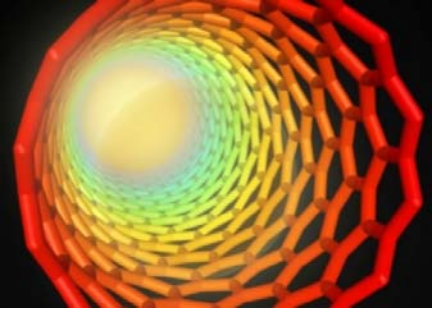
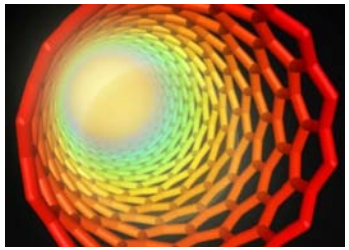


Risk assessment - carbon nanotubes

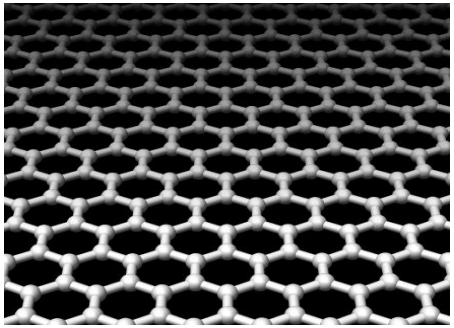
Exposure

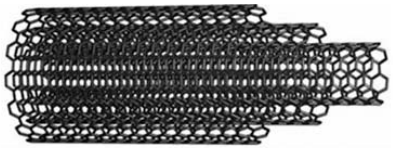
Toxicology

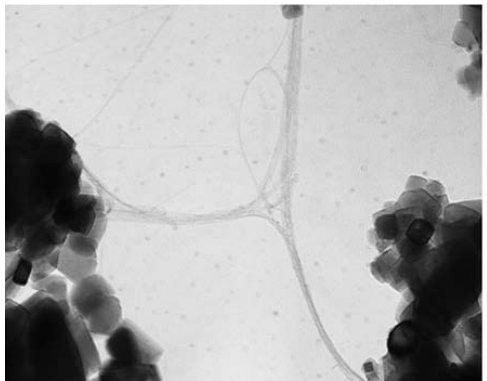
Protective measures

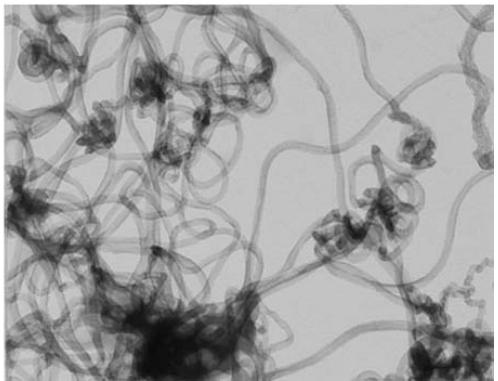


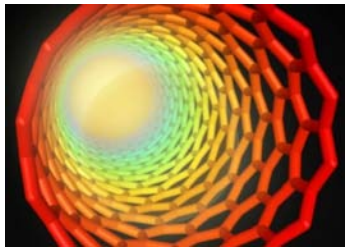
- Group of materials
- Pure carbon structure
- Graphene sheet forming a cylinder
  - Single-walled (SWCNT)
  - Multi-walled (MWCNT)

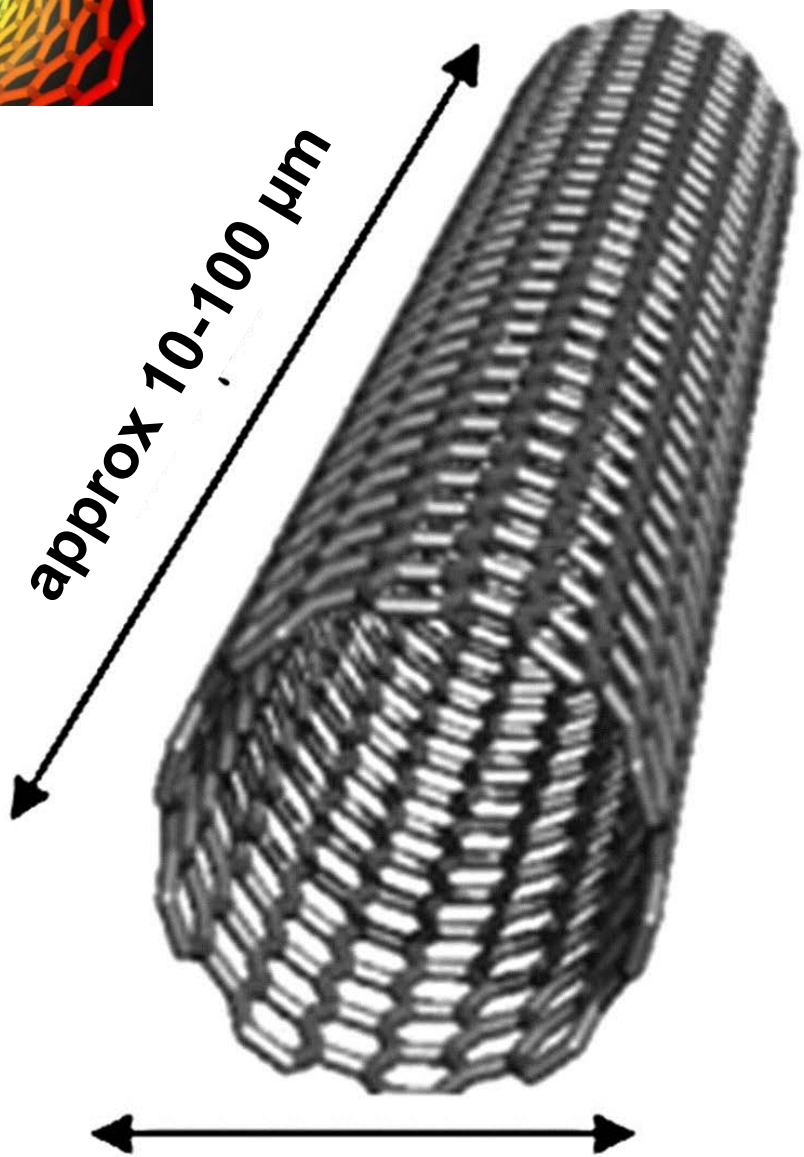










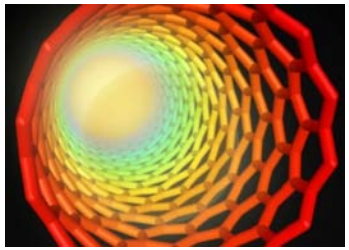


(MWCNT 10-100 nm)

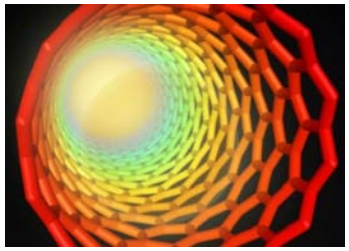
Low bulk density
- **1-100 mg/cm^3**

Large surface/mass
- **300 -1300 m^2/g**

High aspect ratio
- **L/D 100-1000**



- Use
- Risk identification: Is there a risk?
- Risk assessment: Exposure and effects
- Risk management: Recommendations



Strong, inert, conductive

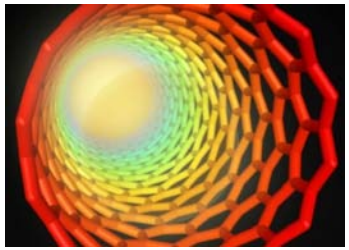
- Composites (plastics and rubbers; 1-10%)
  - cars/aircrafts, sport articles, wind power
- Lithium ion batteries (mobile phones/laptops)
- Fouling release paints (marine coating)
- Advanced sports equipment (hockey sticks)
- Many potential applications
  - Textiles, electronics, medicine, energy

Production (tonnes/year)

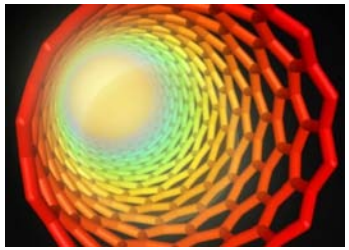
Year	2000	2010	2015
SWCNT	7		
MWCNT	300		
Totalt	307	710*	9300*

***Prognosis**

SWCNT= Single-walled carbon nanotubes
MWCNT= Multiewalled carbon nanobubes

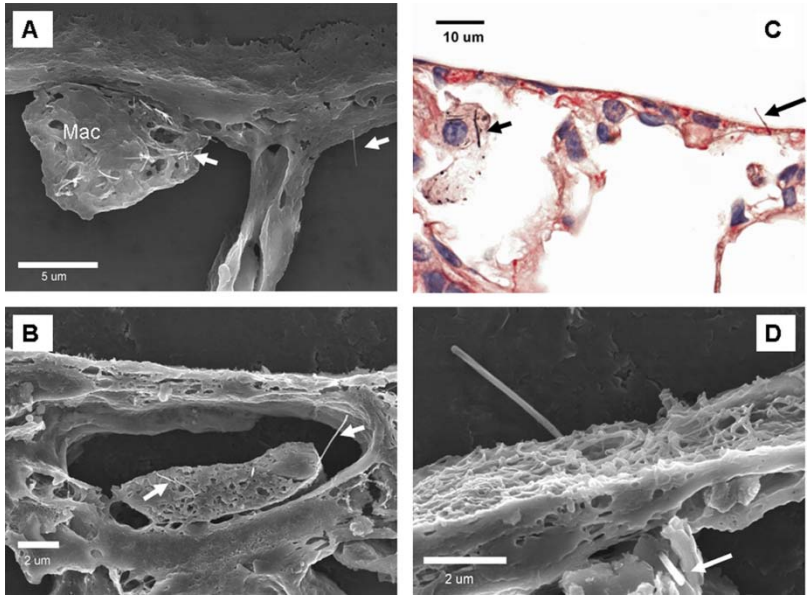


Toxicology

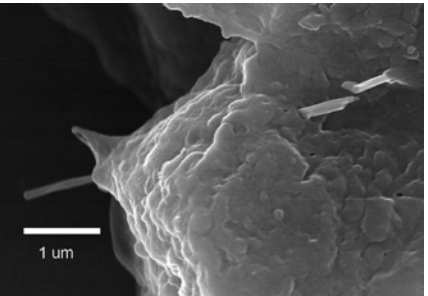


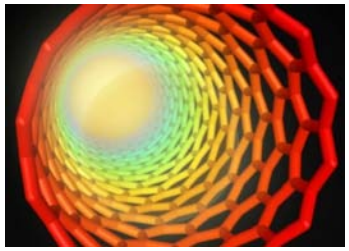
Uptake and distribution

- Inhalation/intra-tracheal instillation
  - Lung (SWCNT, MWCNT)
  - Pleura (MWCNT)
  - Lymph nodes (MWCNT)
- Oral/tube-feeding
  - Gastrointestinal tract
    - Systemic uptake – observed for short SWCNT, 50-200 nm



Mercer et al 2010



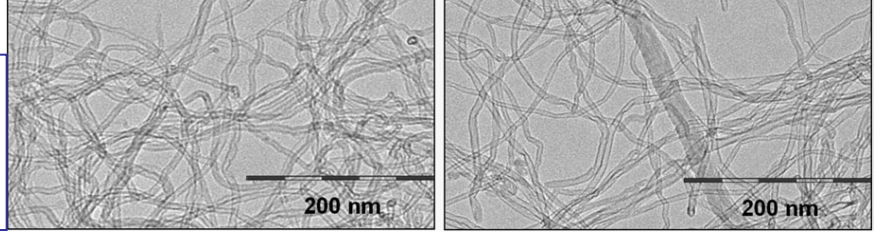


Single dose effects

- Inhalation, instillation, aspiration
- Fibrosis, granuloma (lung, pleura)
- ROS – oxidative stess
- Communication with systemic circulation (cardiovascular effects)
- Increased allergic inflammation

TOXICOLOGICAL SCIENCES **112(2)**, 468–481 (2009)
doi:10.1093/toxsci/kfp146
Advance Access publication July 7, 2009

0.1, 0.5, and 2.5 mg/m^3,
L= 0.1-10 µm/D=5-15 nm
9.6% AlO



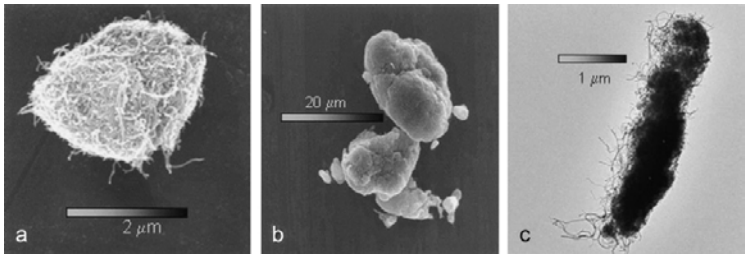
Inhalation Toxicity of Multiwall Carbon Nanotubes in Rats Exposed for 3 Months

Lan Ma-Hock,* Silke Treumann,* Volker Strauss,* Sandra Brill,* Frederic Luizi,† Michael Mertler,‡ Karin Wiench,* Armin O. Gamer,* Bennard van Ravenzwaay,*[,1] and Robert Landsiedel*

Product Safety, BASF SE, 67056 Ludwigshafen, Germany; †Nanocyl S. A., 5060 Sambreville, Belgium; and ‡Process Engineering, BASF SE, 67056 Ludwigshafen, Germany

TOXICOLOGICAL SCIENCES **113(1)**, 226–242 (2010)
doi:10.1093/toxsci/kfp247
Advance Access publication October 12, 2009

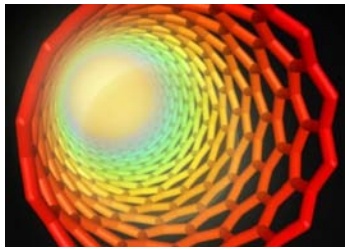
0.1, 0.4, 1.5, and 6 mg/m^3,
L = 0.2-0.3 µm/D = 10 nm



Subchronic 13-Week Inhalation Exposure of Rats to Multiwalled Carbon Nanotubes: Toxic Effects Are Determined by Density of Agglomerate Structures, Not Fibrillar Structures

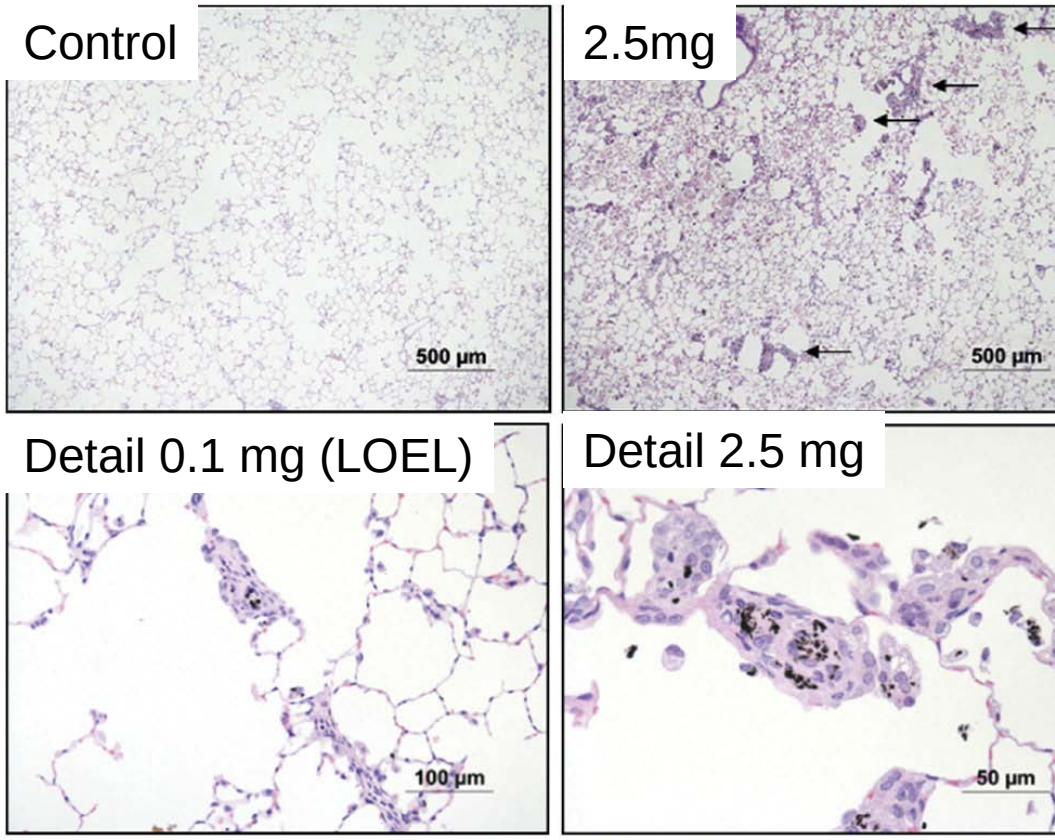
Jürgen Pauluhn[1]

Department of Inhalation Toxicology, Institute of Toxicology, Bayer Schering Pharma, Building Number 514, 42096 Wuppertal, Germany



Subchronic inhalation (90 days)

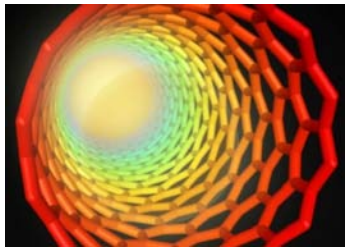
- Airways fibrosis
- Granuloma
- Inflammation
- No systemic effects



Ma-Hock et al. (2009)

Genotoxicity

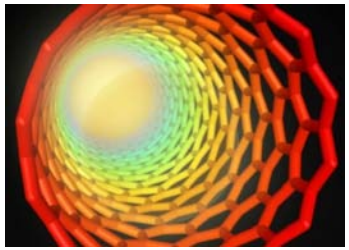
- Both SWCNTs and MWCNTs induce mutagenic and genotoxic effect (micronucli, DNA fragmentation and modification of DNA bases)
  - oxidative DNA-damage at 0.06 mg SWCNT/kg (rat)
    - D=1nm, L<1 µm (Folkmann 2009)
- Ames text generally negative



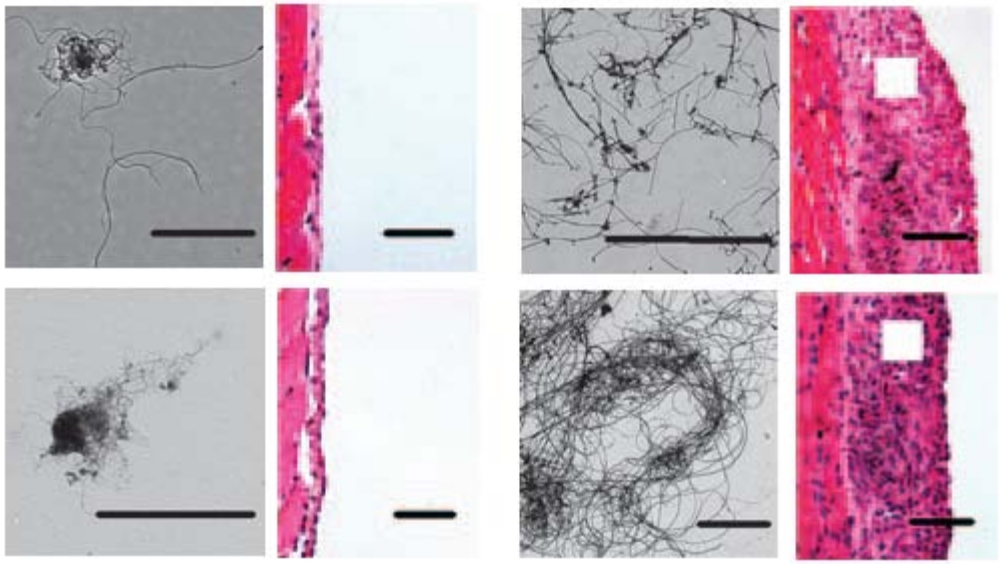
Carcinogenicity

- MWCNT may cause mesothelioma (local injection) in the
  - peritoneum (110 mg/kg, p53+/- mice; Takagi et al 2008
  - scrotum (1 mg/kg, rat, Sakamoto et al 2009)
    - Also increas of s-mesothelin (Sakamoto et al 2010)
- Not shown for
  - short MWCNT (6- 25 mg/kg, Muller et al 2009),
  - SWCNT (L=4-15 µm, 25 mg/kg/rat; Varga 2010)
- Not investigated for the pleura

Diameter	Length	Reference
MWCNT 70-110 nm (82%)	**3 µm (72,5%)**	**Sakamoto et al 2009**
MWCNT 70-170 nm	**1-5 µm (72,5%)**	**Takagi et al 2008**
MWCNT 11 nm	**0.7 µm**	**Muller et al 2009**



Theories on effects

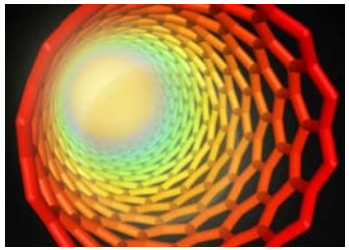


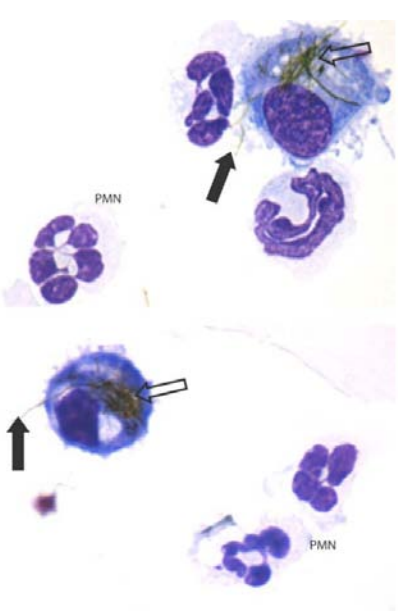
Shorter, more compact´tubes

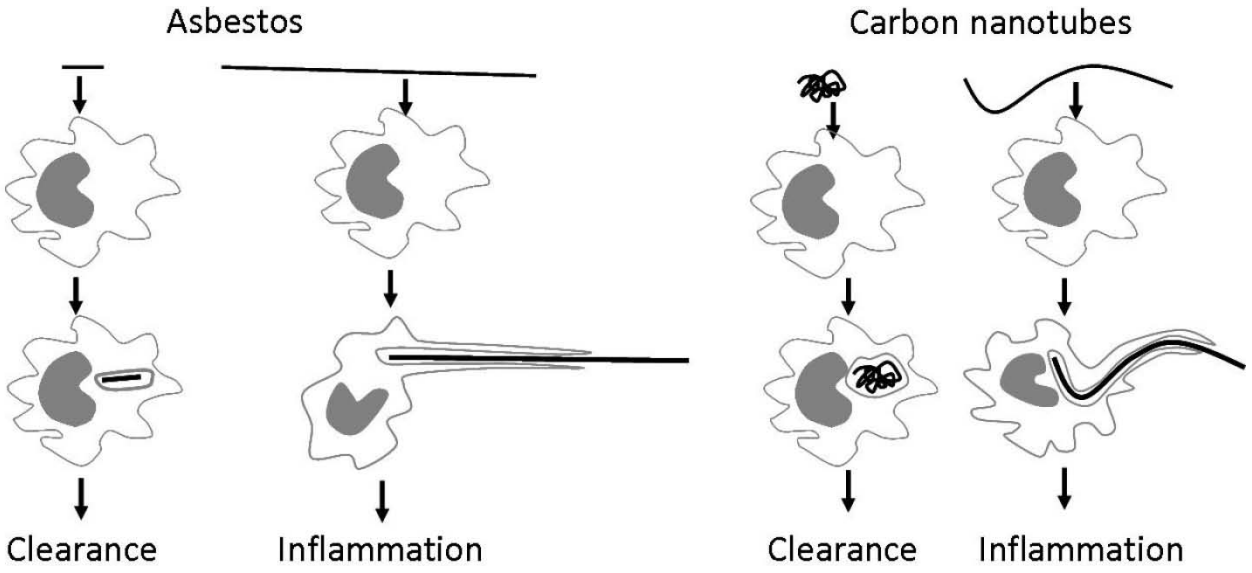
Longer, more fibrous tubes

Increased effects

Poland et al. (2008)

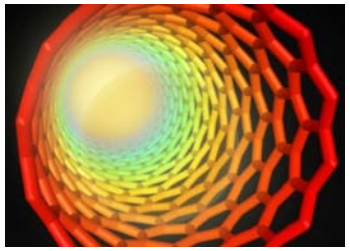




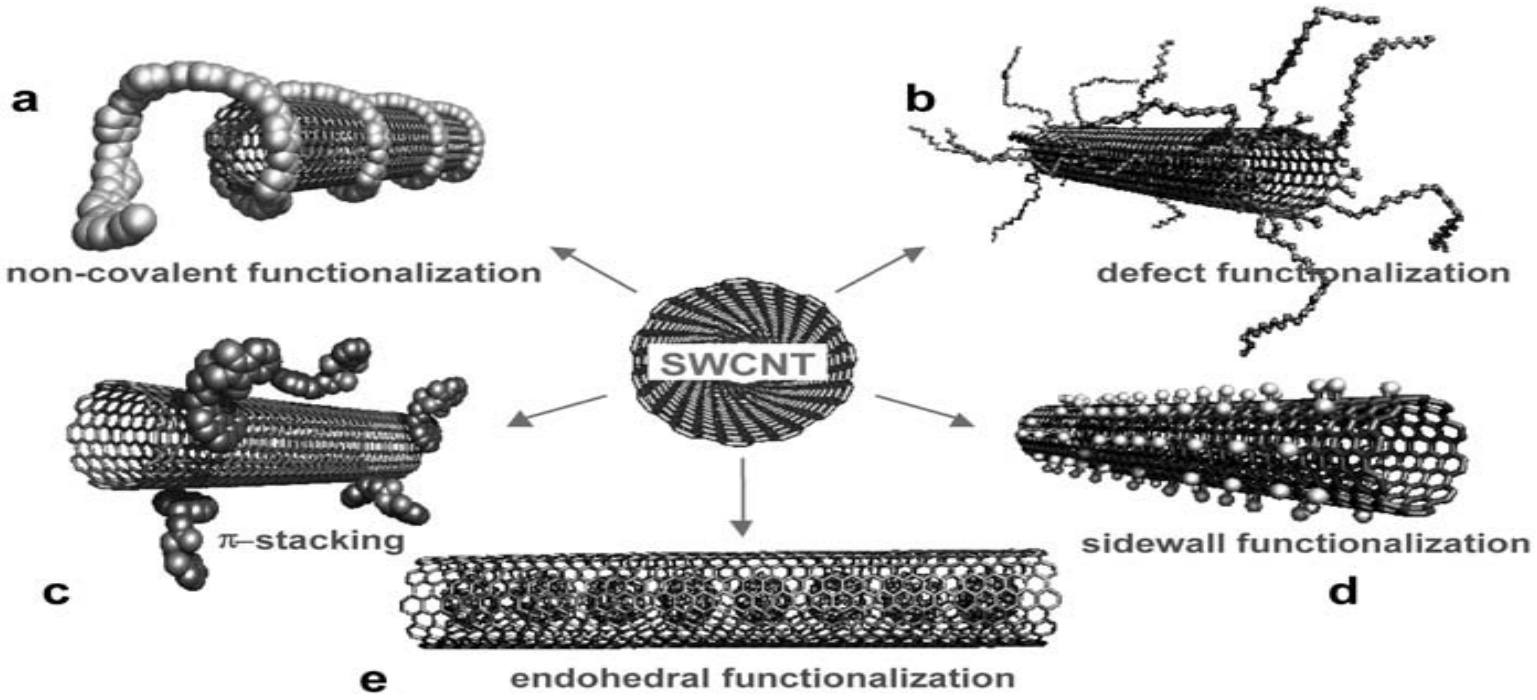


Frustrated phagocytosis

Donaldson et al. (2010)



Functionalization



Hirsch and Vostrowsky 2005

- Affects blood half-time and distribution
- May increase or decrease toxicity

Liu et al 2007

Risk identification

- May cause fibrosis and granuloma after inhalation
- Systemic effects after inhalation
  - single dose only
- Genotoxic in several assays
- Cancer?
- Reproduction?

Risk assessment

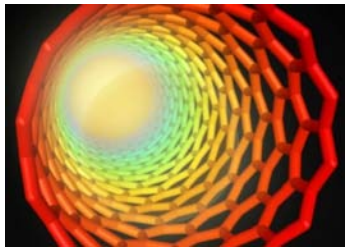
- Lowest observed effect levels?
- Observed exposure levels?

Lowest observed effect level

- 0.06 mg/kg DNA-damage
  - Single dose (gavage), rat
- 0.2-0.3 mg/kg (rat) or 0.1 mg/m^3 airways inflammation/granuloma
  - inhalation: 6 h, 65 times/ 90 d
- ≥1 mg SWCNT/kg (rat, mice) cardiovascular effects (baro-reflex, myocyte degeneration)

Available work-place concentrations (median, range) from personal sampling

Site	µg/m^3	f/ml
Production (n=4, 0.5h) - Emptying reactor (Maynard 2004)	Total dust 23 (0.7-53)	-
Production (n=1;1.5h) (Bello 2008)	-	N.D
Research lab (n=8; 4-6h) - Manual handling (Han 2008)	Total dust ND (ND-332)	0.005 (ND-194)
Production (3-7h) - Handling (Lee et al 2010)	Total dust 106 (7.8-321)	-
Packaging (n=4) (Takaya 2010)	Total dust 1,340 (290-2,390) Respirable dust 235 (80-390)	-



Suggested guidance values

Type of CNT	TLV	Reference
MWCNT	2.5 µg/m^3	Nanocyl, 2009
MWCNT	50 µg/m^3	Bayer, 2010
MWCNT	7 µg/m^3	Schulte et al., 2010
CNTs	0,01 fiber/cm^{3a}	IFA, 2009

[A] Benchmark limit

Work-place safety measures

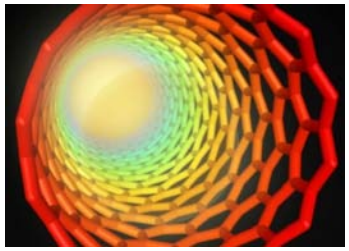
- Consider alternatives
- Closed process, or
- Exhaust ventilation + PPE
  - Respirator (PF>40; individual test of fit)
  - Protective clothes/gloves

Photos from CL Gercia, NIOSH

Photo from Methner et al 2008

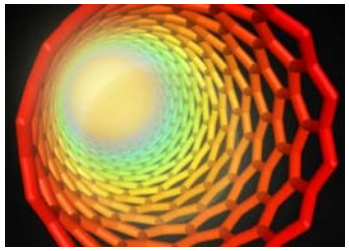
Knowledge gaps - implementation

- Use (unique registration - not as graphene)
- Standardized air sampling with high specificity and predictivity for risk
  - PCOM/gravimetric measures inadequate
- Exposure assessment for down-stream use
- Differential risk assessment for different classes of CNTs (functionalisation, contamination, length)



Research needs

- Agreement on uniform dose-metrics and particle characterization
- Experimental studies
  - Long-term animal inhalation studies
  - Systematic structure-activity studies
    - ”worst fibre”, asbestos positiv control
  - Reproductive effects
- Monitoring of exposed workers



Review

Commissioned by

- Swedish Work Environment Authority

Authors

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- Maria Hedmer (Occupational and environmental medicine)
- Jenny Rissler (Ergonomics and aerosol technology)

Reference group

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- Mats Bohgard, Lund Univ.
- Martin Kanje, Lund Univ
- Steffen Loft, Copenhagen Univ, Denmark

Coming next year: Nordic Expert Group Criteria Document