

On toxicity of carbon nanoparticles

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Outline

- Introduction
- Experimental studies
- Conclusions



Introduction

- CNT/CNF are relatively new materials; only a few studies on toxicity available
- pulmonary and cutaneous toxicity are the most studied areas
- *in vitro* and *in vivo* experimental research
- studies were performed on mice, rats and guinea pigs

Design of experiments

- intratracheal instillation (ITI) — dust installed into the trachea of a small animal (changes in pulmonary region)
- artificial distribution of dust in the lung
- most of the animal studies on CNT pulmonary toxicity so far have been performed by ITI or similar techniques
- exposure by inhalation — histopathological changes in the upper respirable tract (usually not done!)

CNF in the lungs, study 1

- CNT in guinea pigs (Huczko *et al*, 2001): 25 mg of CNT per animal, by ITI
- no abnormalities of pulmonary function, or measurable inflammation
- lung pathology not examined!

CNF in the lungs, study 2

- CNF in mice (Lam, 2004)
- *respirable sized* CNT — 1 μm sized particles
- doses of 0.1 and 0.5 mg CNT/50 μl /mouse
- interstitial granulomas in the lungs of mice after 7 days
- granulomas more evident after 90 days + fibrosis
- carbon black caused only minimal tissue reactions

CNF in the lungs, study 3

- SWCNT in rats (Wahrheit *et al*, 2004)
- SWCNT of 30 nm in diameter, 0, 0.25 and 1.25 mg/rat
- granulomas in the lung tissue *non-dose-dependent*(!)
- “non-specific response to instilled aggregates, which may not have physiological relevance”

CNF in the lungs, study 4

- SWCNT in mice (Shvedova *et al*, 2005)
- purified CNT >99%(no metals), 10, 20, or 40 $\mu\text{g}/\text{mouse}$
- acute inflammation, dose dependent granulomas, progressive fibrosis
- CNTs were intrinsically toxic (irrespective if CNTs contained metals or not!)

fullerene in the lungs, study 5

- C₆₀ in rats (Baker *et al*, 2008)
- particles of 55 nm in diameter, 2.35 mg/m³ for 3 hours a day, 10 consecutive days
- minimal toxicity: no exposure related (histopathological) changes in respiratory tract
- slight decrease in red blood cells (3%, uncertain toxicological significance)

Summarized data

CNT Acute Pulmonary Toxicology Studies

Species	Nanoparticle ^d	Administration route/study duration	Dose	Adverse effects/lesions	Ref.
Mice	MWCNT	Intratracheal instillation/1, 2, 3, 7 and 30 days	1, 2.5 and 5 mg/kg	<ul style="list-style-type: none"> • Dose-dependent lethality^b • Inflammation • Dose- and time-dependent fibrosis and granulomas 	Carrero-Sanchez <i>et al.</i> , 2006
Guinea pig	MWCNT	Intratracheal instillation/4 weeks	25 mg/animal	<ul style="list-style-type: none"> • No evidence of inflammation • No perturbation of lung function 	Huczko <i>et al.</i> , 2001
Guinea pig	MWCNT	Intratracheal instillation/90 days	15 mg/animal	<ul style="list-style-type: none"> • Nonspecific desquamative interstitial pneumonia-like reaction • Increased lung resistance 	Huczko <i>et al.</i> , 2005
Mice	SWCNT	Intratracheal instillation/7 and 90 days	0.1 and 0.5 mg/animal	<ul style="list-style-type: none"> • Deaths in high dose group • Progressive, dose-dependent multifocal epithelial granulomas • Interstitial inflammation • Peribronchial inflammation and necrosis 	Lam <i>et al.</i> , 2004
Rats	MWCNT	Intratracheal instillation/1 and 2 mo	0.5, 2 and 5 mg/animal	<ul style="list-style-type: none"> • Inflammation and dose-dependent fibrosis • Bronchiolar granulomatous lesions 	Muller <i>et al.</i> , 2005
Mouse	SWCNT	Pharyngeal aspiration/1, 3, 7, 28 and 60 days	40 µg/animal	<ul style="list-style-type: none"> • Transient inflammatory response • Dose-dependent epithelioid granulomas and interstitial fibrosis • Decreased bacterial clearance, and dose-dependent loss of pulmonary function 	Shvedova <i>et al.</i> , 2005
Rats	SWCNT	Intratracheal instillation/24 h, 1 week, 1 and 3 months	1 and 5 mg/kg	<ul style="list-style-type: none"> • Deaths in high dose group^b • Transient inflammatory and cell injury responses • Nonprogressive, non-dose-dependent multifocal granulomas 	Warheit <i>et al.</i> , 2004

^aMWCNT = multiwall carbon nanotube, SWCNT = single-wall carbon nanotube.

^bDeaths were attributed to mechanical obstruction of upper airways by nanotube aggregates.

- exposure by contact with the external surfaces of the body
- mild irritation as a response (rare cases!)
- nanoscale metal oxides — used in commercially available sunscreens
- carbon based materials did not produce any notable irritant or allergic responses (*in vivo*)
- cytotoxic and proinflammatory to dermal cells *in vitro* (limited dermal penetration)



Summarized data

Cutaneous Toxicology Studies

Species	Nanoparticle ^a	Study design/duration	Dose	Adverse effects/lesions	Ref.
Human	CNT soot	Patch test/96 h	Unknown, aqueous suspension	• No irritation or signs of allergic response	Huczko and Lange, 2001
Rabbit	CNT soot	Ocular irritation (modified Draize test)/24, 48, and 72 h	Unknown, aqueous suspension	• No irritation or signs of allergic response	Huczko and Lange, 2001
Human	Fullerene soot	Patch test/96 h	Unknown, aqueous suspension	• No irritation or signs of allergic response	Huczko <i>et al.</i> , 1999
Rabbit	Fullerene soot	Ocular irritation (modified Draize test)/24, 48 and 72 h	Unknown, aqueous suspension	• No irritation or signs of allergic response	Huczko <i>et al.</i> , 1999
Rat	“Hat-stacked” carbon nanofibers	Subcutaneous implantation/ 1 and 4 weeks	Unknown	• Foreign body granuloma • No tissue necrosis • No severe inflammation	Yokoyama <i>et al.</i> , 2005
Rat	CNT	Subcutaneous implantation/ 1 and 4 weeks	0.1 mg	• Foreign body granuloma • No tissue necrosis • No severe inflammation	Sato <i>et al.</i> , 2005
Several studies— human, rabbits and guinea pigs	Nano-scale TiO ₂	Skin and ocular irritation, sensitization, photo-irritation, photo-sensitization/ Various durations	Various doses	• TiO ₂ considered non-irritant to mild irritant in all studies • No evidence of sensitization, photo-sensitization, or photo-irritation in any studies	SCCNFP, 2000
Several studies in humans	Nano-scale ZnO	Skin irritation, sensitization, photo-irritation, photo-sensitization/ various durations	Various doses	• ZnO considered non-irritant and non-photo-irritant • No evidence of sensitization or photo-sensitization in any studies	SCCNFP, 2003

^aCNT = carbon nanotube.

Summary

- nanomaterials behave more like bulk material, than like other, unrelated nanomaterials — CNF are exception!
- everything is relative: chemotherapeutic agents, insecticides, fungicides have $LD_{50} = 7 \text{ mg/kg}$
- CNF LD_{50} is not established, no deaths observed up to the maximum dose administered; LD_{50} for fullerene is $>2500 \text{ mg/kg}$

Summary

- there is no life without risk: established risks against the established benefits of nanotechnology
- $\text{risk} = \text{hazard} \times \text{exposure}$
- be careful, but not afraid!