Multifaceted determinants of MWCNT toxicity

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What makes nanos different in terms of toxicity ?

The same physico-chemical properties that make nanos so attractive for technological applications are potential sources of concern for health :

- *new* properties
- larger surface area
- greater surface reactivity
- larger and different biodistribution

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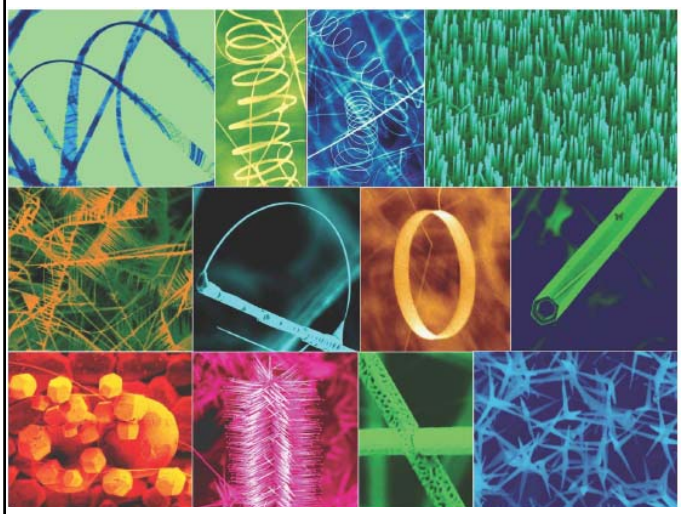
- *new* properties
- larger surface area
- greater surface reactivity
- larger and different biodistribution
- infinite diversity



Chemically identical

Physically significantly different

Role on biological interaction?

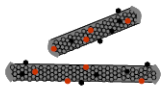
Wang et al. 2005

Respiratory toxicity of CNT

- biopersistence
- inflammation
- fibrosis
- genotoxicity
- cancer ?

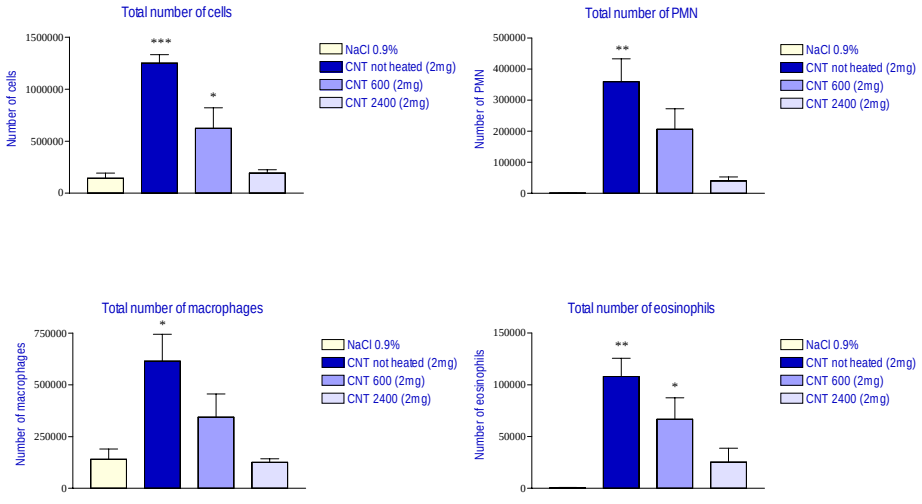
How can we explain this toxicity ?

- Presence of metallic contaminants ?
- Role of surface defects ?
- Carrier effect?
- Crystallinity?



	CNT not heated	CNT 600	CNT 2400
Fe (‰)	0.0048	0.0051	0.0001
Co (‰)	4.94	5.44	0.0015
Al (‰)	19.7	22.5	3.7

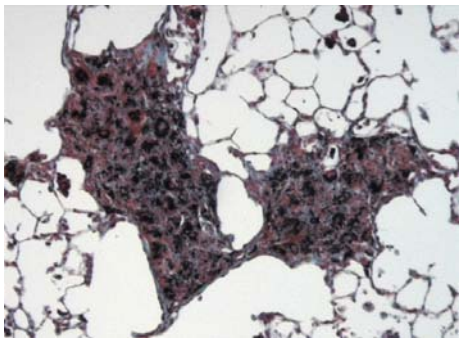
Cellular parameters (3 days)



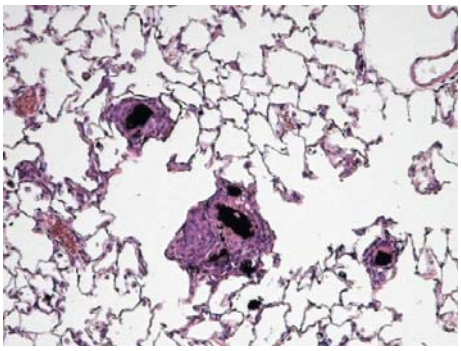
Muller et al., 2008

Histological study (60 days)

CNT not heated



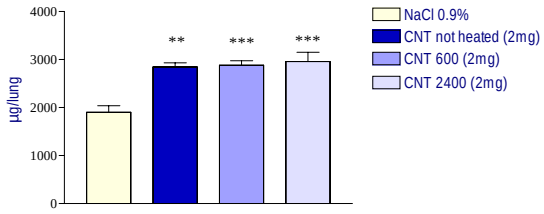
CNT 2400



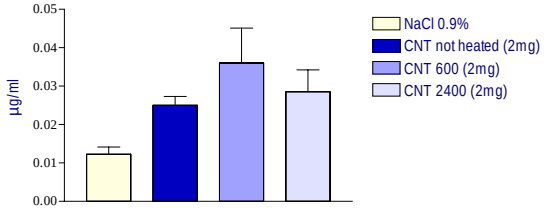
Muller et al., 2008

Fibrotic response (60 days)

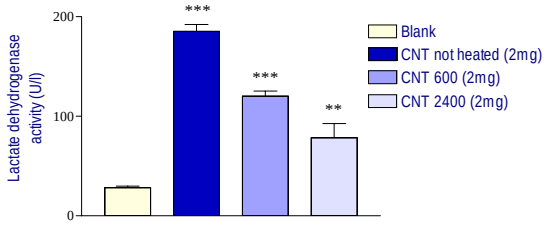
Hydroxyproline



Fibronectin



	CNT not heated	CNT 600	CNT 2400
Fe (µg/l)	0.96	1.02	0.02
Co (µg/l)	988.7	1088.7	0.3
Al (µg/l)	3945	4499	741
Surface oxygen	3.45	0.57	0.10

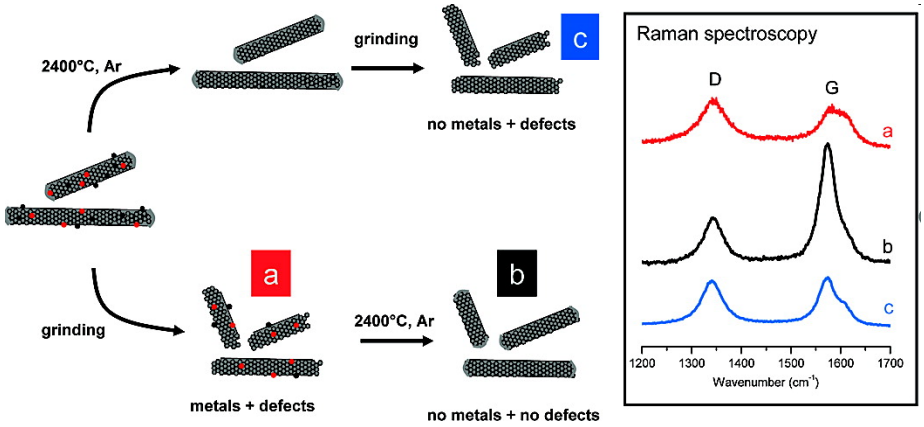


CNT 2400
low toxicity
?

Metallic contaminants

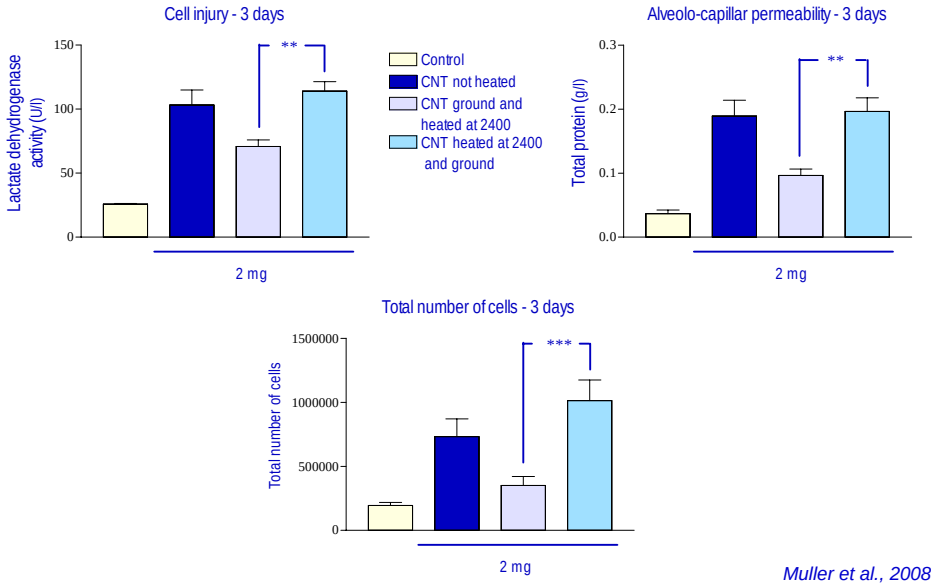
Surface defects

Role of surface defects ?

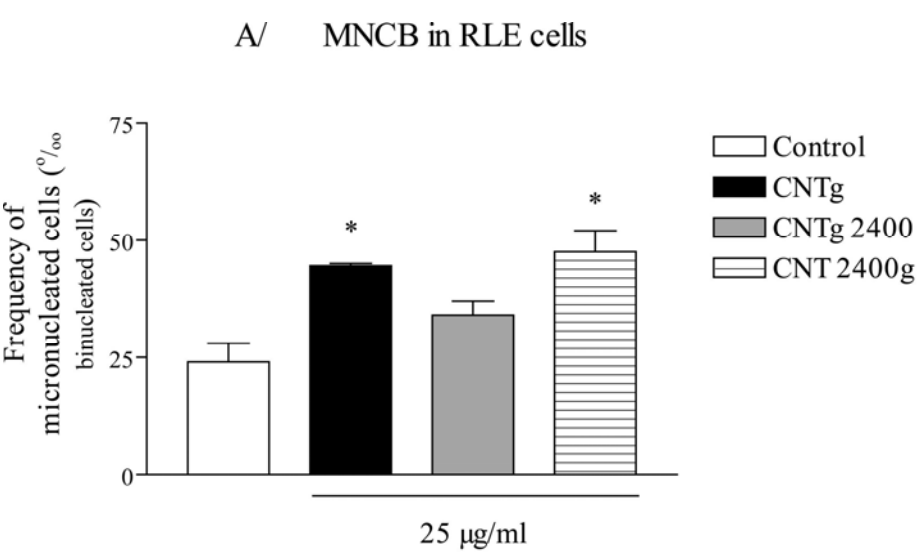


Fenoglio et al., 2008

Role of surface defects ?



Muller et al., 2008



Muller et al., 2008

Respiratory toxicity of CNT

- biopersistence
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TOXICOLOGICAL SCIENCES **110**(2), 442–448 (2009)
doi:10.1093/toxsci/kfp100
Advance Access publication May 8, 2009

Absence of Carcinogenic Response to Multiwall Carbon Nanotubes in a 2-Year Bioassay in the Peritoneal Cavity of the Rat

Julie Muller,* Monique Delos,† Nadtha Panin,* Virginie Rabolli,* François Huaux,* and Dominique Lison*,1

Main Physico-chemical Characteristics of the Tested Materials

	Crocidolite[b,c]	MWCNT+[d]	MWCNT−[d]
Metal content (%)[a]	nd		
Al		1.97	0.37
Fe		0.49	<0.01
Co		0.48	<0.01
Specific surface area (m^2/g)	8	299	190
Extent of defects (I_D/I_G)[e]	nd	1.16	0.58
Reactive sites[f], molar enthalpy of adsorption of H_2O_2 (kJ/mmol)	nd	29.2	0.4
Diameter (nm)	330 (2.1)*	11.3 ± 3.9**	11.3 ± 3.9
Length (μm)	2.5 (2.0)	About 0.7	About 0.7

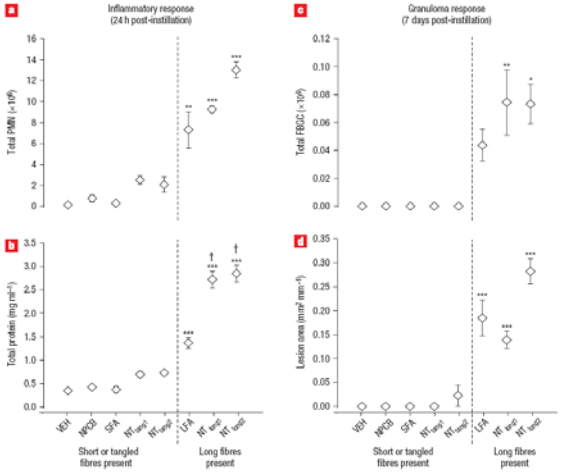
Table 3 : Incidence of abdominal tumors in rats injected intraperitoneally with MWCNT with (+) or without (–) defects, crocidolite (positive control) and vehicle controls.

	Vehicle controls (n=26)	Crocidolite (2 mg) (n=26)	MWCNT+ (2 mg) (n=50)	MWCNT+ (20 mg) (n=50)	MWCNT– (20 mg) (n=50)
Mesothelioma					
before terminal sacrifice	♦ (21.6 months)	♦ (14.6) ♦ (16.8) ♦ (17.5) ♦ (19.5) ♦ (20.4) ♦ (20.6) ♦ (22.3) ♦ (22.8) ♦ (23.2)	♦ (20)		♦ (10.7) ♦ (18.9) ♦ (19.8)
at terminal sacrifice			♦		
total (%)*	**1 (3.8)**	**9 (34.6)**	**2 (4)**	**0 (0)**	**3 (6)**
Other peritoneal tumors					
before terminal sacrifice			♦ lipoma (16.6)	♦ lipoma (13.8)	-
at terminal sacrifice		♦ granuloma ♦ granuloma	-	♦ angiosarcoma ♦ liposarcoma	♦ lipoma ♦ lipoma ♦ lipoma
total (%)	**0 (0)**	**2 (7.6)**	**1 (3.8)**	**3 (6)**	**3 (6)**

Muller et al., 2009

Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study

CRAIG A. POLAND[1], RODGER DUFFIN[1], IAN KINLOCH[2], ANDREW MAYNARD[3], WILLIAM A. H. WALLACE[1], ANTHONY SEATON[4], VICKI STONE[5], SIMON BROWN[1], WILLIAM MacNEE[1] AND KEN DONALDSON[1]*



Carcinogenicity of CNT

- Tagaki et al., 2008
  MWCNT 27%>5 µm
  intraperitoneal, mouse *p53+/-*

- Sakamoto et al., 2009
  MWCNT 27%>5 µm
  intrascrotal, rat (n=7)

Determinants of CNT toxicity

- for which endpoint ?

	Inflammation	Granuloma	Fibrosis	Cancer	Genotox	…
SWCNT vs MWCNT	?	?	?	?	?	
Metals	+	?	?	?	?	
Surface defects	+	+	-	-	+	
Length	+	+	?	(+)	?	
Agglomeration	?	?	+	?	?	

Determinants of CNT/nano toxicity ?

No one-size-fits-all

Several toxicity endpoints,
expect several determinants.