Inhalation studies using carbon nanotubes

Rachel Smith, HPA

Workshop on manufacture, use and disposal of CNTs

17th August 2011

23 August 2011

HPA Role

The Health Protection Agency is an independent UK organisation set up by the government to protect the public from threats to their health from infectious diseases and environmental hazards.

It does this by providing advice and information to national and local government, health professionals and the general public.

The Agency's advice, information and services are underpinned by evidence-based research.

HPA Organisation

Centre for Infections (CFI) (communicable disease surveillance and specialist microbiology)

Centre for Emergency Preparedness and Response (CEPR) (applied microbiological research and emergency response)

The National Institute of Biological Standards and Control (NIBSC) (standardisation and control of biological medicines such as vaccines)

The Centre for Radiation, Chemical and Environmental Hazards (CRCE)

HPA CRCE


Centre for Radiation, Chemical
and Environmental Hazards
Health
Protection
Agency

HPA and Nanotechnology

Role to advise government departments and others on the potential hazards and risks to human health associated with exposure to nanomaterials

Responded to the challenge of the health concerns and knowledge gaps associated with nanomaterials by establishing the

National Nanotoxicology Research Centre

To develop facilities and expertise to undertake a wide range of in vitro and in vivo studies, supporting experimental work and modelling studies

NNRC Research Areas I

Toxicology

In vivo studies

Inhalation (radioactive toxico-kinetic studies, HRV, CNT)

Ingestion

In vitro studies

Dermal

Others, eg heamolysis

Research Areas II

‘Physics’ studies

Aerosol deposition behaviour (focus on carbon nanotubes)

Interaction of NPs with lung surfactant (PhD)

Modelling

Lung deposition of fibres (building on modelling for spherical particles)

Toxico-kinetics (PBPK) models for NPs

Exposures

UK population exposure to NPs

NNRC Collaborating Group

Professor Jon Ayres, University of Birmingham

Professor Kelly Berube, Cardiff University

Dr Alison Crossley, Oxford University, Begbroke Science Park

Professor Ken Donaldson, University of Edinburgh

Dr Allen Gibbs, Llandough Hospital, Cardiff

Dr Rosemary Gibson, HSL

Dr Paul Harrison, PTCH Consultancy Ltd

Professor Roy Harrison, University of Birmingham

Professor Stephen Holgate, Southampton General Hospital

Professor Vyvyan Howard, University of Ulster

Dr J Jenner, dstl Porton Down

Dr Tim Jones, Cardiff University

Professor Frank Kelly, Kings College London

Professor Kevin Kendall, University of Birmingham

Dr Michaela Kendall, University of Exeter

Dr Wolfgang Kreyling, Helmholtz Institute, Munich

Dr Marcello Lotti, University of Padua

MRC Toxicology Unit, University of Leicester

Dr Margaret Saunders, University Hospital, Bristol

Professor A Seaton, Institute of Occupational Medicine, Edinburgh

Professor Vicki Stone, Heriot-Watt University Edinburgh

Professor Terry Tetley, Imperial College London

Dr Lang Tran, Institute of Occupational Medicine, Edinburgh

External Projects

RESAC

Respiratory effects of silver and carbon nanomaterials

US NIEHS Funded (£1.83M): 5 year study, UK Lead: Professor Terry Tetley, Imperial College.

Nanomaterials: silver ('spheres' and nanowires) and carbon (carbon nanotubes, fullerene and carbon black).

RAMNUC

Risk Assesment of Manufactured nanomaterials used in consumer products

Joint NERC-US EPA Funded (£1.38M), 4 year study, UK Lead: Professor Terry Tetley, Imperial College.

Nanomaterials: Silver, CeO2, ZnO

FABLE

From Airborne Exposures to Biological Effects: the impact of nano-particles on health

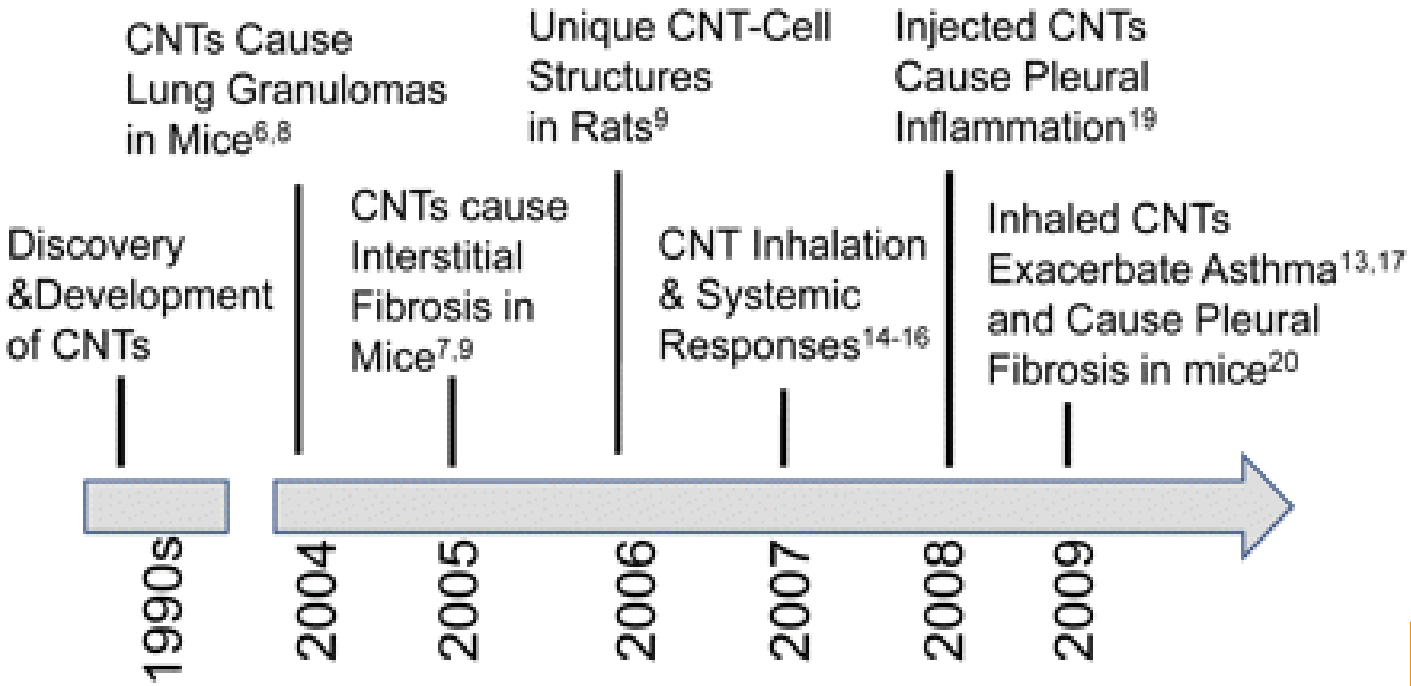
NERC/MRC Funded (£2.12M), 3.5 year study, Lead: Professor Jon Ayres, Birmingham University

Nanomaterials addressed in study: CeO2, V2O5 and ZnO (vehicle exhaust proxy 'spherical*ish*')

Why are we interested in carbon nanotubes?

- Inflammatory responses
- Granulomas
- Fibrosis
- Systemic immune responses
- Exacerbates allergic responses
- Cardiac effects?
- Mesothelioma?

Timeline of CNT toxicological studies on rodents

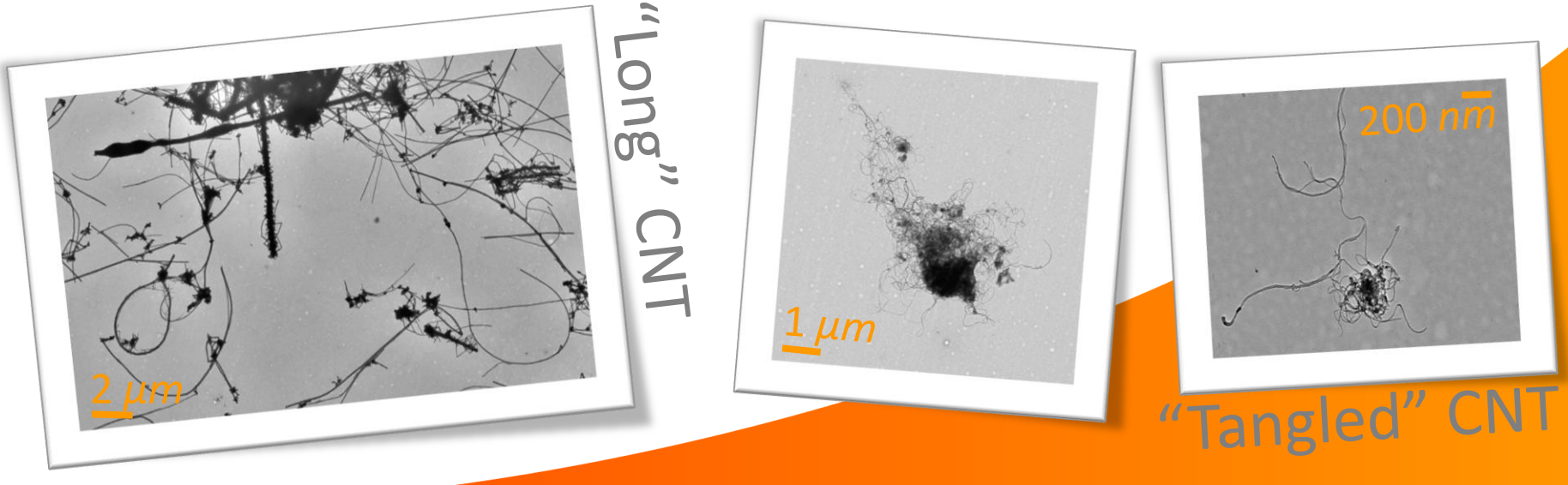


Bonner J (2010), Proceedings of the American Thoracic Society

Mesothelioma?

Poland et al. (2008) *Nature Nanotech.*, **3**, 423-428

- **Long** (> 15 µm), relatively **straight** CNT introduced into the abdominal cavity of mice displayed **"asbestos-like" pathogenic behaviour**.
- The effect **was not** seen with **shorter** and **tangled** CNT.



UK Nanotechnologies Strategy

Research Priorities in UK Nanotechnologies Strategy

Inhalation, Ingestion, Dermal Uptake, Transplacental movement

- *In vitro* studies – Interaction of NPs with cells and surface fluids at sites of entry (epidermal/lung/gut epithelium, endothelial cells of capillaries), dispersion across tissue barriers, effects on cells following uptake of NPs, mutagenicity, carcinogenicity.
- *In vivo* studies – Toxicokinetics (dispersion, storage, excretion), dispersion across blood-brain and placental barriers, mutagenicity studies, reproductive toxicity studies, volunteer studies e.g. intrapulmonary inflammatory responses.

Priority nanomaterials – High Aspect Ratio Nanoparticles (HARNs), Nanosilver, Metal Oxides

NNRC – proposed work with CNT

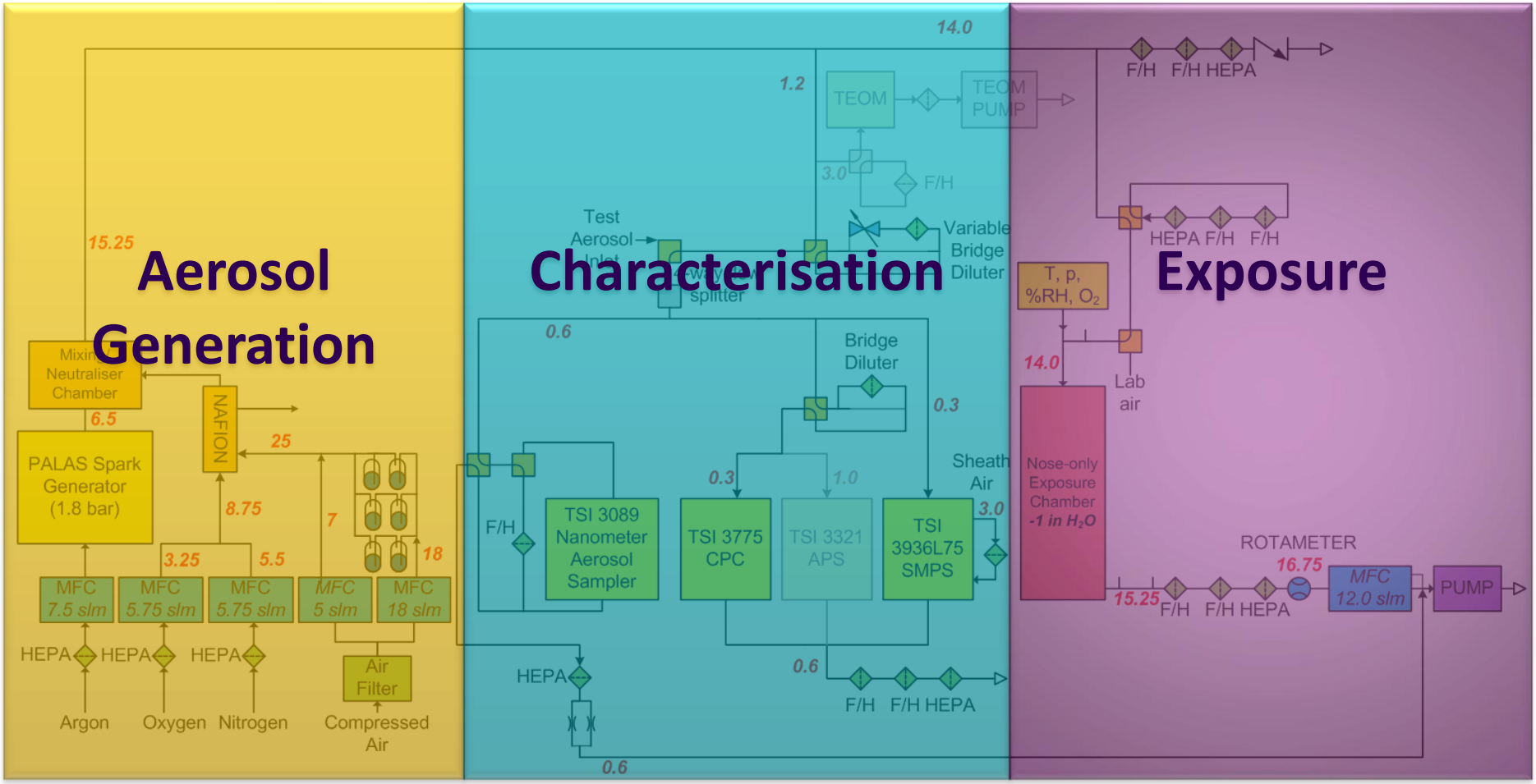
Inhalation Toxicology Studies

2011 Set-up exposure system

2012 Inhalation studies

Theoretical/Modelling studies of aerodynamic and deposition behaviour of CNT

Aerosol Generation, Characterisation and Exposure System



Acoustic Aerosol Generator

McKinney et al, Inhalation Toxicology, 21(12):1053-1061, 2009

NNRC – proposed work with CNT

Inhalation Toxicology Studies

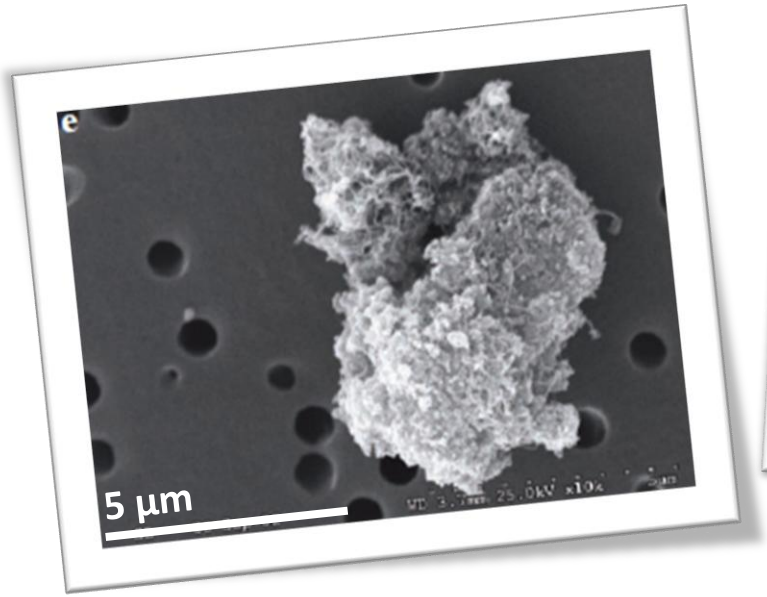
Theoretical/Modelling studies of aerodynamic and deposition behaviour of CNT

2011	Review forms of CNT
	Theoretical evaluation of aerodynamic and diffusion equivalent diameters
	Initial assessment of suitability of lung deposition models for use with CNT
2012	Measurements of aerodynamic/mobility diameters
	Development of appropriate transport and deposition modelling approaches

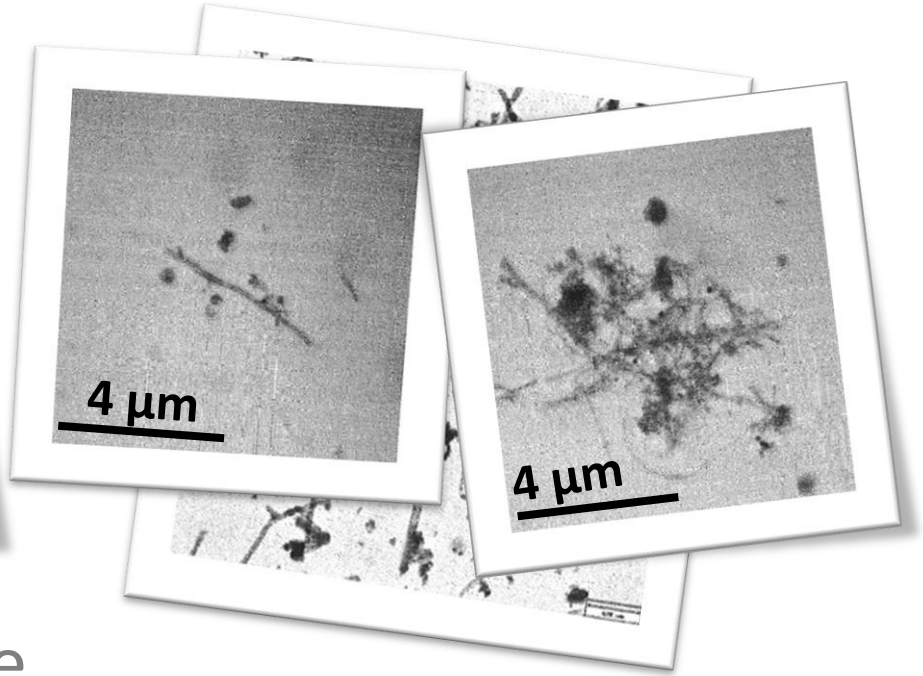
CNT Manufacturing Workplace Air Monitoring Studies

Authors	Year	CNT Type	Facility	Activates
Maynard et al.	2004	SWCNT (HiPCO and laser ablated)	Production (research scale) Laboratory	Removing CNT from production vessel Agitation of CNT by vortex
Han et al.	2008	MWCNT	Production (research scale)	Recovering CNT; blending composites
Bello et al.	2008	MWCNT composite	Production (research scale)	Removal and detaching of CNTs
Bello et al.	2009	MWCNT composite	Research	Machining (dry and wet cutting/band-saw/rotary cutting wheel)
Bello et al.	2010	MWCNT composite	Research	Drilling of CNT composites
Lee et al.	2010	MWCNT	Lab, research and industry	Various, including production; handling; ultra-sonication; spraying
Johnson et al.	2010	Raw and Hydroxylated MWCNT	Laboratory	Weighing, transferring to liquid and ultra-sonication

Real CNT Aerosol Particles

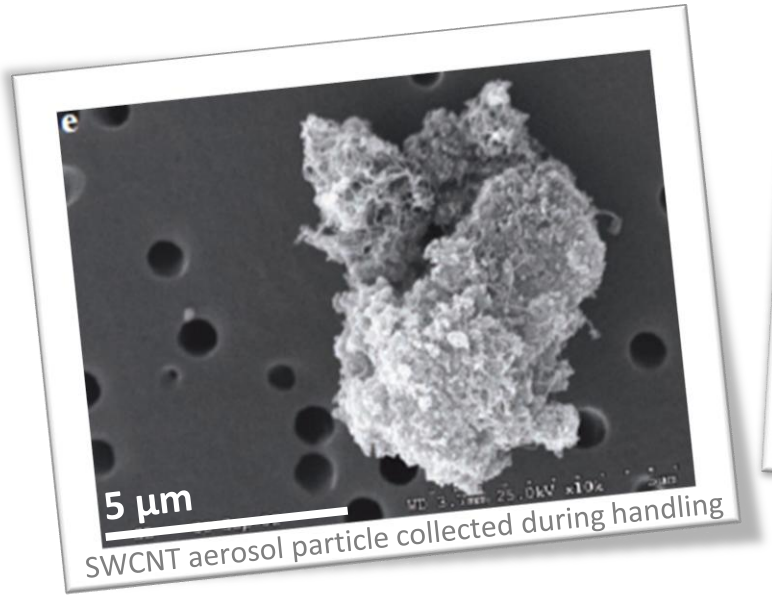


SWCNT aerosol particle collected during handling of laser ablation nanotube material (Maynard et al. 2004)

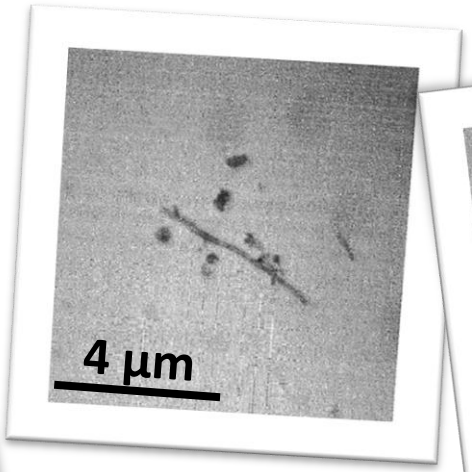


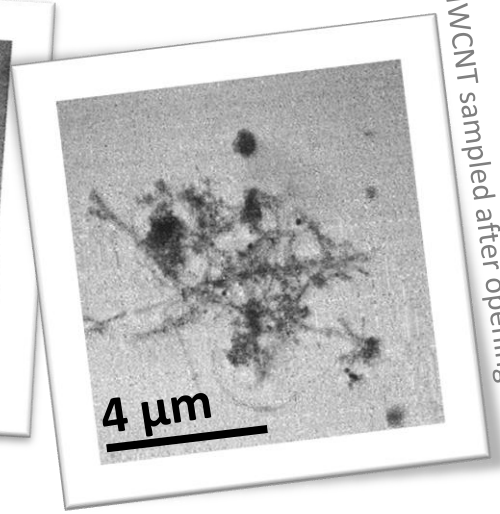
MWCNT sampled after opening of the furnace Han et al. 2008)

Real CNT Aerosol Particles



SWCNT aerosol particle collected during handling

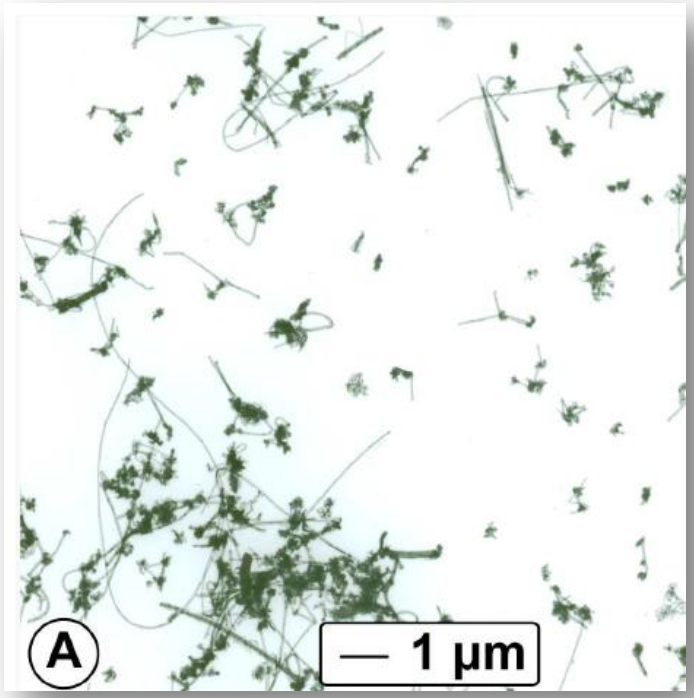




MWCNT sampled after opening furnace

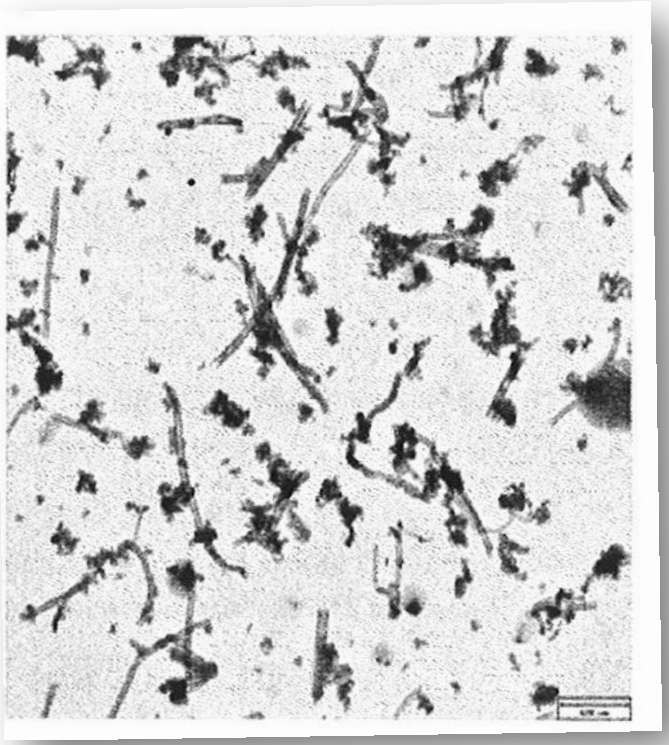
Type	SWCNT Agglomerates	'Fibre-like' MWCNT	MWCNT Agglomerates
Dimensions	~ 1 µm – 1 mm	~ 50 nm diameter < 10 µm in length	~ 0.5 µm – 5 µm
Density	100 – 1000 kg m^{-3} (Maynard et al. 2004)	1740 ± 160 kg m^{-3} (Kim et al. 2009)	100 – 1000 kg m^{-3} (Hao et al. 2003)

Acoustic Aerosol Generator



Acoustic Generator

(McKinney et al, 2009)



MWCNT Research Facility (Han et al, 2008)

Transport and deposition of CNT in the respiratory tract

‘Sphere-like’ particles (SWCNT & MWCNT)

Wide range of aerodynamic diameters 10nm to > 100µm, low density. Current HRT deposition models probably adequate. Deposition in alveolar region max. 20%

‘Fibre-like’ particles (MWCNT)

Current fibre deposition models predict few% to few10s% alveolar deposition but use may be inappropriate. Alveolar deposition dominated by diffusion.

Asbestos fibres – deposition levels may be similar for some particles but sedimentation rather than diffusion the dominant deposition mechanism.

Detailed results to be published in Toxicology of Carbon Nanotubes, ed K Donaldson, Cambridge University Press, 2011

Health and Safety - Approach

- Involvement of Health and Safety Advisor (from earliest stage, part of project team)
- Health and Safety Plan developed and monitored
- Top risks identified
- Control measures identified
- Wherever possible used hierarchy of control principles

Health and Safety – Regs/Advice

Regulations

HSW 1974, IRR 1999, COSHH 2002

Guidance Documents

HSE LEV

HSE Risk management of carbon nanotubes

EA Statement on carbon nanotube wastes

Others eg Nanosafe (esp re filters, gloves etc.)

Advice

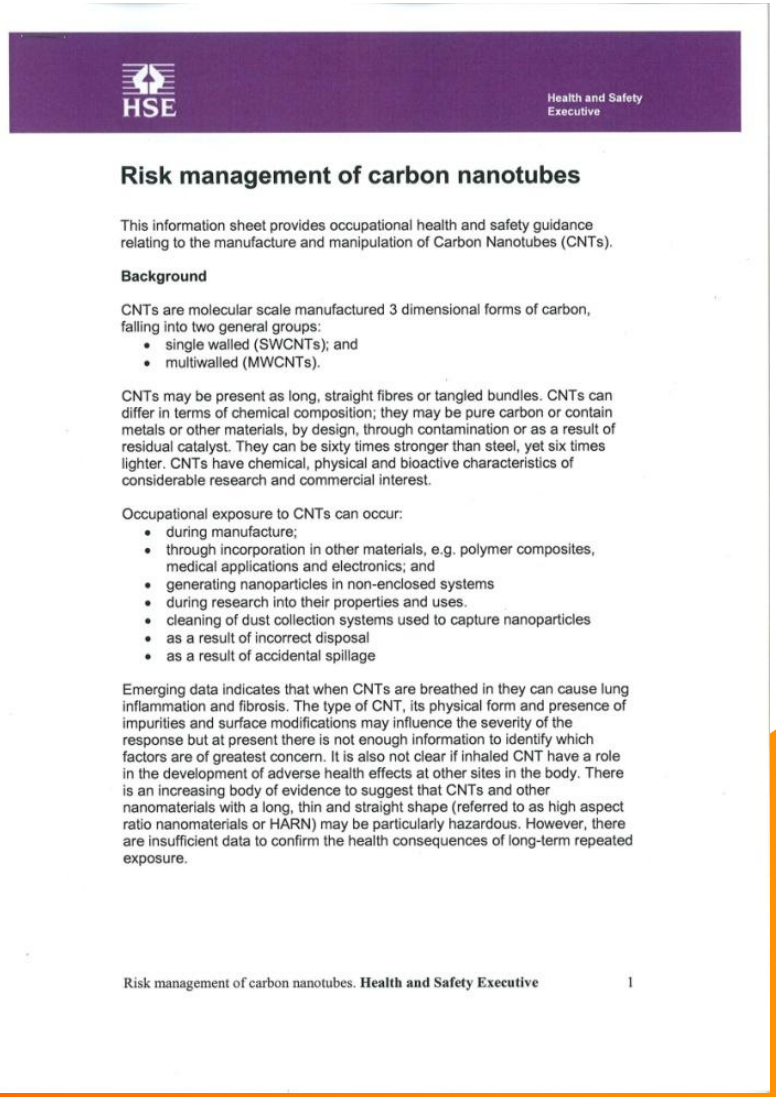
HSL, H&S consultants

HSE/EA

Health Protection Agency

Environment Agency

‘Unbound carbon nanotubes to be treated as hazardous waste’



HSE

Health and Safety Executive

Risk management of carbon nanotubes

This information sheet provides occupational health and safety guidance relating to the manufacture and manipulation of Carbon Nanotubes (CNTs).

Background

CNTs are molecular scale manufactured 3 dimensional forms of carbon, falling into two general groups:

- single walled (SWCNTs); and
- multiwalled (MWCNTs).

CNTs may be present as long, straight fibres or tangled bundles. CNTs can differ in terms of chemical composition; they may be pure carbon or contain metals or other materials, by design, through contamination or as a result of residual catalyst. They can be sixty times stronger than steel, yet six times lighter. CNTs have chemical, physical and bioactive characteristics of considerable research and commercial interest.

Occupational exposure to CNTs can occur:

- during manufacture;
- through incorporation in other materials, e.g. polymer composites, medical applications and electronics; and
- generating nanoparticles in non-enclosed systems
- during research into their properties and uses.
- cleaning of dust collection systems used to capture nanoparticles
- as a result of incorrect disposal
- as a result of accidental spillage

Emerging data indicates that when CNTs are breathed in they can cause lung inflammation and fibrosis. The type of CNT, its physical form and presence of impurities and surface modifications may influence the severity of the response but at present there is not enough information to identify which factors are of greatest concern. It is also not clear if inhaled CNT have a role in the development of adverse health effects at other sites in the body. There is an increasing body of evidence to suggest that CNTs and other nanomaterials with a long, thin and straight shape (referred to as high aspect ratio nanomaterials or HARN) may be particularly hazardous. However, there are insufficient data to confirm the health consequences of long-term repeated exposure.

Hierarchy of control

- Eliminate
- Substitute
- Technical/Engineering controls
- Organisational and administrative
- Personal Protective equipment

Control Measures I

- Workplace Ventilation
- Glove boxes
- LEV
- Fume Cupboards
- HEPA filtration
- Animal transport boxes
- PPE

Control Measures II

- Risk Assessments for task and processes
- Information, instruction and training
- SOPs and local rules
- Monitoring of workplace

Monitoring Airborne Concentrations of NP

General

Direct measurement of airborne particulates

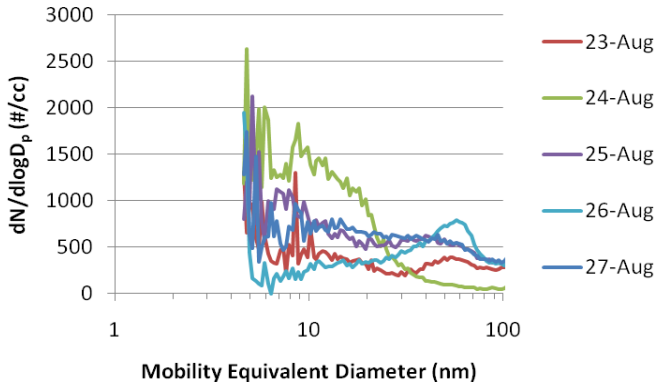
SMPS, APS

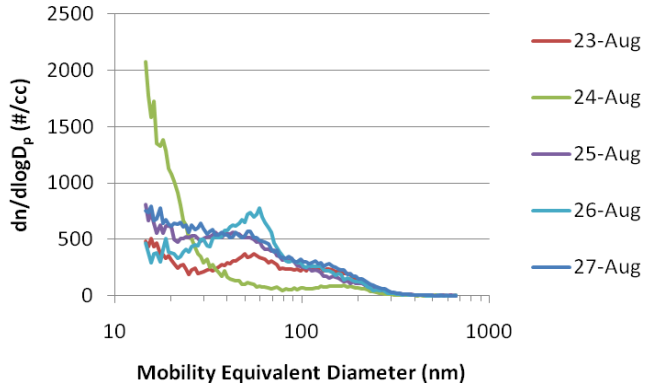
Radioactive NP

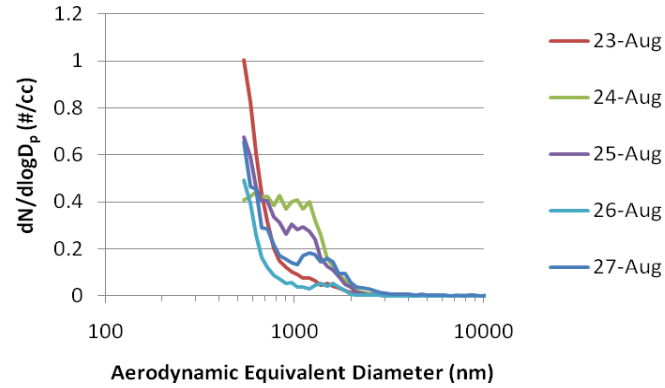
Air sampling and counting

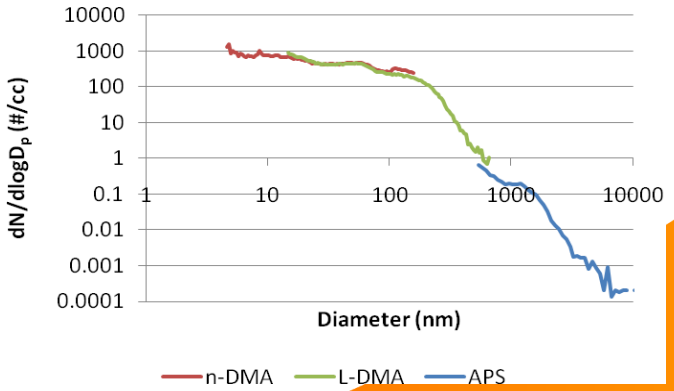
Key issues: background and identification

Background Air Concentrations









H&S Conclusions

Involve H&S Advisor at earliest stage

Complex range of risks

Need for specialist advice (especially on air handling, extracts, filters etc.)

Concluding Remarks

Health Protection Agency

Overview of research activities at HPA's National Nanotoxicology Research Centre

NNRC carbon nanotubes studies

Approach to Health and Safety

CRCE NNRC

Robert Maynard

Alison Buckley

Chris Howarth

James Wakefield

Vanessa Viegas

Michele Ellender

Rachel Smith

Alan Hodgson

Chang Guo

James Warren

Kai Rothkamm

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