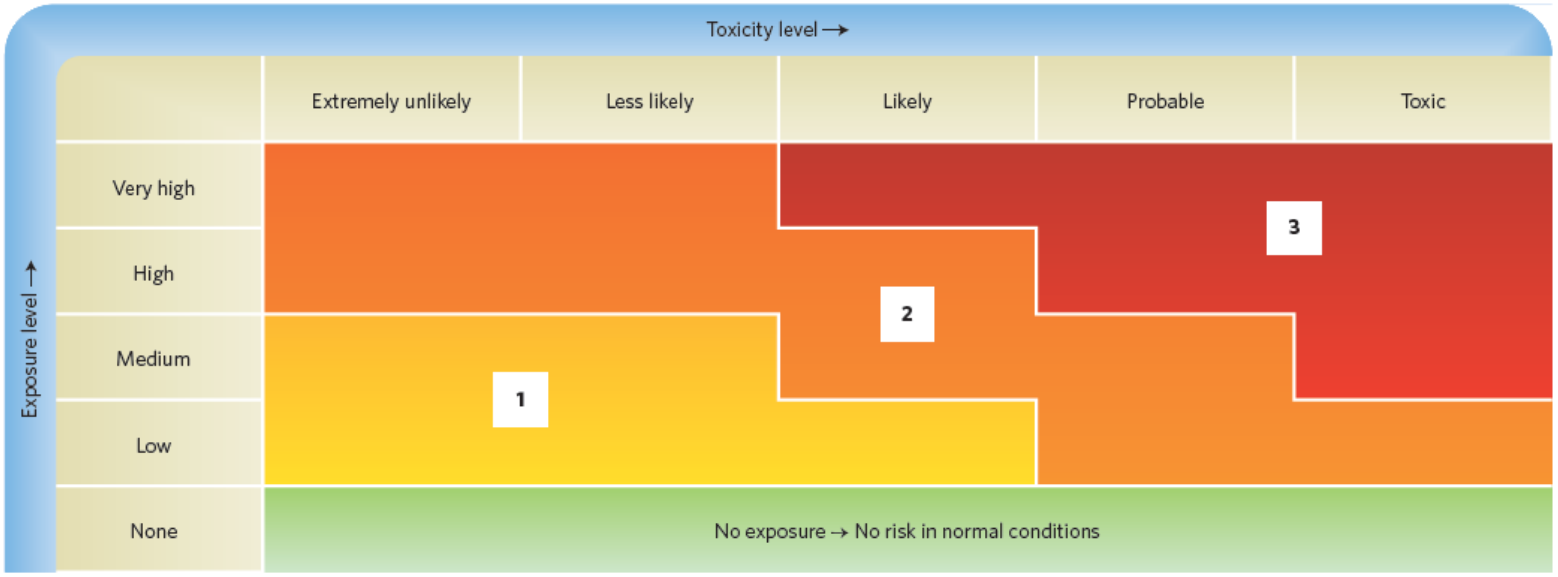
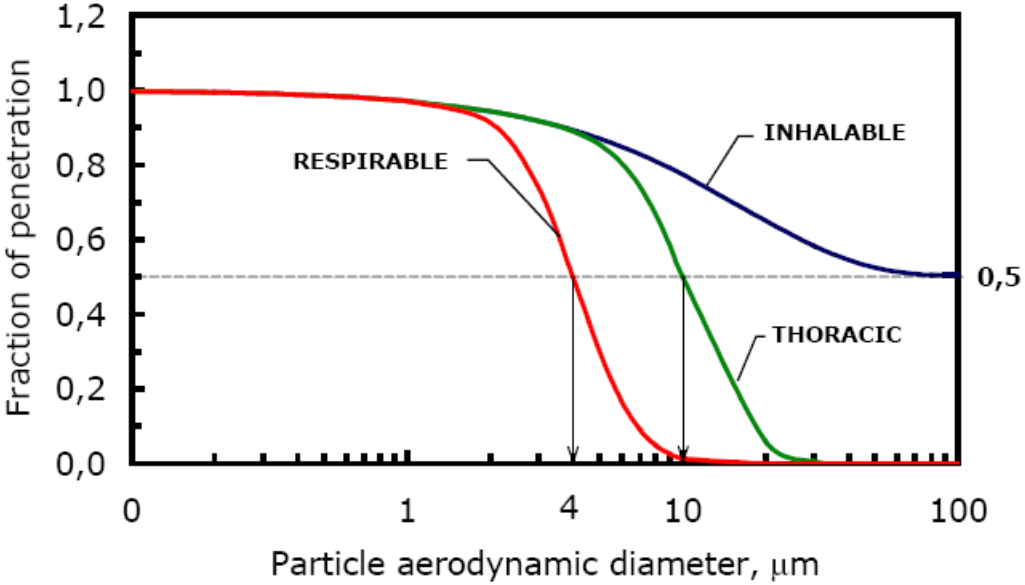
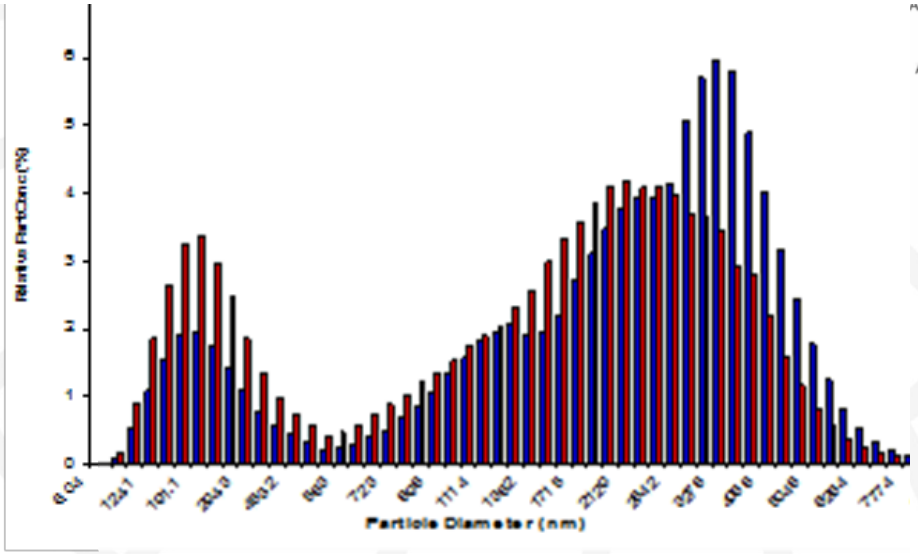
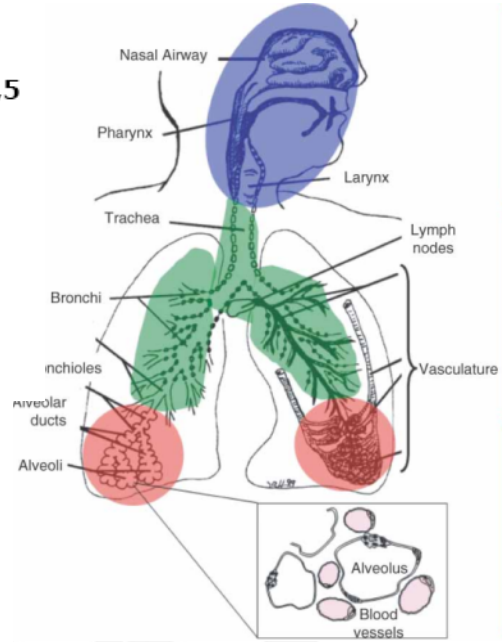


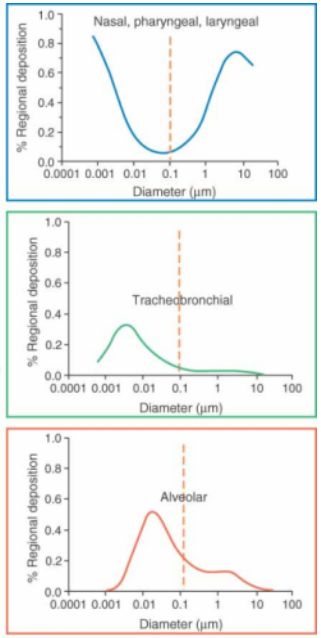
Risk level	Situation	Underwriting decision
1 (low)	Acceptable	Insurable
2 (moderate)	To be improved	Insurable subject to extra precautionary measures taken to manage worker's exposure to nanomaterials. This may include adherence to standard operating procedures to reduce exposure or chemical coating to reduce the toxicity (if applicable). Another alternative would be to adjust the contract wording to limit exposure to a claims made basis only (the occurence has to take place during the insured period thus eliminating long-tailed risk).
3 (high)	Unacceptable	Uninsurable

Being safe with nanotechnology is <u>not just</u> about nano-sized particles…









Nanotechnology world

in association with NANO Channels

Is nanotechnology safe in the workplace?

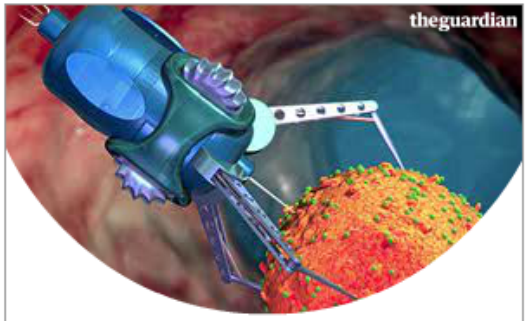
As an increasing number of products which use nanotechnology begin appearing on the market, how can we ensure the workers who make them are protected from the possible risks of working with such minuscule materials?

Duncan Graham-Rowe
guardian.co.uk, Tuesday 14 February 2012 00.01 GMT

More on this site

Live debate: How nanotechnology is prolonging life
Don't miss your chance to join a live streamed debate on 31 January
4 comments

The holy grail of molecule -making



The scale may be small, but the implications are enormous

Alok Jha on nanotechnology

Alok Jha is the Guardian's science correspondent. These are his tweets on the subject of nanotechnology

alokjha: Ever wondered how #nanotech might help prolong life? Live at 3pm TODAY, debate feat @markmiodownik + others http://t.co/wwQsZqLB #debatenano
about 2 weeks, 1 day ago

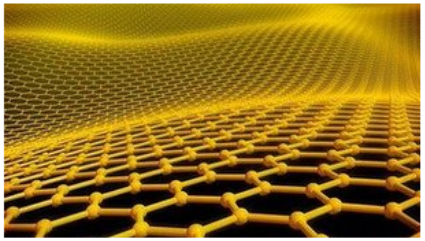
alokjha: Live debate next week: How nanotechnology is prolonging life http://t.co/wwQsZqLB feat @markmiodownik and chaired by me #debatenano
about 2 weeks, 5 days ago

alokjha: Small scale, massive impact: live nanotechnology Q&A with @markmiodownik on Thurs Dec 15 - post your questions http://t.co/2JW705OC
about 2 months ago

20 February 2012 Last updated at 00:46

Graphene 'could pose health risk' to workers

People involved in making a material used to enhance computer and phone touch screens could be at risk of lung damage, according to new research.



Graphene has been heralded as a revolutionary material and is used in touch screen technology

Scientists at the University of Edinburgh have been studying the behaviour of the so-called miracle material, graphene.

They say, when produced in a certain form, the ultra-thin carbon contains tiny particles known as nanoplatelets.

These can lodge in the lungs and may cause health problems, the study found.

Graphene, first identified in 2004, has been hailed a revolutionary material and heralded for its superconductive properties.

The flexibility of these disc-shaped particles, known as nanoplatelets, allows them to be readily incorporated into plastic and rubber, giving them new and useful properties.

They can also be used to enhance the electronic properties of touch screens.

The Edinburgh scientists found that the nanoplatelets, which are less than one carbon atom thick and invisible to the naked eye, behave like tiny frisbees and stay airborne.

But the researchers said their aerodynamic properties also mean that when inhaled, they can find their way deeper into the lungs compared with other forms of graphene.

The scientists said the particles could accumulate in the lungs and cause damage.

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More uses for 'miracle material'

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UK invests in graphene technology

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“There are *known knowns*; there are things we know we know.

We also know there are *known unknowns*; that is to say we know there are some things we do not know.

But there are also *unknown unknowns* – the ones we don't know we don't know.”

Narrowing-down what and how to characterise

- Regulation
- Standards
- Guidance
- Reference materials
- Protocols

What are p-c properties and which need to be characterised?

Characterization (Off-line)	Human exposure	Toxicity Screening Studies		
		Supplied material	Administered material	Material *in vivo*/*in vitro*
Size distribution (primary particles)	E (Combine with agglomeration state)	E	D	D
Shape	E	E	O	O
Surface area	D	E	D	O
Composition	E	E	O	O
Surface chemistry	D	E	D	D/O
Surface contamination	D	N	D	N
Surface charge – suspension/solution	O	E	E	O
Surface charge – powder (use bio fluid surrogate)	O	E	N	O
Crystal structure	O	E	O	O
Particle physicochemical structure	E	E	D	D
Agglomeration state	E	N	E	D
Porosity	D	D	N	N
Method of production	E	E	--	--
Preparation process	--	--	E	--
Heterogeneity	D	E	E	D
Prior storage of material	E	E	E	--
Concentration	E	--	E	D

E: These characterizations are considered to be essential.
D: These characterizations are considered to provide valuable information, but are not recommended as essential due to constraints associated with complexity, cost and availability.
O: These characterizations are considered to provide valuable but non-essential information.
N: These characterizations are not considered to be of significant value to screening studies.

Source: “Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy”; Particle and Fibre Toxicology 2005, 2:8

Properties & Measurement Techniques

Engineered Nanoparticles: Review of Health and Environmental Safety

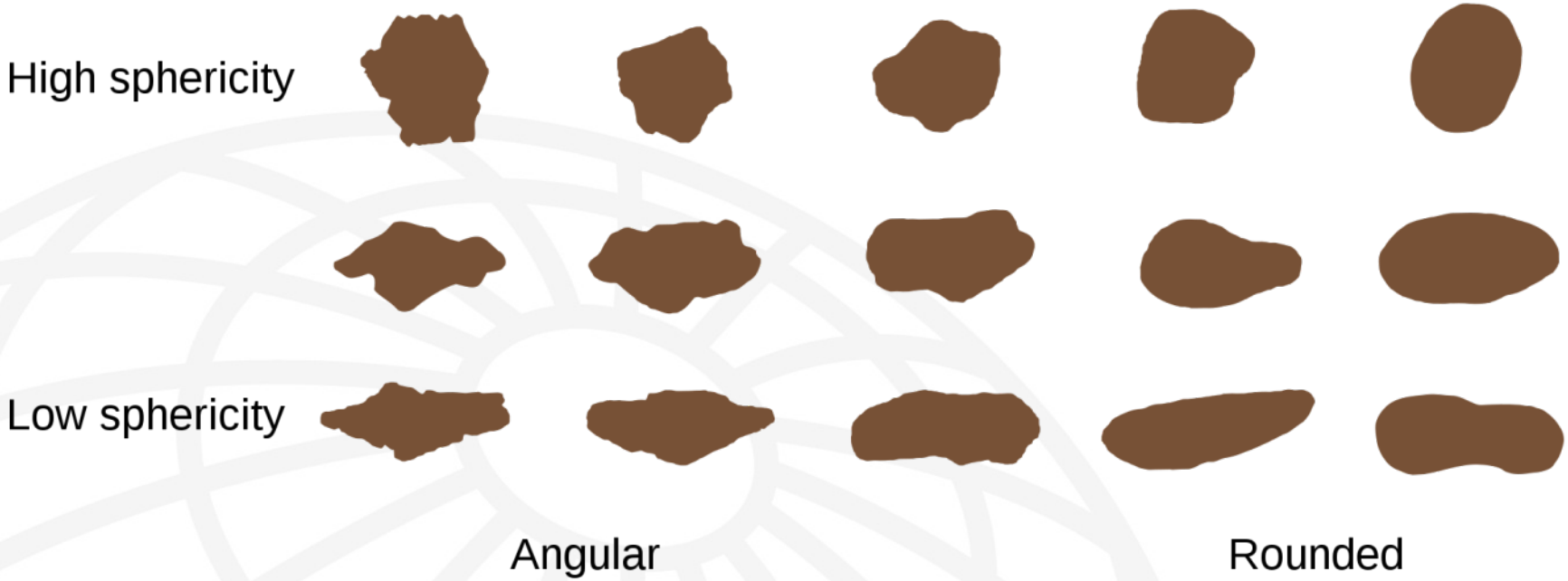
Table 3.1 Overview of techniques for the characterisation of key physico-chemical properties of nanoparticles (adapted from Zuin *et al.* 2007)

	Nanoparticle attribute										
Technique / Instrument	*Mass*	*Number*	*Size distribution*	*Shape*	*Aggregation state*	*Surface area*	*Chemical composition*	*Purity*	*Surface chemistry*	*Surface charge*	*Crystal structure*
Scanning Electron Microscopy		✓ A B bm	✓ A B bm	✓✓ A B bm	✓✓ A B bm						✓ A
Transmission Electron Microscopy		✓ A B bm	✓ A B bm	✓✓ A B bm	✓✓ A B bm						✓ A
Scanning Probe Microscopy (AFM, STM)		✓ A B bm	✓ A B bm	✓✓ A B bm	✓✓ A B bm						
Tapered Element Oscillating Microbalance (TEOM)	✓✓ A										
Differential Interference Contrast Microscopy Confocal Laser Scanning Microscopy Fluorescence Microscopy			bm	bm	bm						
Differential Mobility Analyser Condensation Particle Counter		✓✓ A	A								
Dynamic Light Scattering			✓✓ A B								
Scanning Mobility Particle Sizer Electrical Low Pressure Impactors	✓ A	✓✓ A	✓✓ A			✓ A					
Epiphaniometer (diffusion charging)						✓ A					
BET Adsorption Measurement			✓			✓✓					
Zeta Potential Analysis										✓✓ B	
Thermogravimetric Analysis Differential Scanning Calorimetry							✓	✓	✓		✓
Flow Field Flow Fractionation			✓✓ B bm		✓ B bm		✓ B bm		✓ B bm		
X-ray Diffraction							✓				✓✓ A
Auger Electron Spectroscopy							✓✓		✓		
X-ray Photoelectron Spectroscopy							✓	✓	✓✓		
FT-IR Spectroscopy							✓	✓	✓		✓
UV-vis Spectroscopy			✓				✓ B	✓	✓✓		
Raman Spectroscopy							✓	✓	✓		✓
NMR Spectroscopy					✓✓		✓✓		✓✓		✓
Electron Spin Resonance							✓ B bm		✓ bm		✓ bm
Aerosol TOF-MS		✓ A	✓ A				✓ A	A			
Secondary Ion Mass Spectrometry							✓✓ bm				
ICP-MS Atomic Absorption / Optical Emmision Spectroscopy							✓✓ A B bm				
High Performance Liquid Chromatography Gel Permeation Chromatography			✓ B bm				✓ bm		✓ bm		

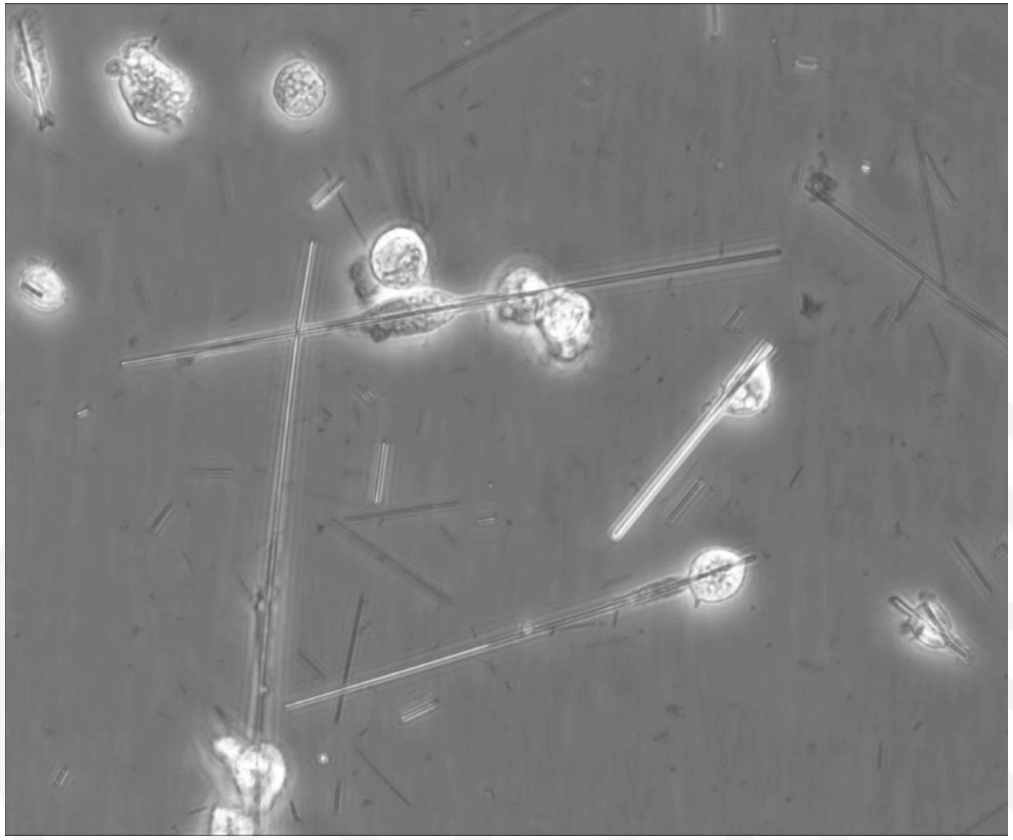
Highly applicable (✓✓) or applicable (✓) for characterising **as-supplied** nanoparticles; applicable for characterising **administered** nanoparticles as a suspension in aerosol (**A**) or in biological fluid (**B**); applicable for **after-administration** characterisation in biological matrices (**bm**).

ENRHES report available from: **http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report**

How do we describe particle shape?



High Aspect Particles - a problem for the lungs



Thin

Small aerodynamic diameter enables deposition beyond the ciliated airways

Bio-persistent

Retains its long term shape over long-term residence in the lungs

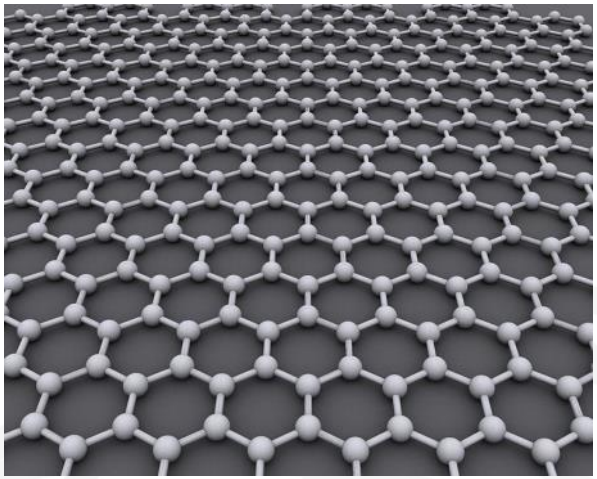
Long

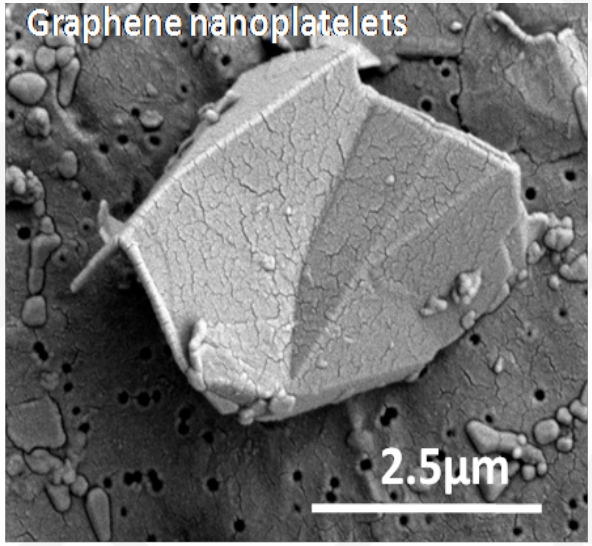
Cannot be completely enclosed by a macrophages producing frustrated phagocytosis

Longer than 15-20µm

High Aspect represents an attribute conveying enhanced toxicity to a particle due to the physical hindrance of normal clearance from the deep lung and interaction with cells

The safety 'anomaly' with plate-like nanomaterials



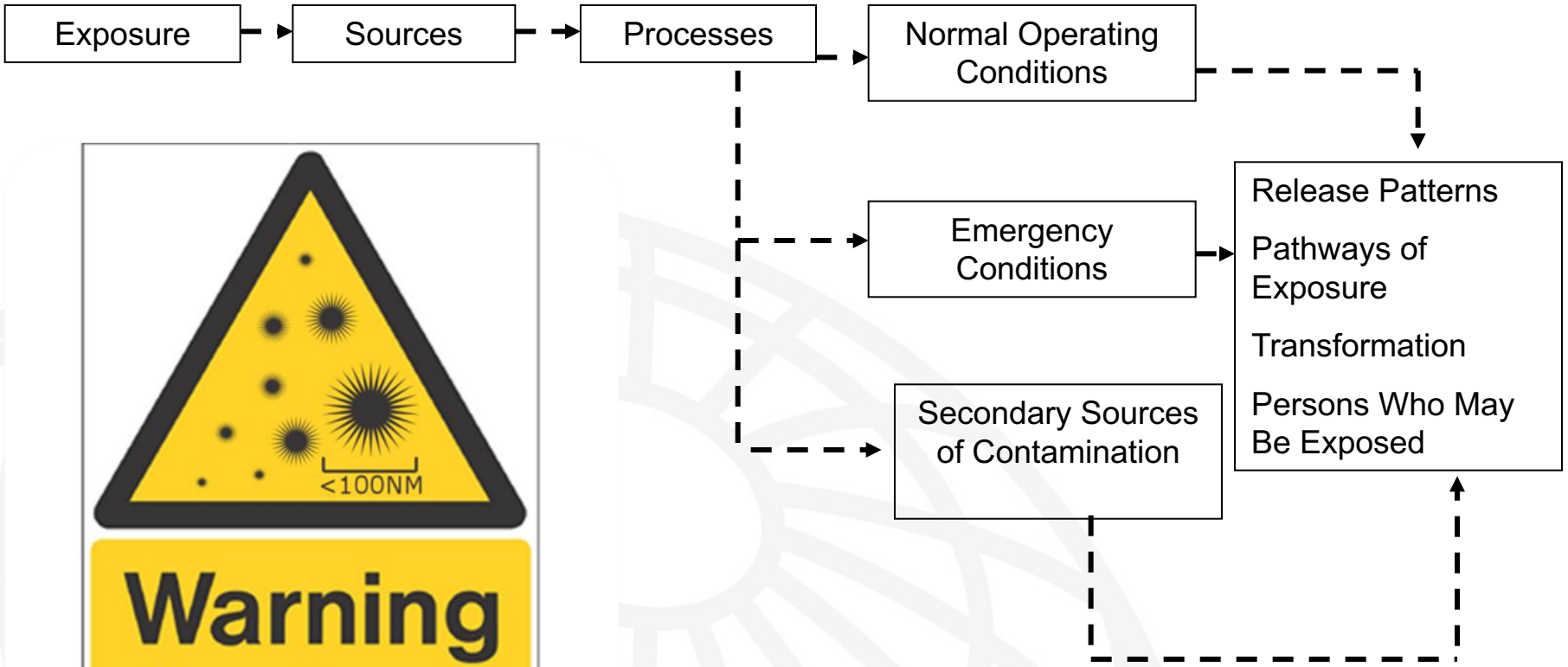


- Sheet-like plates of material ranging in depth from a single atom thick (graphene) but a diameter up to tens of microns
- Low aerodynamic diameter which could allow alveolar deposition
- Problems for cell mediated clearance should it deposit in the alveolar region

Projected area diameter d_{proj} [µm]	Thickness t [µm]	Aerodynamic diameter d_{ae} [µm]
5	0.01	**0.42**
10	0.01	**0.59**
15	0.01	**0.73**
20	0.01	**0.84**
5	0.1	**1.33**
10	0.1	**1.88**
15	0.1	**2.30**
20	0.1	**2.66**
25	0.1	**2.97**

Schinwald et al. ACS Nano. 2012 Jan 24;6(1):736-46.

Exposure assessment



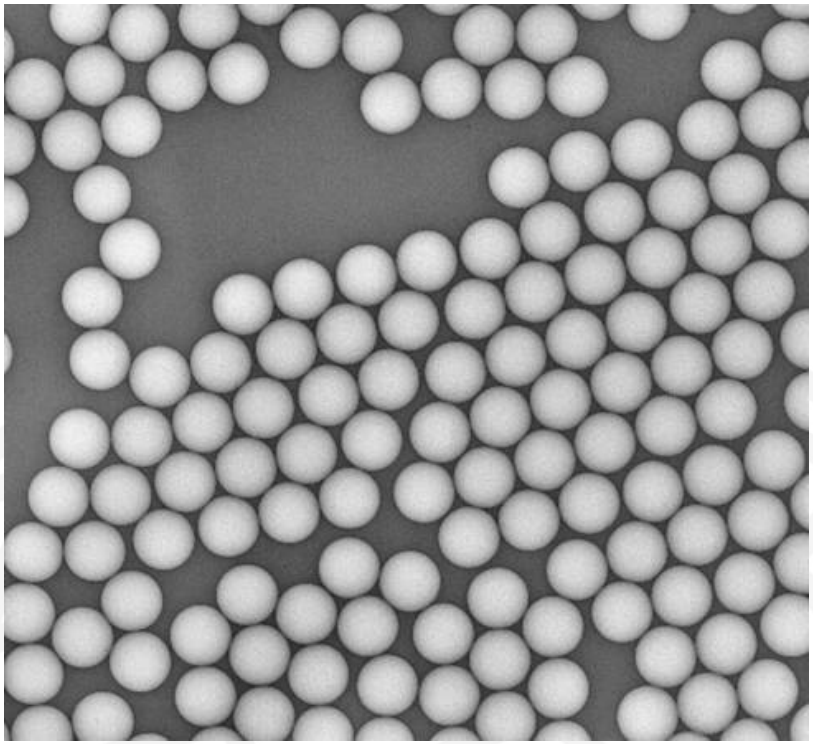
Key Standards & Guidance for NP Measurement & Sampling

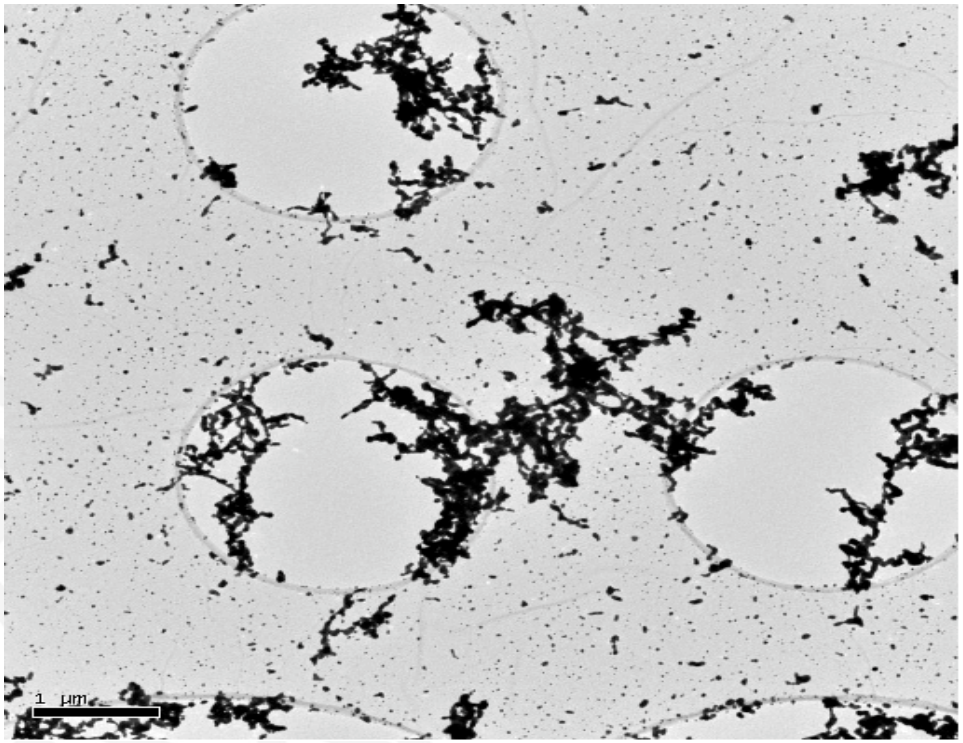
- ISO 7708:1995 Air quality -- Particle size fraction definitions for health-related sampling
- BS EN 1540:2011 Workplace Exposure – Terminology

- BS PD6699-3:2010 Part 3: Guide to assessing airborne exposures
- ISO/TR 27628:2007 Workplace atmospheres -- Ultrafine, nanoparticle and nano-structured aerosols -- Inhalation exposure characterization and assessment
- ISO/TS 12901-1 Occupational risk management applied to engineered nanomaterials

- MDHS 14/3 General methods for sampling
- NIOSH NEAT method
- OECD ENV/JM/MONO(2015)19 - Harmonized tiered approach to measure and assess the potential exposure to airborne emissions of engineered nano-objects and their agglomerates and aggregates at workplaces

Measuring particles is easy, isn't it?

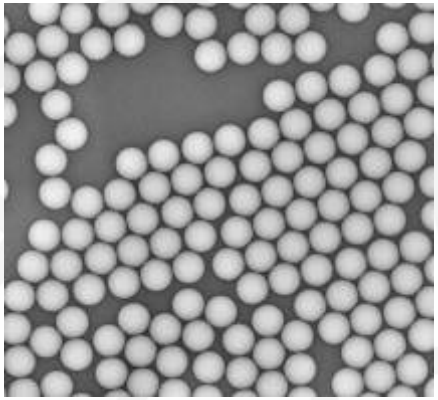


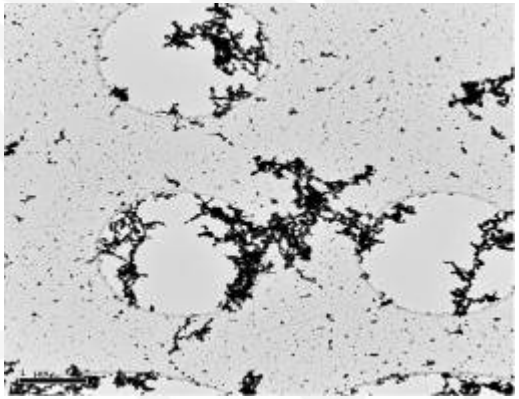


A variety of metrics can be used
but are they meaningful for risk assessment?

What metrics can be used for exposure?

- Particle concentration per unit volume
- Conventionally mass metric – mg/m^3
- Particle / fibres number metric – n/m^3
- Now surface area metric is useful
- But,
  - conversion between metrics is not simple
  - is a particular size limit or size fraction important?
  - particle morphology may present challenges to measurement…





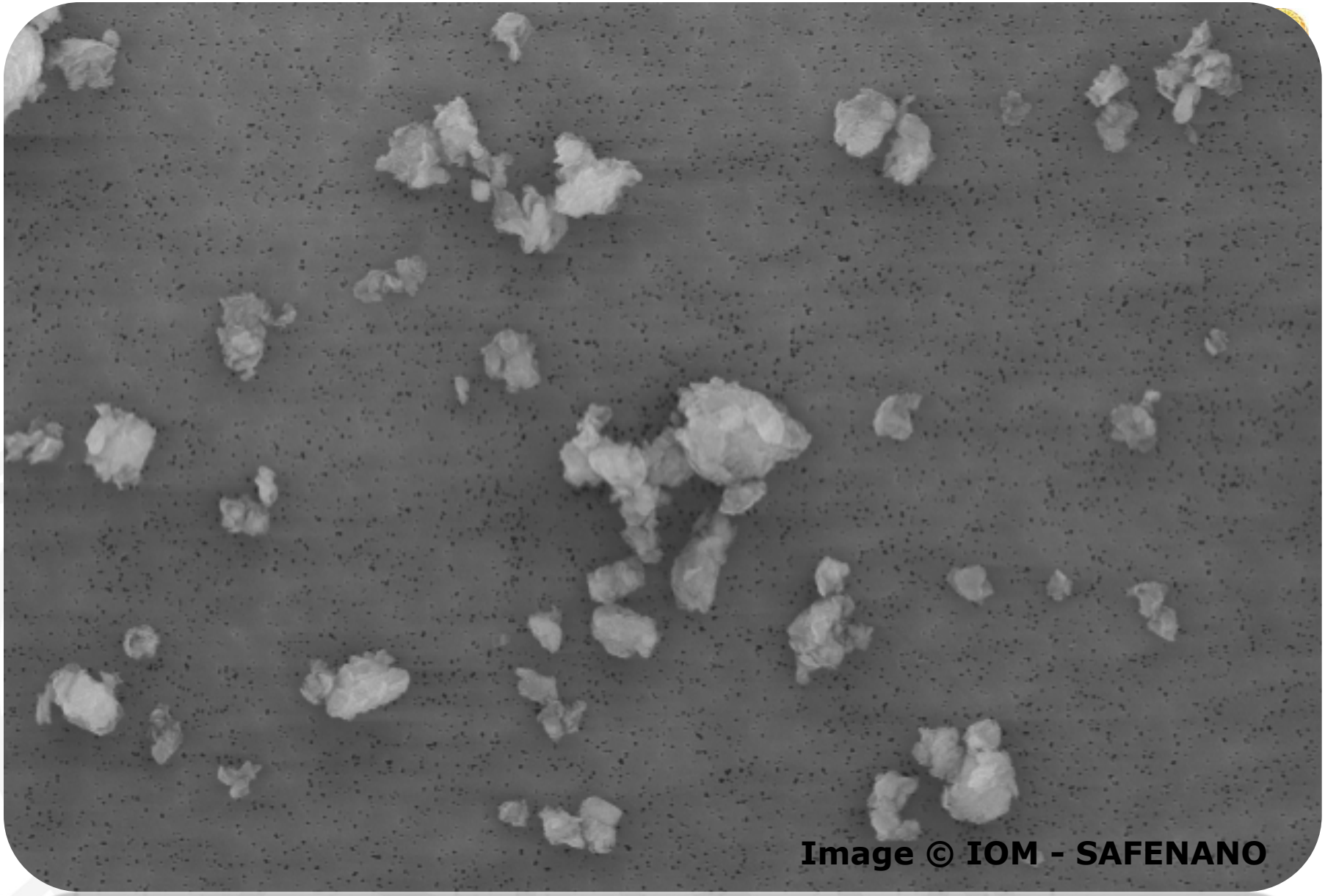
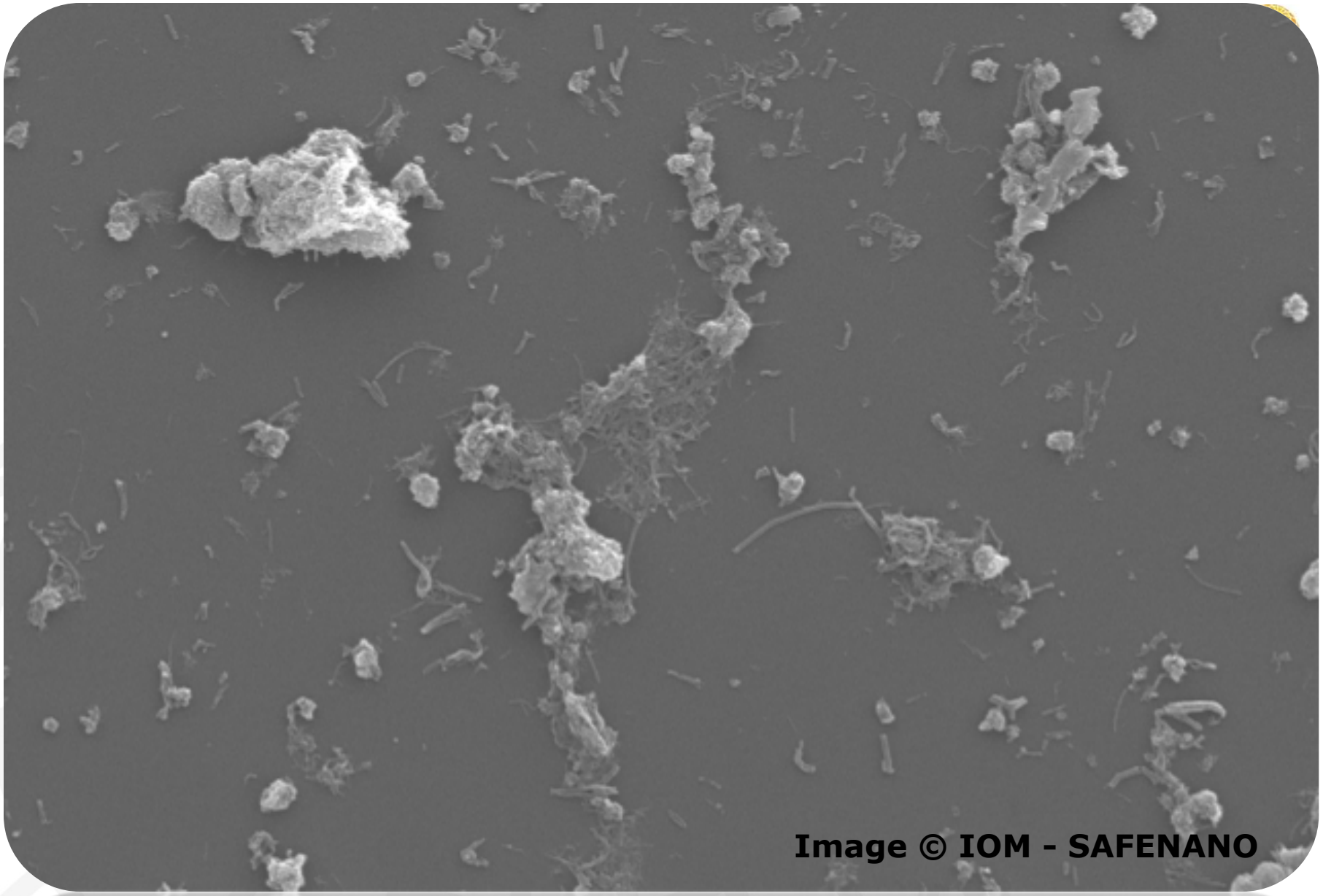


Image © IOM - SAFENANO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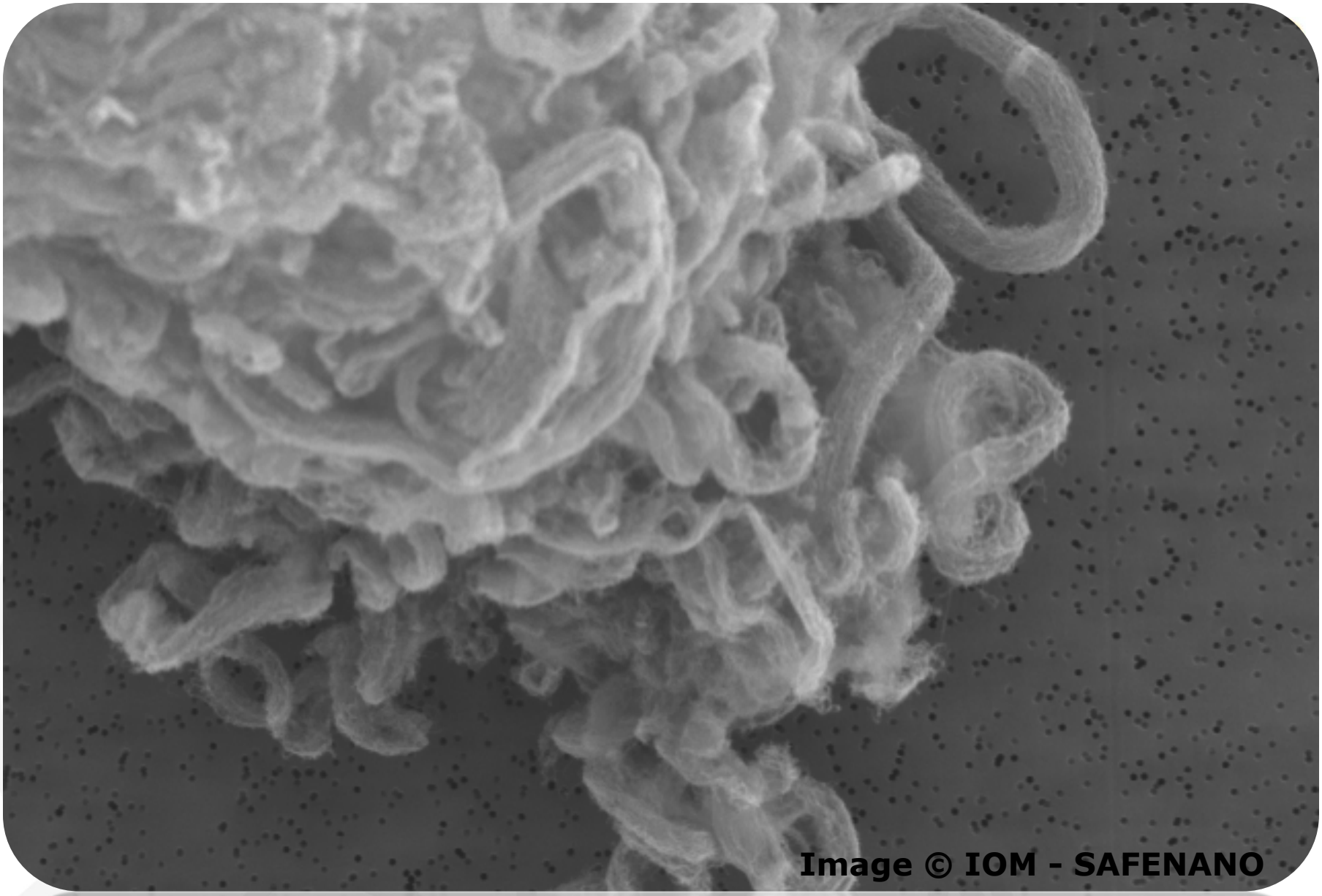
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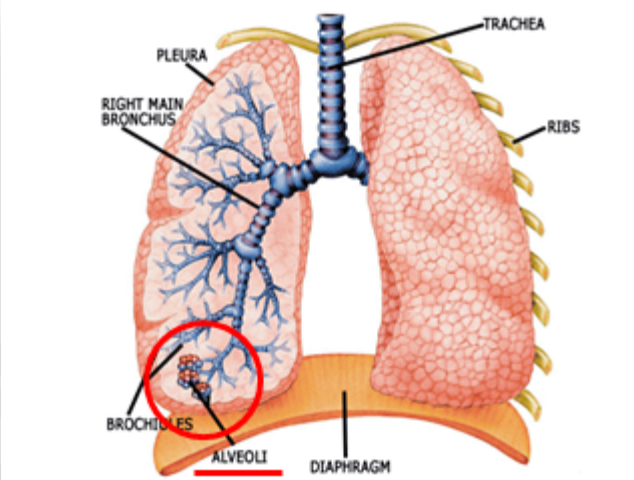
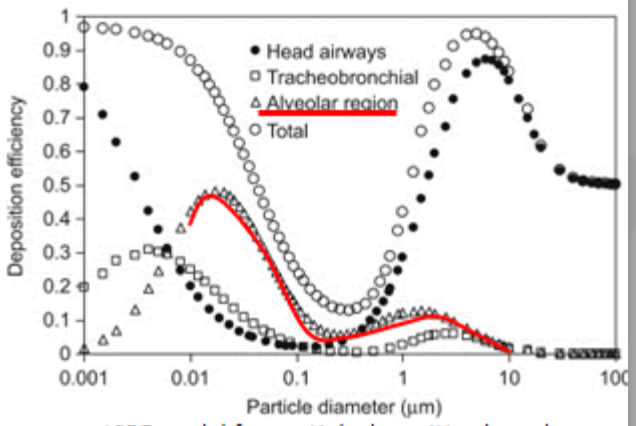
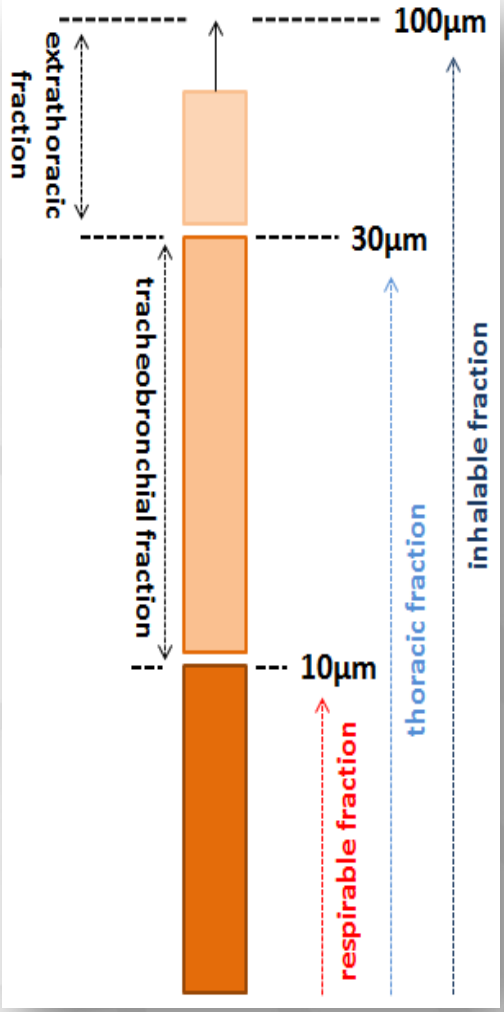
Particle Release & Exposure Assessment: Real-time Measurement Instruments





ICRP model for particle deposition based on aerodynamic equivalent diameter



What methods are available?

		number	mass	Surface area	size
Condensation Particle Counter*	**CPC**				
Optical Particle Counter	OPC				
Size Selective Personal Sampler*	**SSPS**				
Size Selective Static Sampler*	**SSSS**				
Time-of-flight spectrometer*	**TOF**				
Tapered Element Oscillation Microbalance	TEOM				
Diffusion Charger*	**DC**				
Scanning / **Fast Mobility Particle Sizer***	SMPS **FMPS**				
Electrical Low Pressure Impactor	ELPI				
Electron Microscopy (SEM*, TEM**)**	**EM**				

*Methods available from SAFENANO

Condensation Particle Counters

Our hand-held Condensation Particle Counters (CPC) provides **real-time high-sensitivity detection of particles from 10 nm to >1 µm** over a concentration range of 1 to 100,000 particles / cm^3, at a rate as fast as 1 measurement per second **for rapidly changing situations**.

Fast Mobility Particle Sizer

Our Fast Mobility Particle Sizer (FMPS™) spectrometer measures particles in the range from 5.6 to 560 nm, offering a total of 32 channels of resolution (16 channels per decade)., producing **particle-size-distribution measurements with one-second resolution**, providing the ability to visualise particle events and changes in particle size distribution in real time.

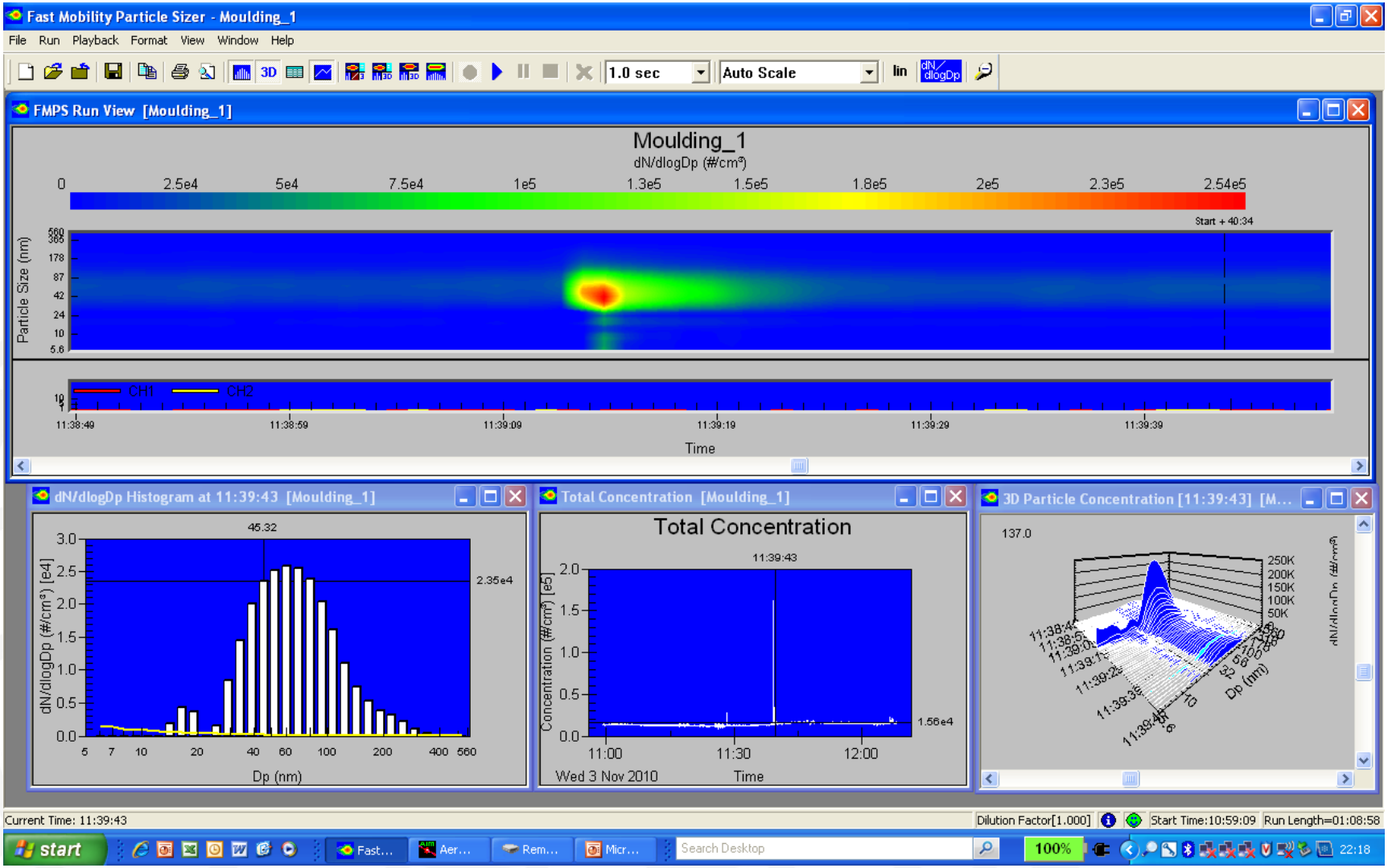
Aerodynamic Particle Sizer

Our Aerodynamic Particle Sizer (APS) spectrometer provides high-resolution, **real-time aerodynamic size measurements of particles** from 0.5 to 20 µm. Aerodynamic diameter is the most significant aerosol size parameter because it determines the particle's behaviour while airborne. Knowledge of a particle's aerodynamic diameter allows you to determine if and where the particle will be deposited in the human respiratory tract and how long the particle will remain airborne in the atmosphere or in an aerosol.

DustTrak Personal Aerosol Monitors

Our DUSTTRAK Aerosol Monitors provide real-time **aerosol mass concentration** simultaneously for PM1, PM2.5, Respirable, PM10 and Total particulate.

Example FMPS data



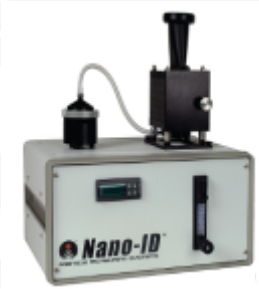
Particle Release and Exposure Assessment: Particle Sampling

IOM Sampler

0 - 100µm AED

Measurement of total inhalable particle mass.

Additional chemical analysis by ICP if required.

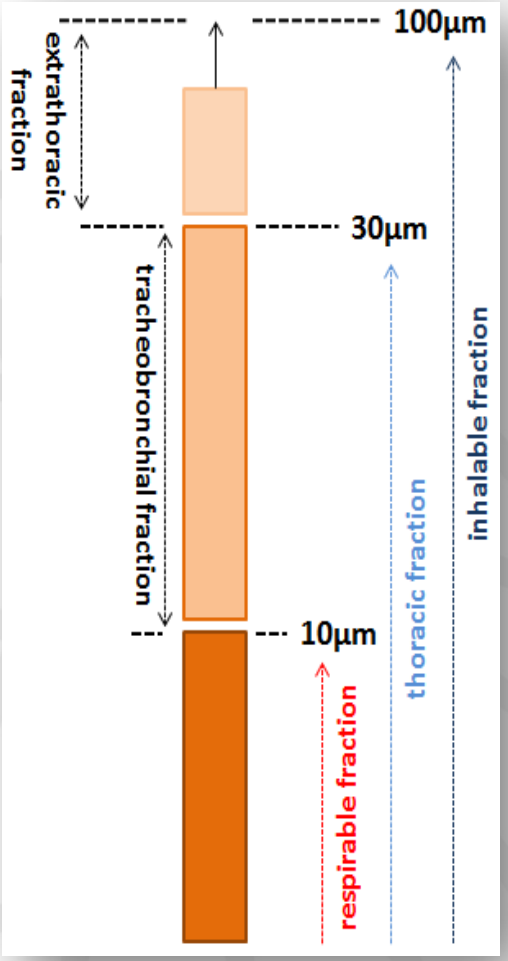


Nano-ID

0 - 35µm AED

Size-fractionated sampling on 7-stages.

Analysis by SEM / EDXS



Respirable Cyclone

d_{50}<4µm AED

Analysis by SEM / EDXS

Cowl Head

Non-size selective particle sampling.

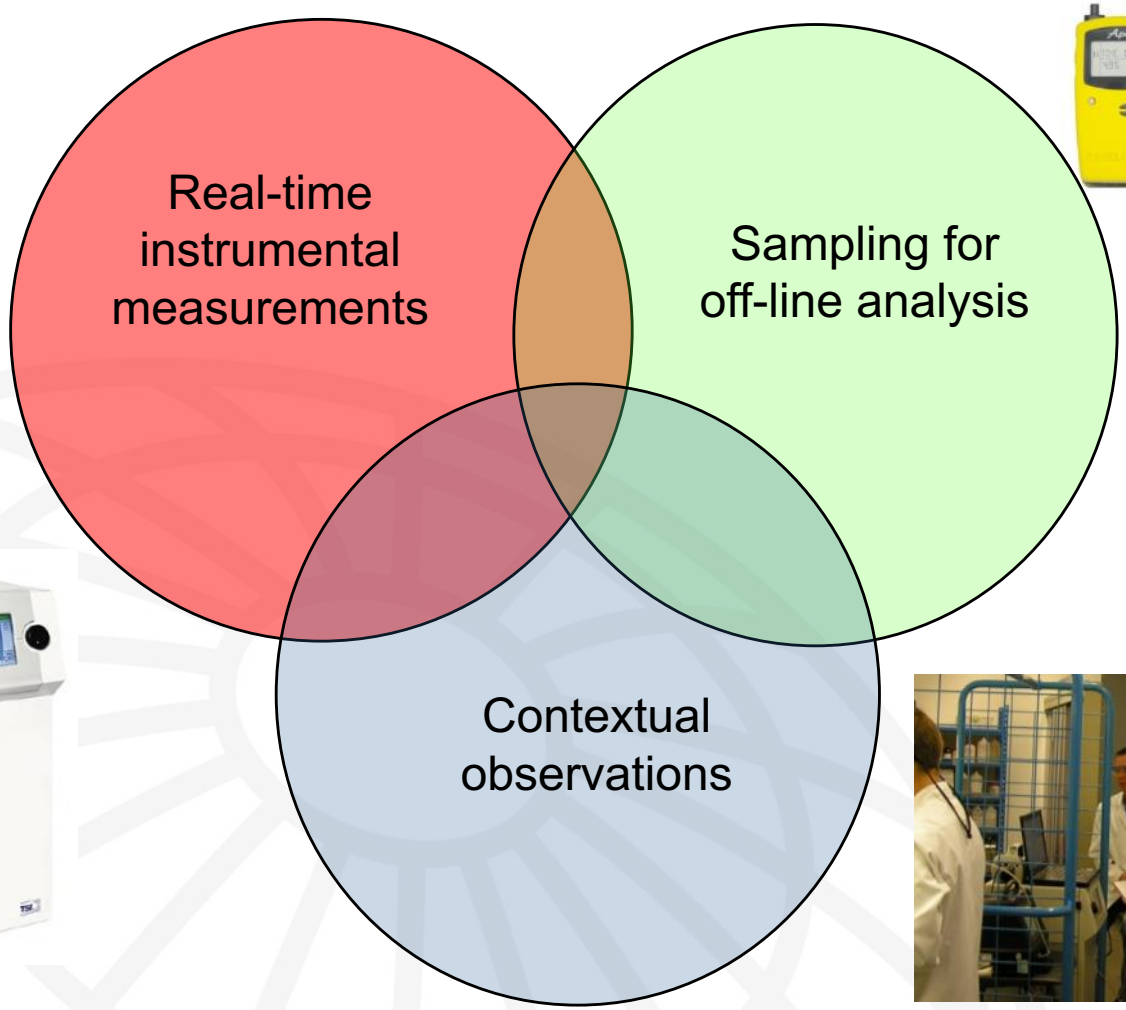
Analysis by SEM / EDXS

25mm Cassette

Quartz Filter

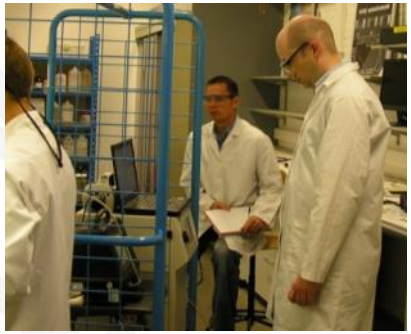
Non-size selective particle sampling.

Samples analysed for Elemental Carbon as a proxy for CNT / CNF / Graphene


Real-time instrumental measurements
Sampling for off-line analysis
Contextual observations

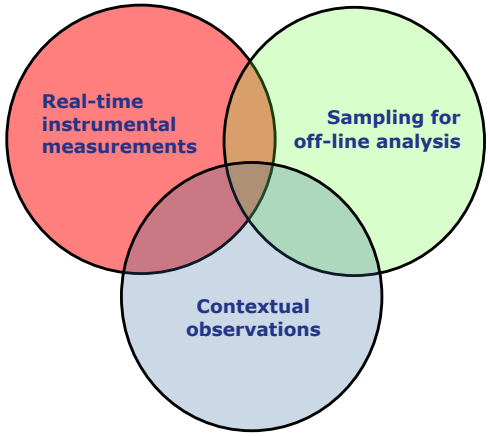

Nano-ID


Slide mailer



Recommended Strategies (OECD 2015)

- Measuring **before** and **after** processing or handling of nano-objects and comparing to measurements taken **during** processing or handling of nano-objects (time variance approach)
- Measuring **simultaneously** at a co-location not influenced by the investigate process and comparing the results to those from the occupational environment (spatial variance approach)
- Investigating the same work process **with and without** the nano-object (material variance approach)
- A **combination** of any of the above three approaches allows trends in aerosol profiles **relative to background** to be used as a practical screening indictor for processes that may require additional control for particle emission



- Conducting real-time measurements in the possible exposure zones close to and away from potential sources to characterize the evolution of the size distribution over time.
- Identifying appropriate sampling locations for fixed area monitors that are unaffected by HVAC, doorways, or other air flow patterns that could impact measurements.
- Documenting events during measurements, including worker's positions, activities, and behaviours and other occupational activities, such as forklift traffic, doors opening and closing, and HVAC systems turning on and off.

Measurement strategy

Currently, no *single* method can be used to *comprehensively* characterise exposure.

Characterisation of workplace exposure to nanoparticles needs to use a multifaceted approach, involving the following steps:

1. Identify the source of nanoparticle emissions.
   A CPC provides acceptable capability for this purpose. It is important to determine ambient or background particle counts before measuring particle counts during the manufacture or processing of the nanoparticles involved. If the chemical identity of nanoparticle is of interest, area sampling with a filter suitable for analysis by electron microscopy should also be employed.

2. Once the source of emissions is identified, aerosol surface area, mass and size distributions should be determined using static (area) monitoring.

Measurement strategy

3. Area or Personal sampling (ideally, size-fractionated) using filters or grids suitable for analysis by electron microscopy or chemical identification may be employed, particularly if measuring exposures to specific nanoparticles is of interest. Electron microscopy can be used to identify the particles, and can provide an estimate of the size distribution of the particle of interest.

   The use of a personal cascade impactor or a respirable cyclone sampler with a filter, though limited, will help to remove larger particles that may be of limited interest and allow a more definitive determination of particle size.

   Analysis of these filters for air contaminants of interest can help identify the source of the respirable particles. Standard analytical chemical methodologies can be employed.

Measurement strategy

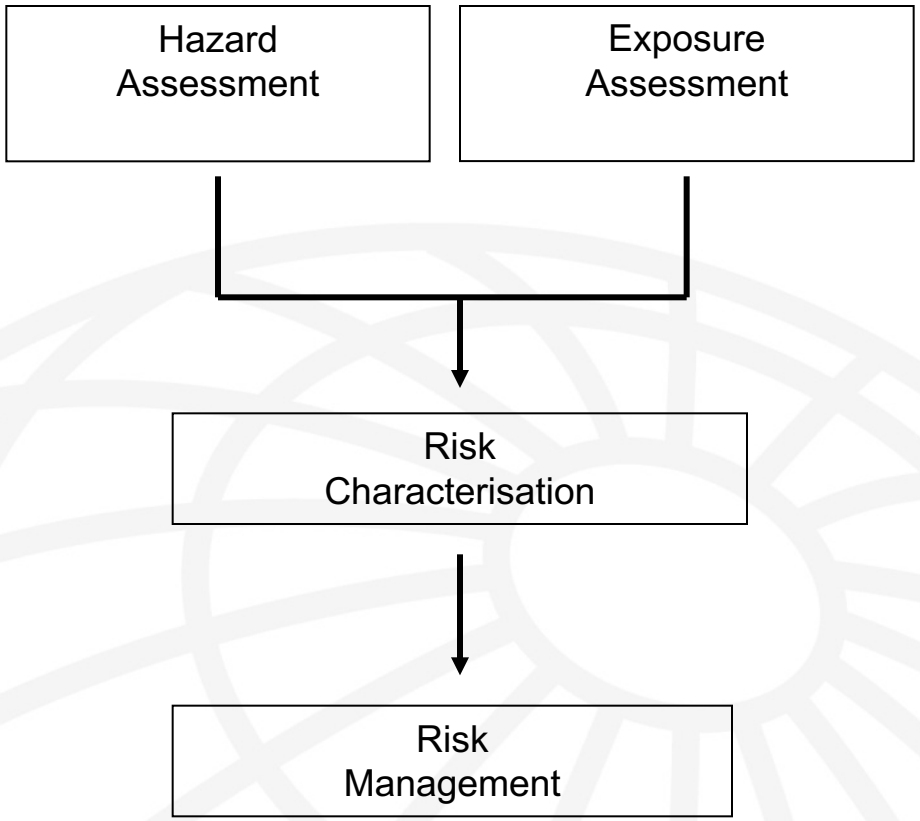
By using a multifaceted approach with a combination of techniques, an assessment of the integrity of containment, (continuing) effectiveness of control measures and potential worker exposure can be conducted.

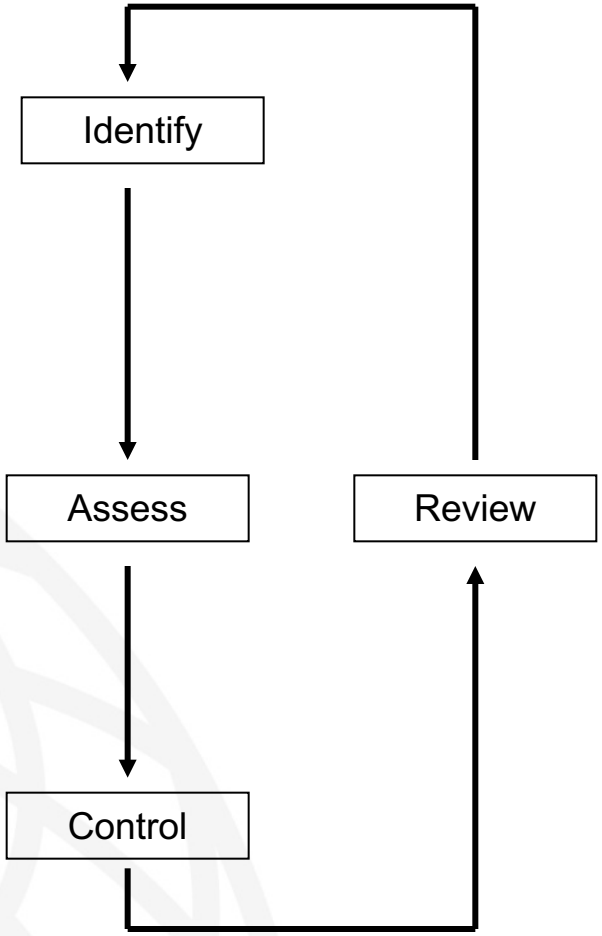
This approach will allow a determination of the presence and identification nanoparticles (and micrometre-sized particles) and the characterisation of the important aerosol metrics.

Since this approach relies primarily on static or area sampling some uncertainty will exist in estimating worker exposures.

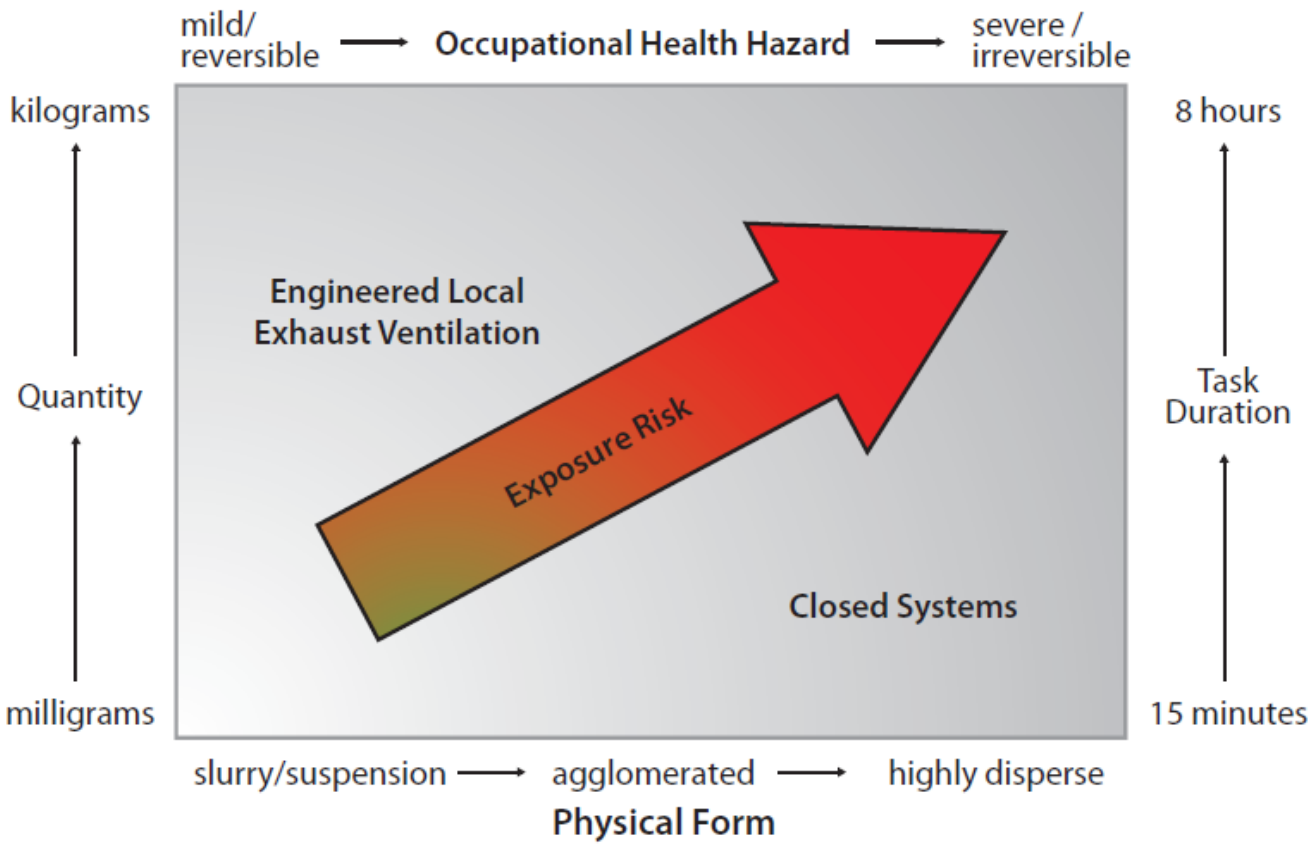
Adopting a strategy for systematic and regular monitoring and interpretation of trends is important to inform decision making and response to changes in trends.

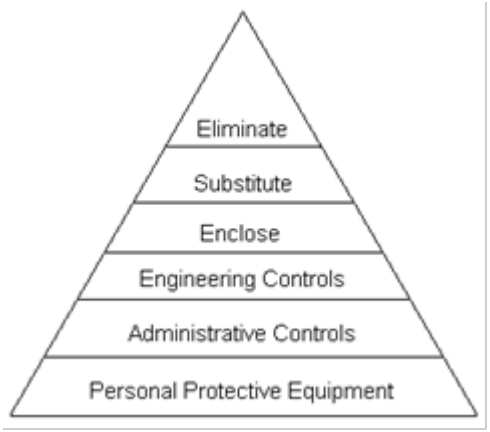
The integrated and cyclical stages in risk assessment





Factors influencing risk & CoSHH





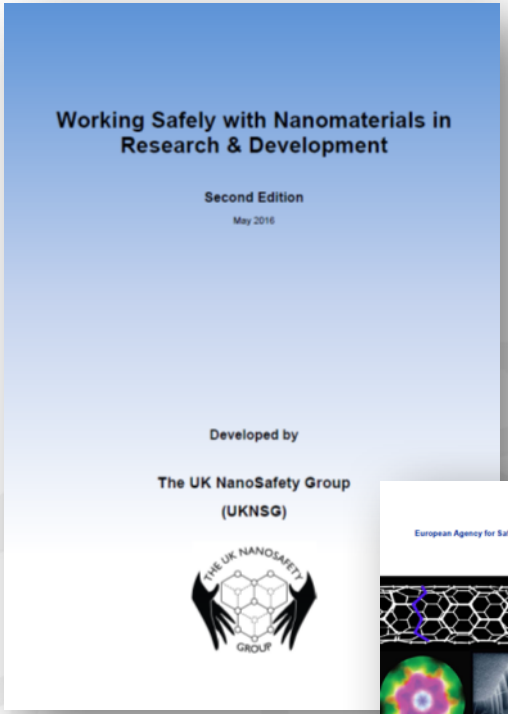
Proposed OELs for Engineered Nanomaterials

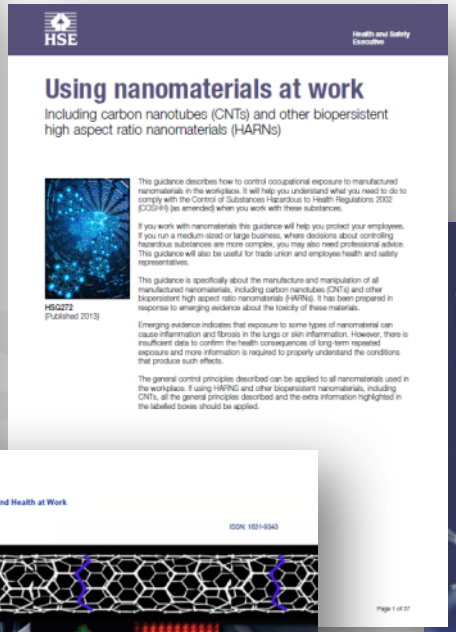
Nanomaterial	Parameter	OEL	References
General	0.004% risk level	Mass-based OEL: 15	OECD (2008)
Titanium dioxide	0.1 risk level particles < 100 nm	0.1 mg/m^3	NIOSH (2005)
General dust		3 mg/m^3	BAuA (2009)
Photocopier Toner	Tolerable risk	0.6 mg/m^3	BAuA (2008b)
	2009 acceptable risk	2.06 mg/m^3	
	2018 acceptable risk	0.006 mg/m^3	
Biopersistent granular materials (metal oxides, others)	Density > 6,000 kg/m^3	20,000 particles/cm^3	IFA (2009)
Biopersistent granular materials	Density < 6,000 kg/m^3	40,000 particles/cm^3	IFA 2009
CNTs	Exposure risk ratio for asbestos	0.01 f/cm^3	IFA (2009)
Nanoscale liquid		Mass-based OEL	IFA (2009)
Fibrous	3:1 length/diameter	0.01 f/cm^3	BSI (2007)
CMAR[a]		Mass-based OEL: 10	BSI (2007)
Insoluble	Not fibrous	Mass-based OEL: 15	BSI (2007)
Soluble	Not fibrous	Mass-based OEL: 10	BSI (2007)
	Not CMAR		
MWCNT	Bayer product only	0.05 mg/m^3	Bayer (2010)
MWCNT	Nanocyl product only	0.0025 mg/m^3	Nanocyl (2009)

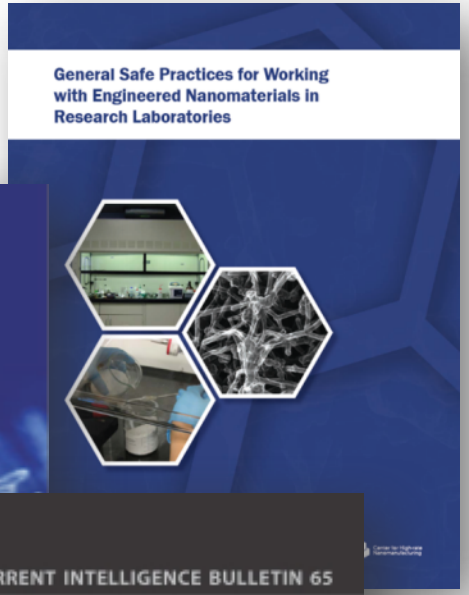
[a] Carcinogenic, mutagenic, asthmagenic, and reproductive toxicants

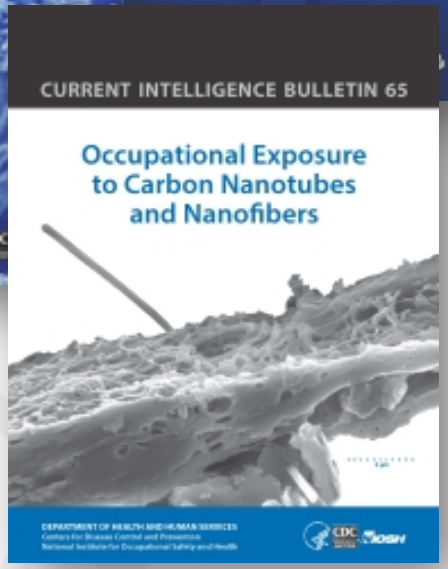
Currently, no *statutory* limits for nanomaterials

Nano-specific guidance to help with Risk Assessment & Management









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Questions?