SAFETY BY DESIGN – LESSONS FROM PARTICLE TOXICOLOGY

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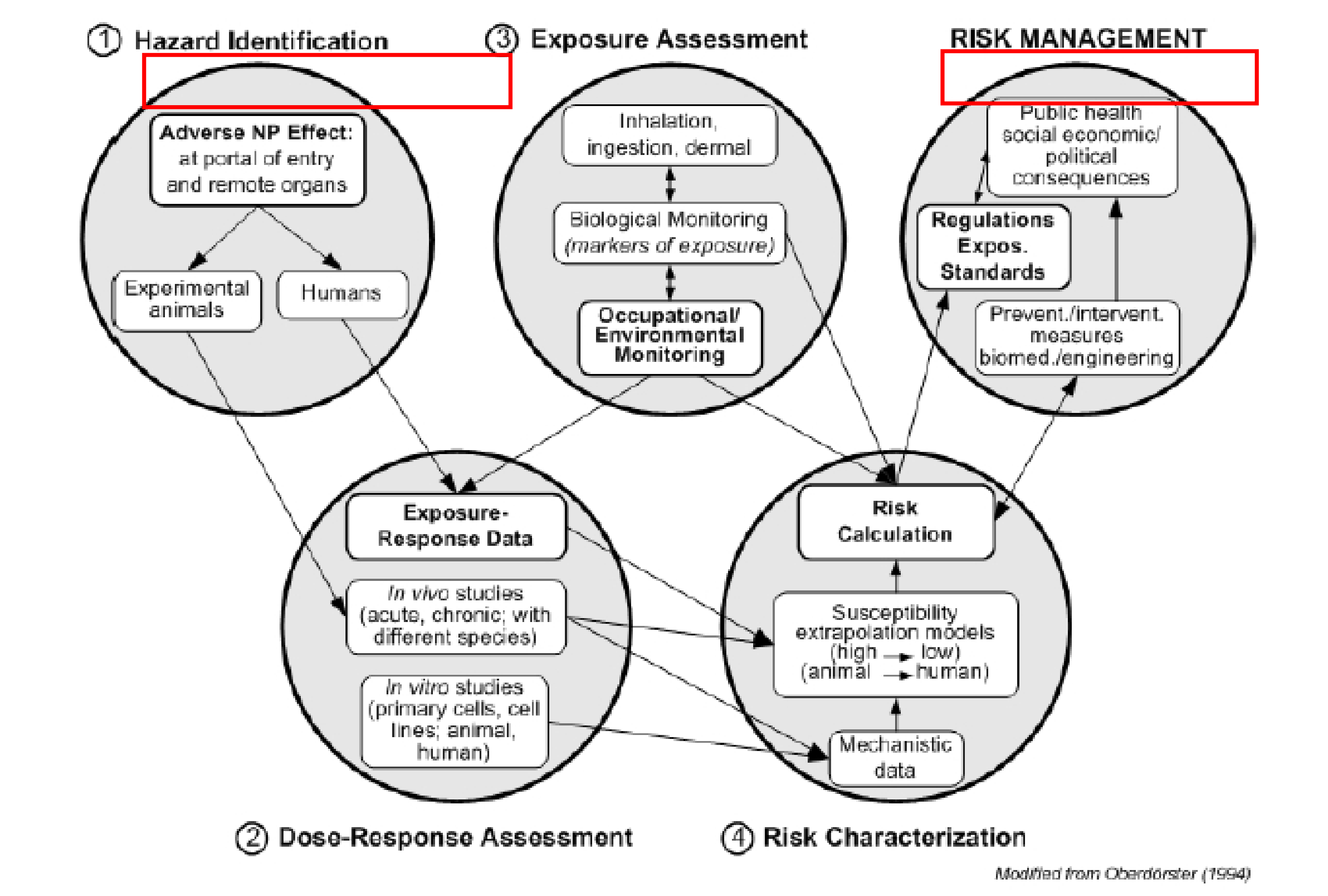
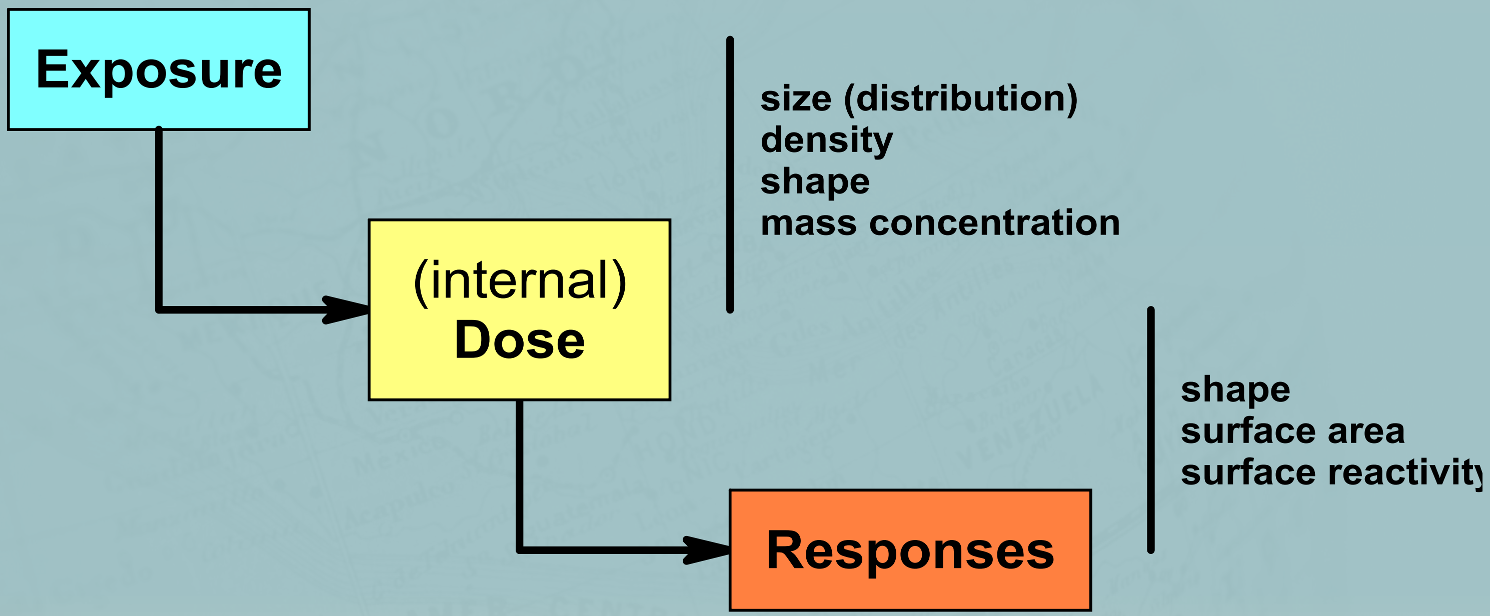
RISK ANALYSIS



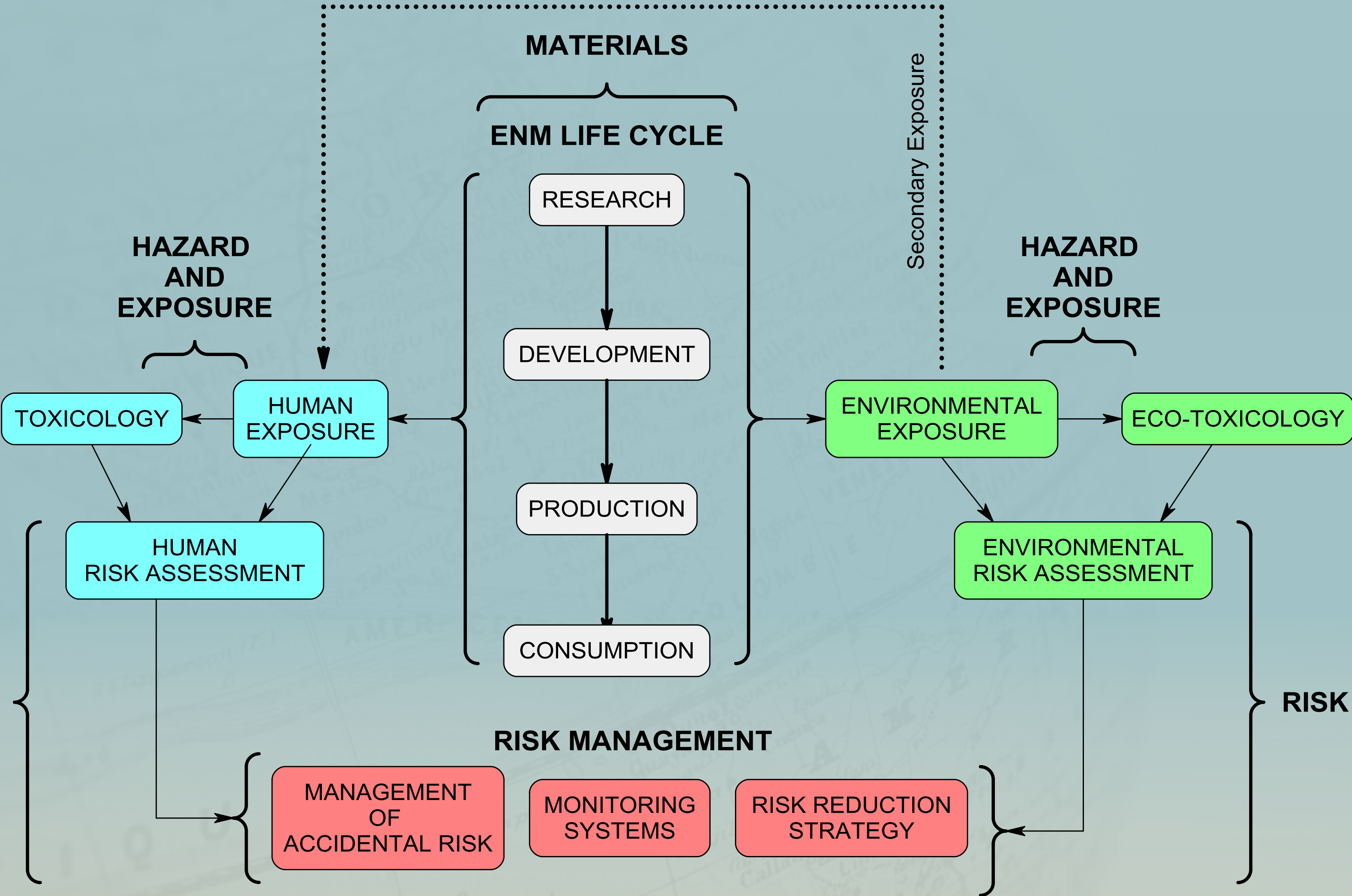
EXPOSURE

- **Emission**
  - Extent
  - Duration
  - Background
- **Mode of Exposure**
  - **Inhalation**
  - Ingestion
  - Dermal
  - Intravenous injection

METRICS FOR EXPOSURE-DOSE-RESPONSE

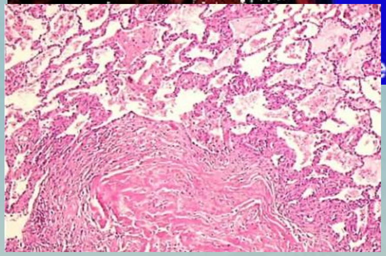


LIFE CYCLE OF ENP

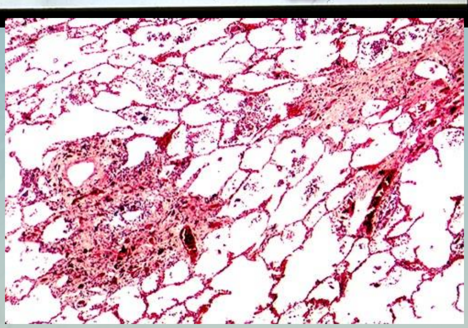


PARTICLE CAUSE LUNG DISEASE

Coal



Quartz, asbestos

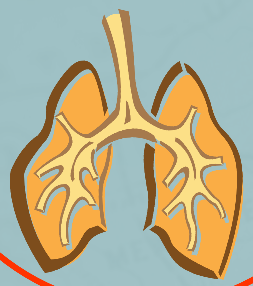


Asbestos

TARGET ORGANS FOR NANOPARTICLES EFFECTS

Lungs

In air



Gut

Cleared from lungs

In foods and drinks

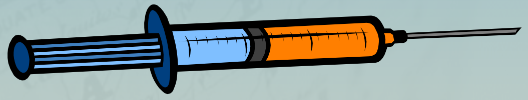
Skin

Present in cosmetics

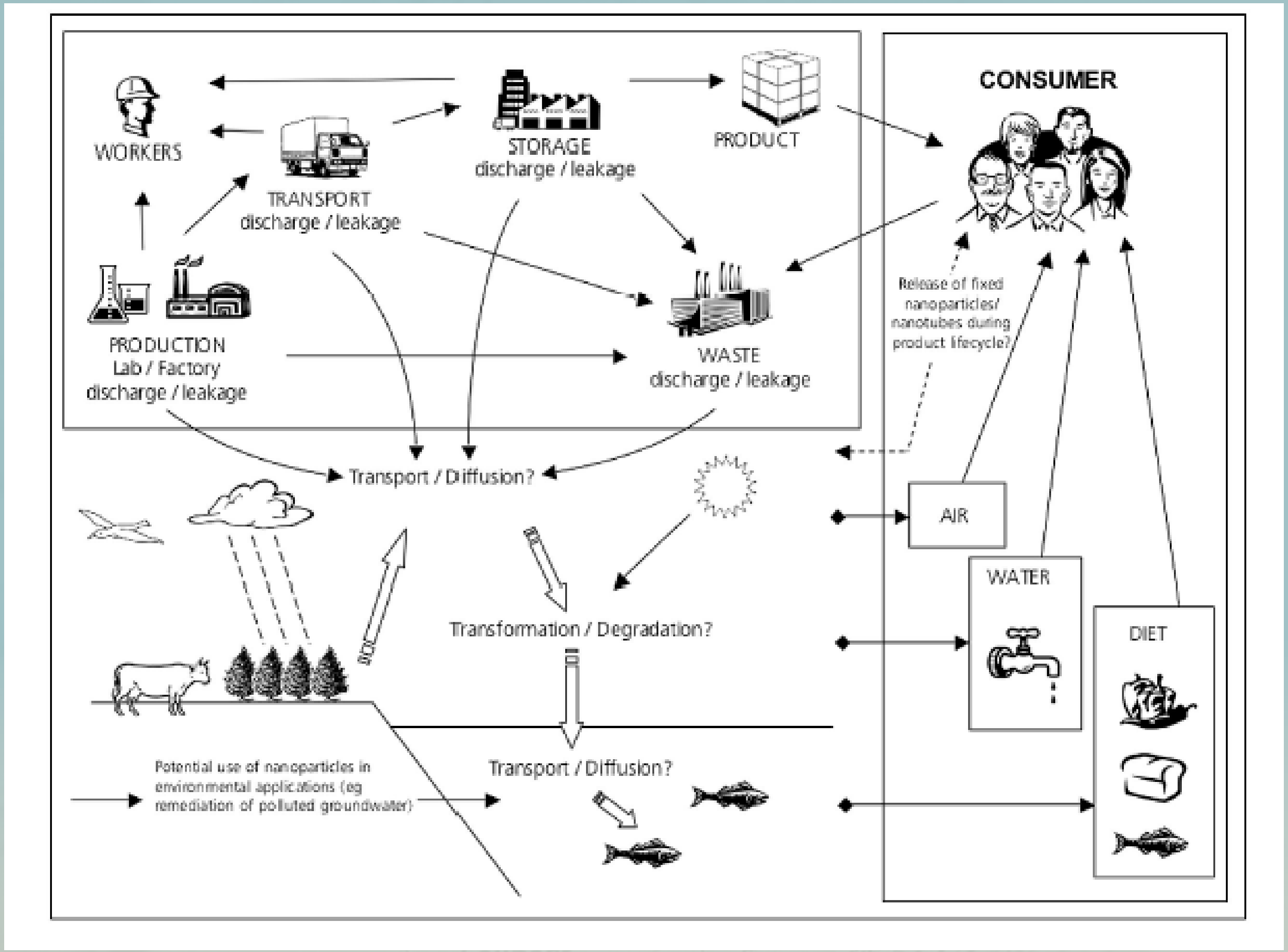
Deposition from air

Lungs, endothelium , RES

Medical nanoparticles



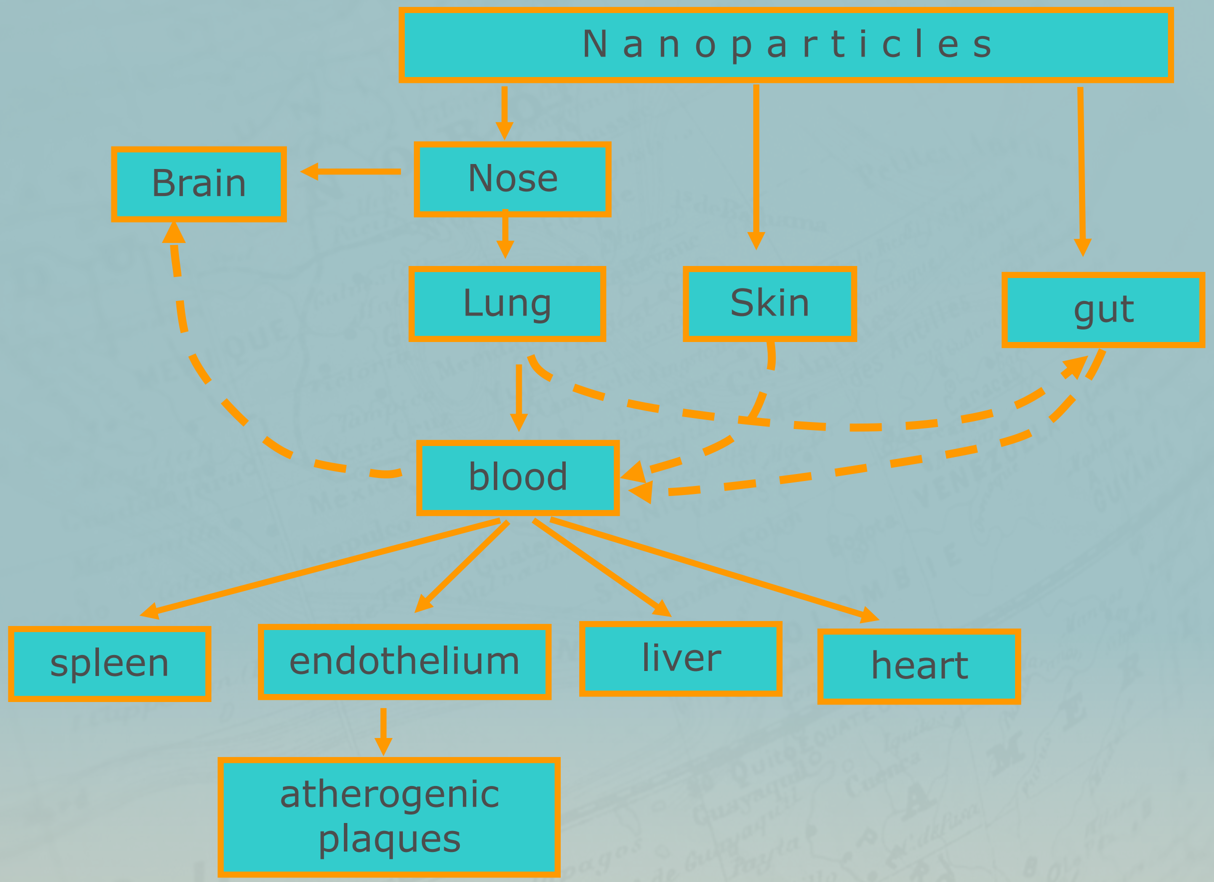
EXPOSURE PATHWAYS



RS Report Nanoscience and nanotechnologies (2004)

FROM EXPOSURE TO INTERNAL DOSE

Hypothetical Toxico-kinetics of Nanoparticles



From Internal Dose to Response

Role of inflammation and oxidative stress in disease

Combustion-derived nanoparticles

↓

This also represents the dominant hypothesis for new nanoparticles

Free radicals / oxidative stress

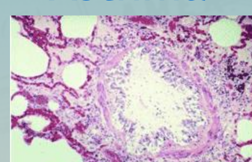
↓

Inflammation

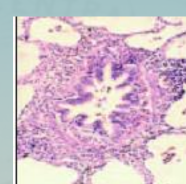
↓

Cardiovascular disease

Asthma



COPD



Scarring

Cancer

lungs

Why be concerned about exposure to nanotubes?

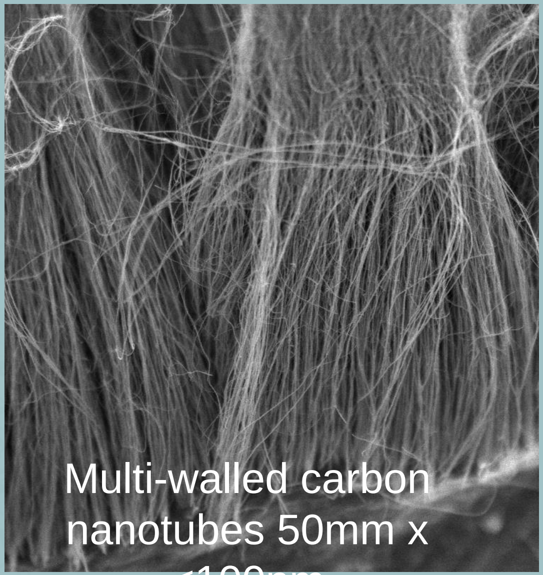
Asbestos/ fibres

↕ ?

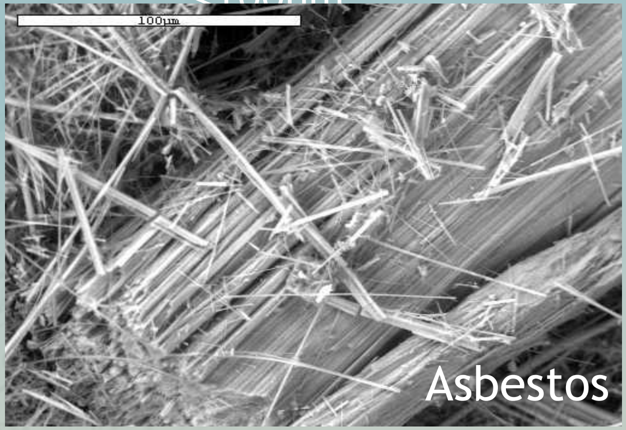
Nanotubes

↕ ?

Nanoparticles

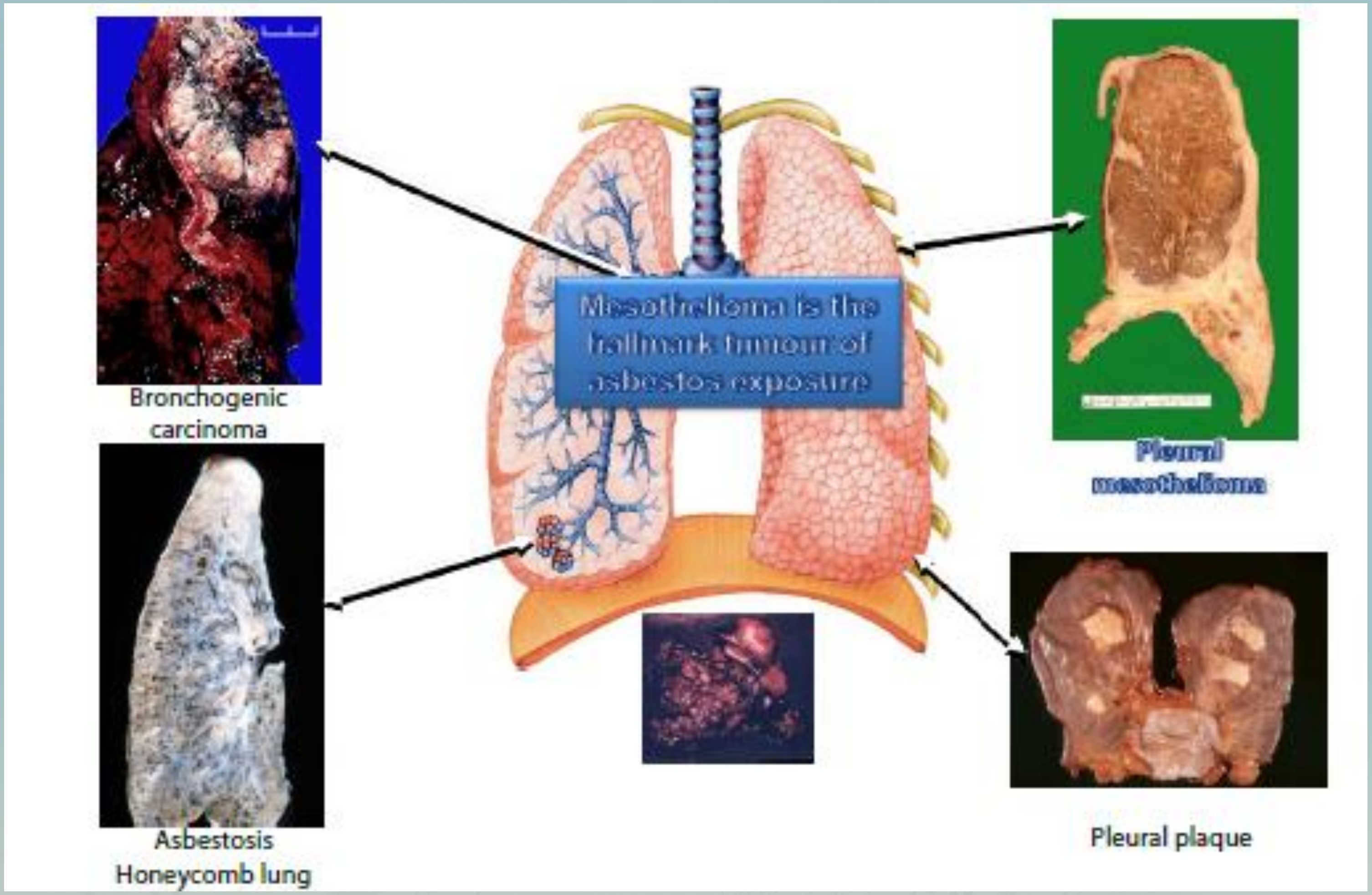


Multi-walled carbon nanotubes 50mm x <100nm



Asbestos

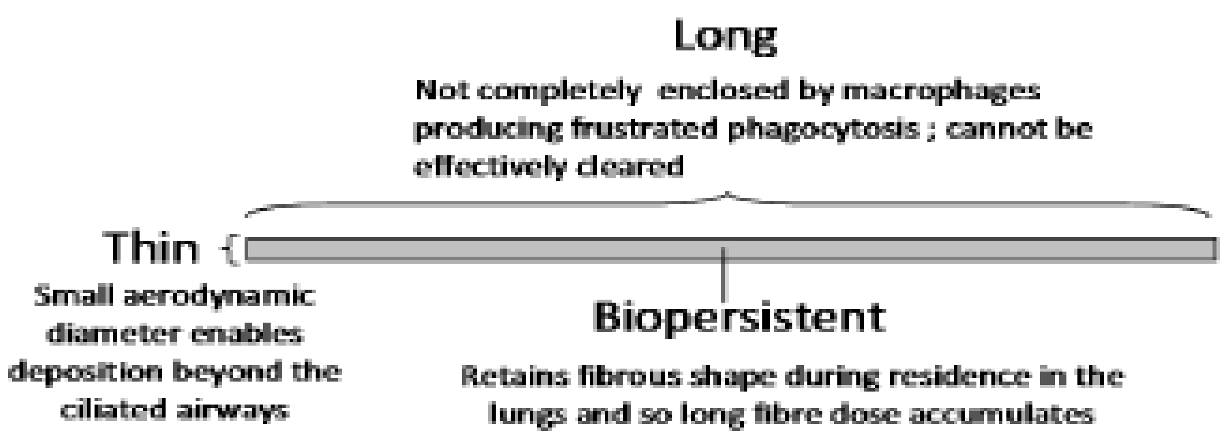
ASBESTOS RELATED DISEASES



FIBRE PATHOGENICITY PARADIGM

The most robust SAR we have in particle toxicology

- The WHO definition of a fibre is a particle which is >5μm in length and has a diameter <3μm (making it respirable) and an aspect ratio of greater than 3:1
- In fact to be pathogenic a fibre must be:



AERODYNAMICS OF LONG FIBRES

ALL OF THE PARTICLES BELOW HAVE AN AERODYNAMIC DIAMETER OF 2 µm: assumes unit density; data courtesy of Dr G. Oberdorster

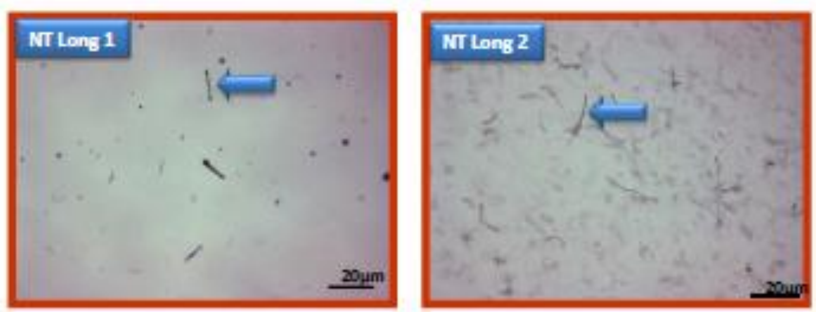
Actual diameter (µm)	Actual length (µm)
0.9	3
0.7	10
0.6	30
2	-

All $D_{ae} = 2$ µm

The aerodynamics of loose bundles

PANEL OF FIBRES AND MWCNT

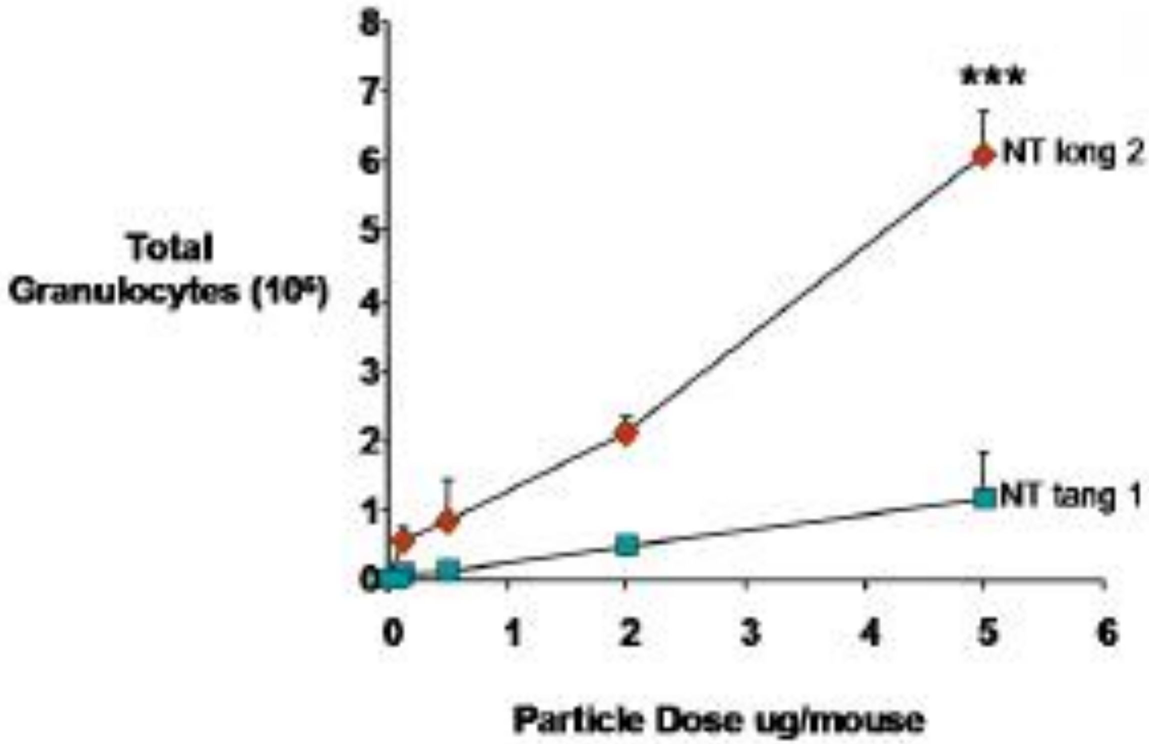
	Length	% greater then 20 mm
NT Tang 1	1-5 μm	~
NT Tang 2	5-15 μm	~
NT Long 1	mean 13μm	24
NT Long 2	max 56μm	84

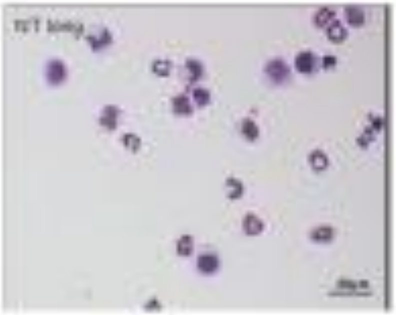


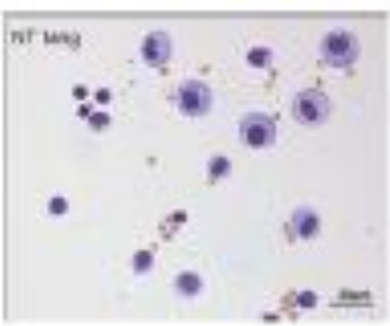
PLEURAL INFLAMMATION
ONLY LONG CNT ARE INFLAMMOGENIC IN PLEURAL SPACE OF MICE

Dose response

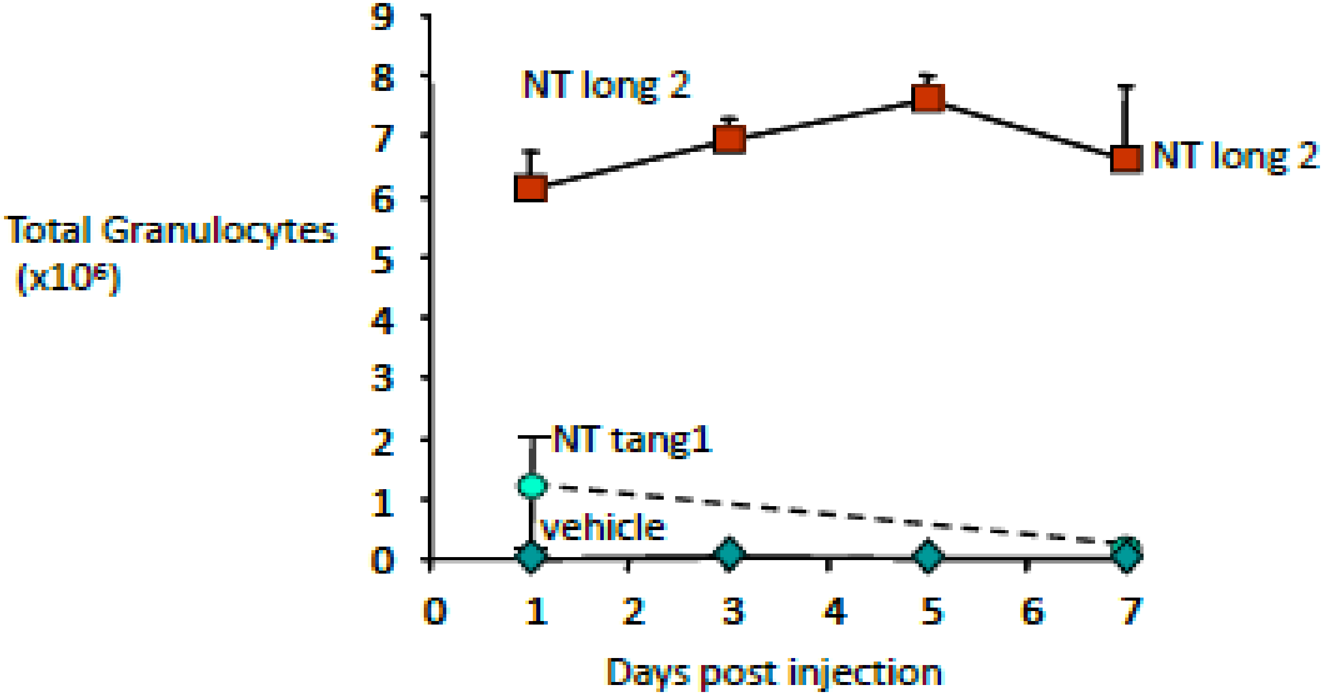
0.1µg-5ug/mouse dose







PERSISTENT INFLAMMATION IN PLEURAL SPACE BY LONG CNT

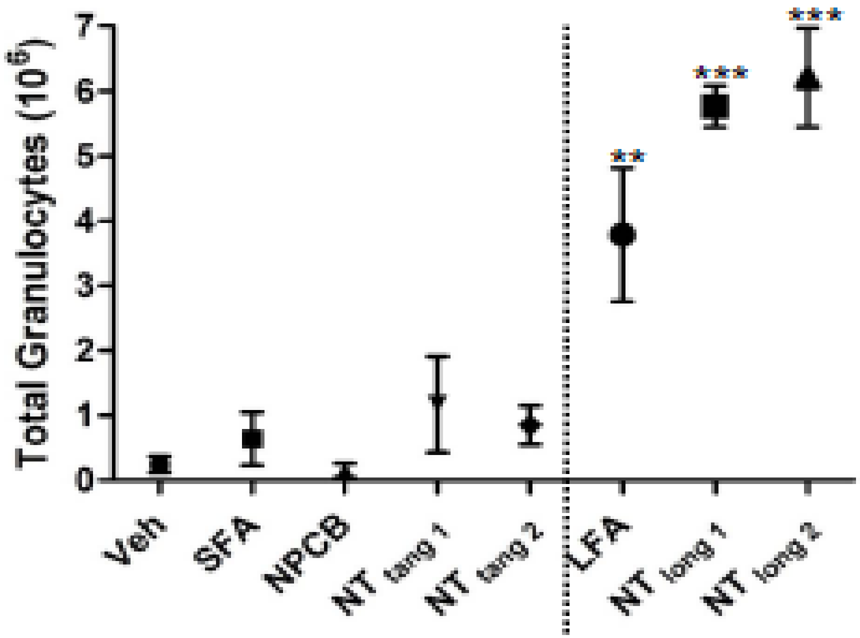


Timecourse

Dose 5µg/mouse

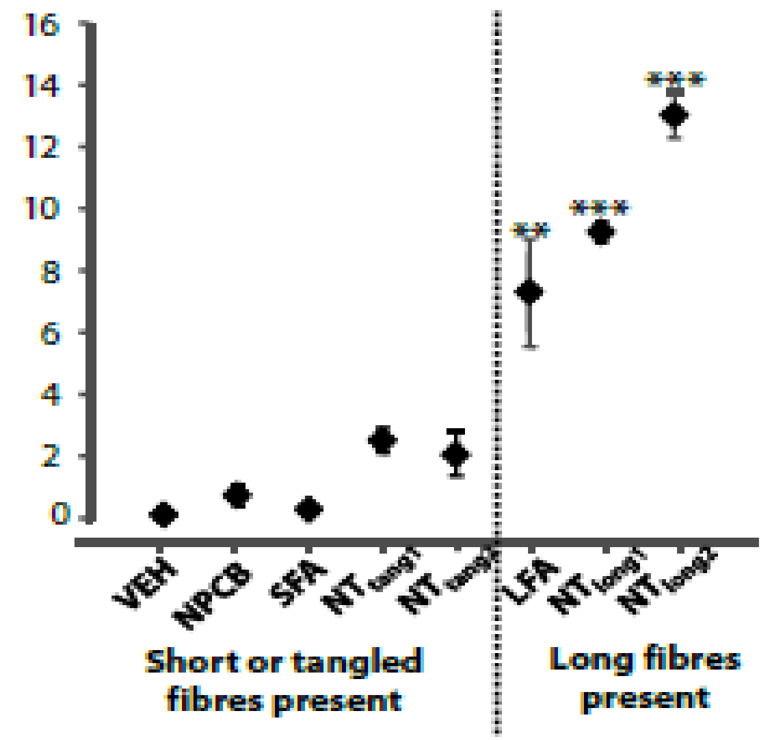
SIMILAR RESPONSES IN PLEURAL AND PERITONEAL CAVITIES TO INSTILLED CNT PANEL

Pleural cavity



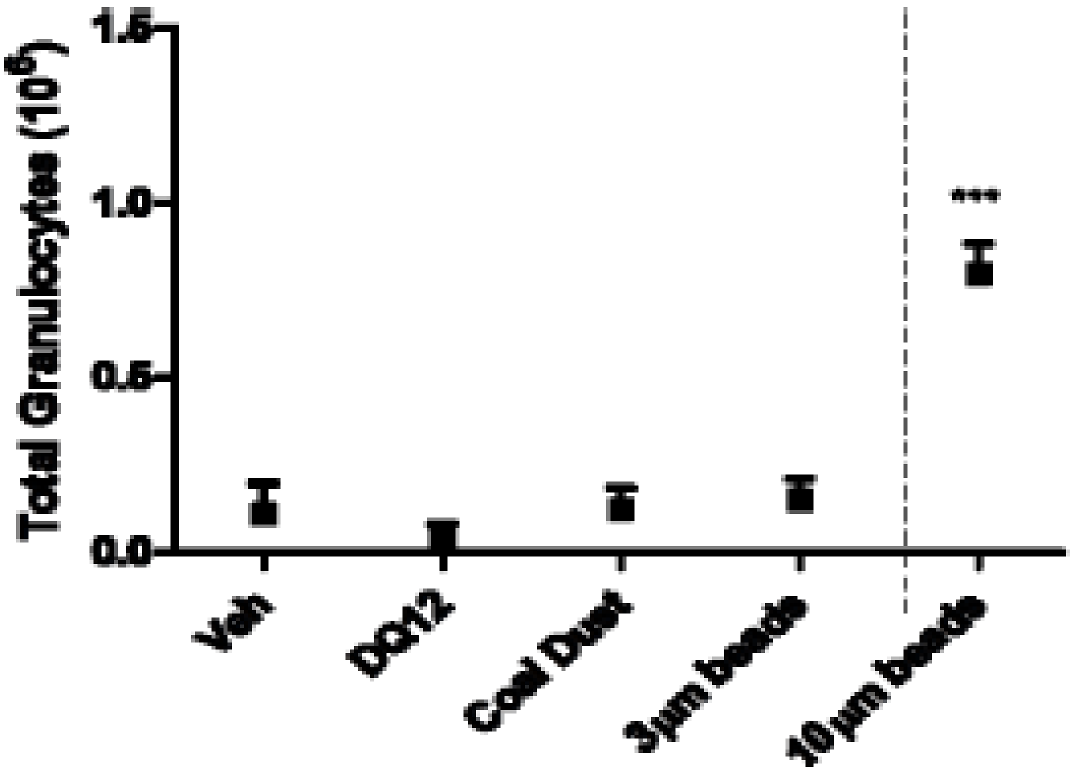
The panel

Peritoneal cavity



Poland et al 2008

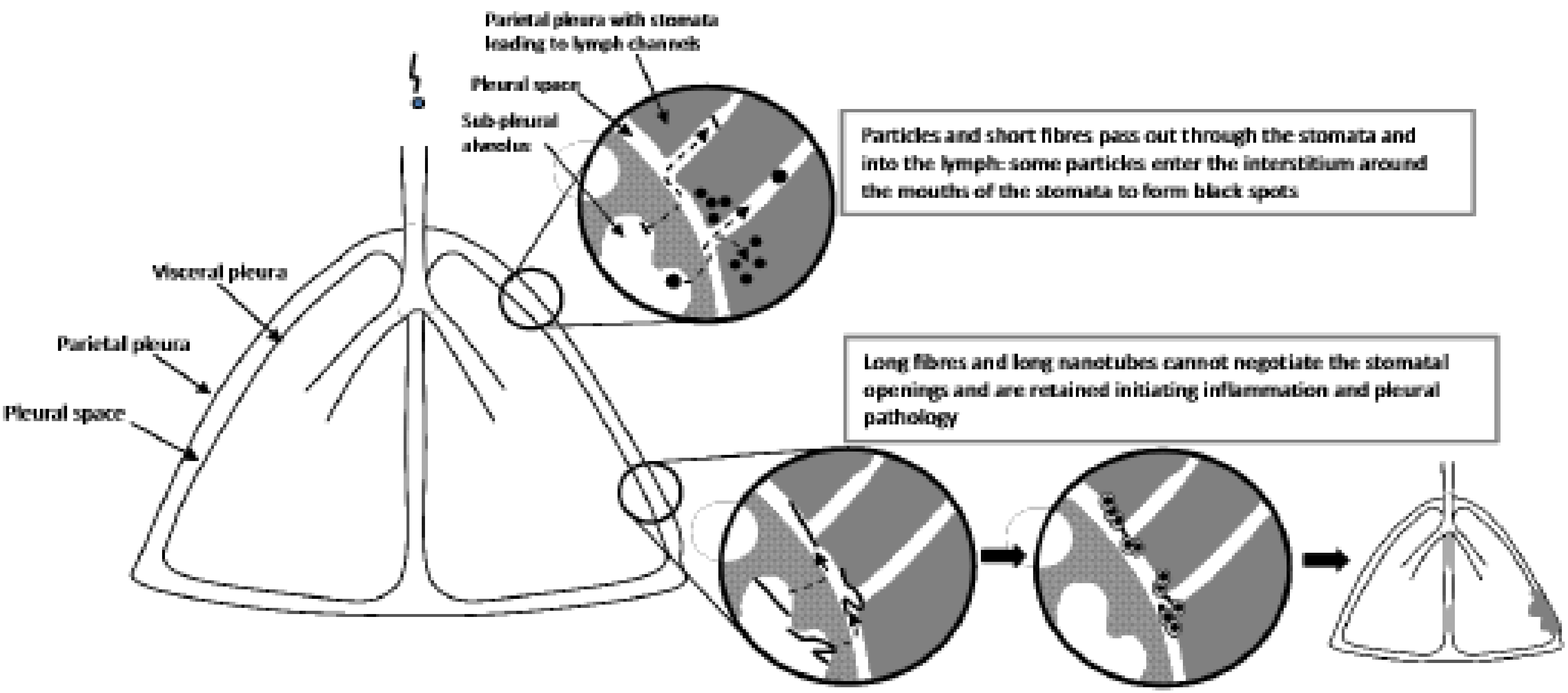
FURTHER VERIFICATION



Even though a proportion of all deposited particles transit through the pleura these data suggest that, for compact particles, no retention (or inflammation) would occur as rapid clearance out through the stomata is the norm

The elutriating effect of the airways ensures that only very small compact particles ever reach the pleura and they easily negotiate the stomata

MECHANISMS FOR MWCNT TOXICITY



BIOPERSISTENCE OF MAN MADE VITREOUS FIBRES

- 2 Man Made Vitreous Fibres
  - MMVF21 – Traditional Stone Wool
  - MMVF34 – HT Stone Wool

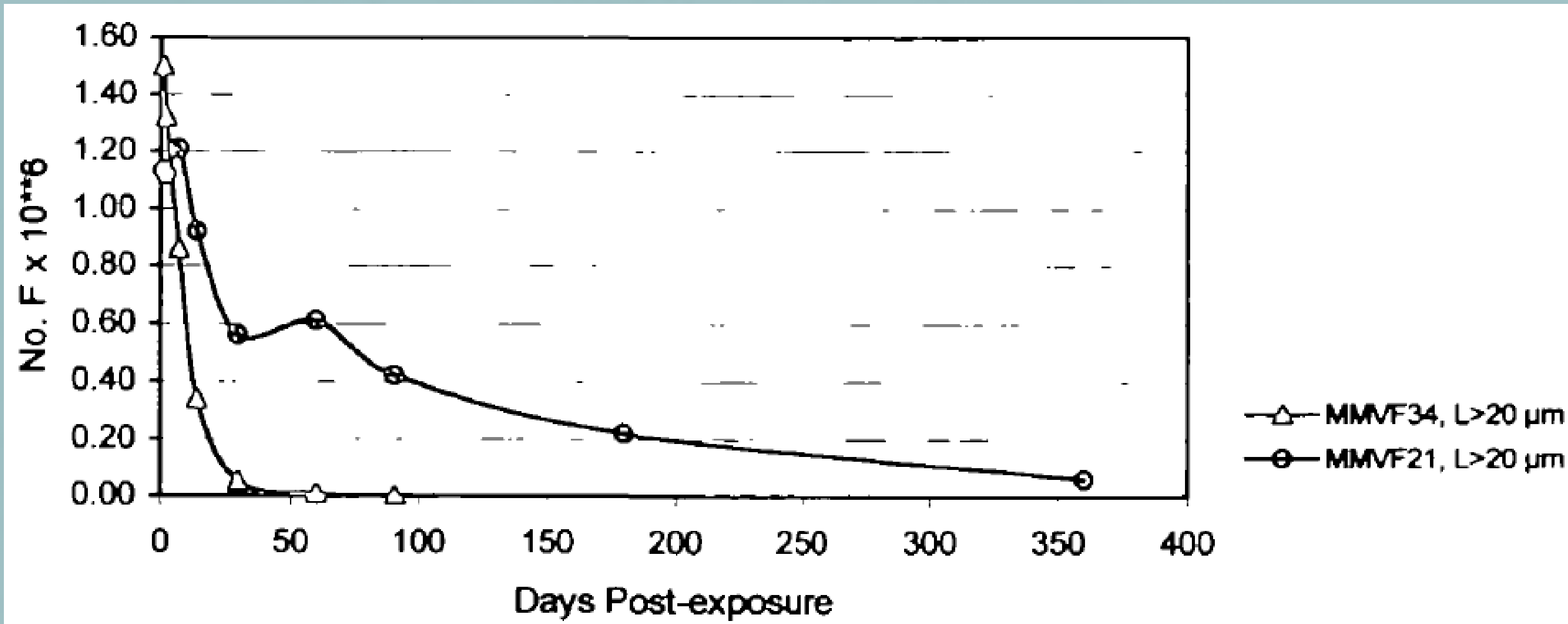
	MMVF21	MMVF34
% SiO2	45.9	38.9
% Al2O3	13.8	23.2
% TiO2	3 0	2.1
% FeO	6.2	6.7
% CaO	17.0	15 0
% MgO	9.5	9.6
% Na2O	2.5	1.9
% K2O	1 3	0.8
Other oxides	0.4	0.9

Fibre Composition: MMVF21/MMVF34

Fibre	Dissolution rate ($ng\,cm^{-2}\,h^{-1}$) pH 7.5	pH 4.5
MMVF21	23 (16–30)	59 (41–77)
MMVF34	59 (41–77)	620 (434–806)

Fibre Dissolution MMVF21/MMVF34 in different pH.

RESULTS FROM SHORT-TERM INHALATION STUDIES



Short term inhalation studies – Rate of removal of Long fibres (l > 20 um)

Study	WHO (F/cm^3)	$>20\ \mu m$ (F/cm^3)	Grav. conc. (mg/m^3)
MMVF21—5 days	467	147	58
MMVF34—5 days	370	161	60
MMVF34—3 months	282	84	31
MMVF34—12 months	264	82	31
MMVF34—18 months	288	86	31
MMVF21—study mean	150	74	16
MMVF21—study mean	243	114	30

Mean aerosol concentrations for MMVF21 and MMVF34

PULMONARY CHANGES AFTER DIFFERENT PERIODS OF EXPOSURE

Table 8. Lung burdens per mg dry lung and pulmonary changes (mean Wagner scores) after different periods of exposure

Fibre	Exposure aerosol		Lung burden (Fibres per mg dry lung $\times 10^3$)				Interstitial fibrosis (Mean Wagner Score[1])			
	mg/m³	L > 20 µm/cm³ WHO/cm³	3 months exposure $L > 20\,\mu m$ WHO	6 months exposure $L > 20\,\mu m$ WHO	12 months exposure $L > 20\,\mu m$ WHO	18 months exposure $L > 20\,\mu m$ WHO	3 months exposure	6 months exposure	12 months exposure	18 months exposure
MMVF21	16.1	74	8	16	37	58	2.2	2.7	2.7	4.0
		150	38	85	210	233				
	30.4	114	18	23	55	62	3.2	3.3	3.3	4.0
		243	83	143	319	283				
MMVF34	30.5	86	8	11	10	11	1.6	2.6	2.6	2.8
		288	108	147	152	222				

*Wagner Score.
Cellular change: 1 = Normal, 2 = Minimal, 3 = Mild
Fibrosis. 4 = Minimal, 5 = Mild, 6 = Moderate, 7–8 = Severe.

THE PARADIGM OF RISK MANAGEMENT

Fundamental to the Strategy for Occupational Health and Safety with Nanotechnology is the Risk Management Paradigm

EXPOSURE **HAZARD**

RISK

= EXPOSURE x HAZARD

↓

Risk Assessment

Unacceptable **Acceptable**

↓ ↓

Reject **Manage**

CONCLUSIONS

- Control limit for exposure to Engineered Nanomaterials is essential for Risk Assessment
- Nanomaterials have high surface to volume ratio and this will lead to low mass based control limit
  - **e.g 7 µg/m^3 for carbon nanotube**
- Can the workplace exposure be controlled at such low (mass based) level of exposure?
- If this is not feasible then we must look forward to a new generation of engineered nanomaterials that are:
  - **SAFE BY DESIGN**
- i.e. We must understand which physico-chemical characteristics of nanomaterials can drive the toxicity and design new industrially useful nanomaterials without these features