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Inhalation of nanoparticles and health effects

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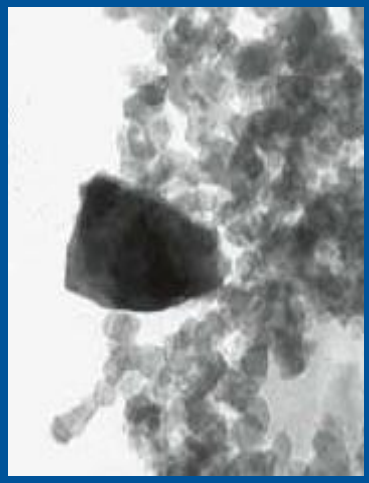
Urban air particles - a health hazard

- Extensive epidemiological studies have demonstrated an association between air pollution particles and mortality and morbidity of lung- and cardiovascular diseases
  - Acute exposure
  - Chronic exposure



Much focus on the importance of the nano-sized fraction (ultrafine) of urban air particles

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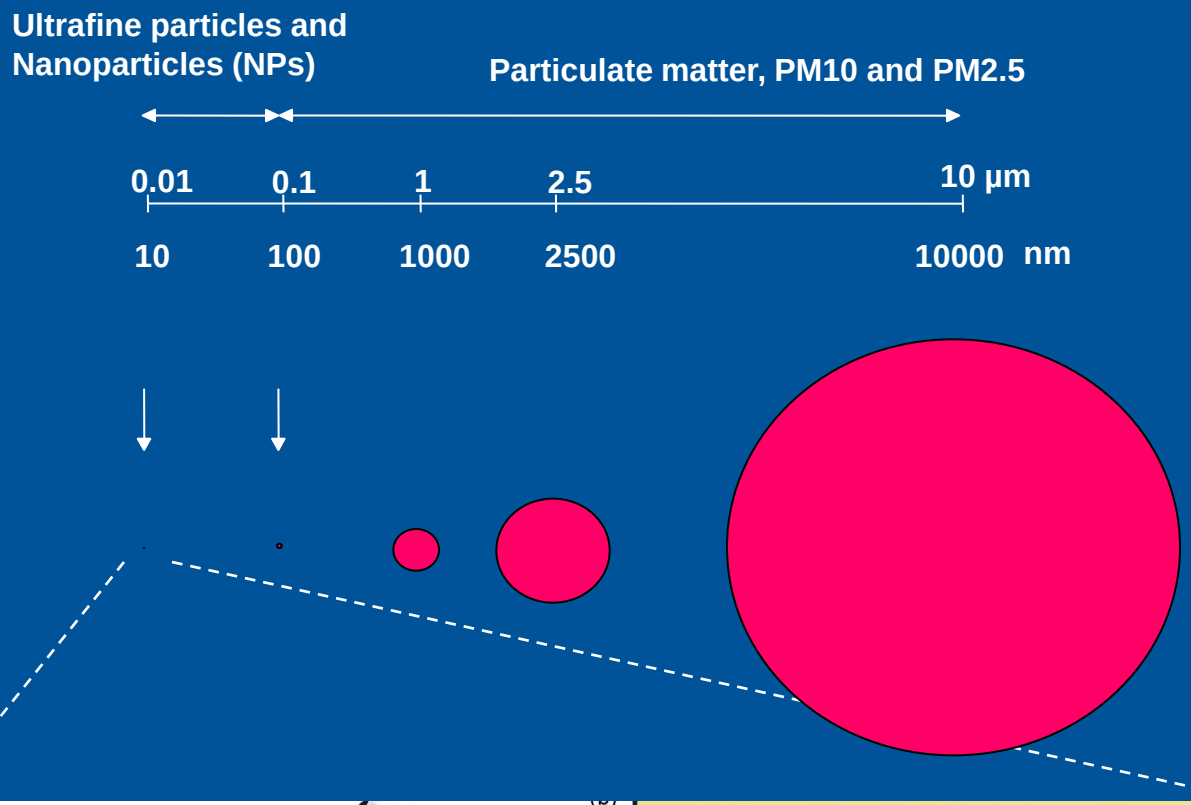
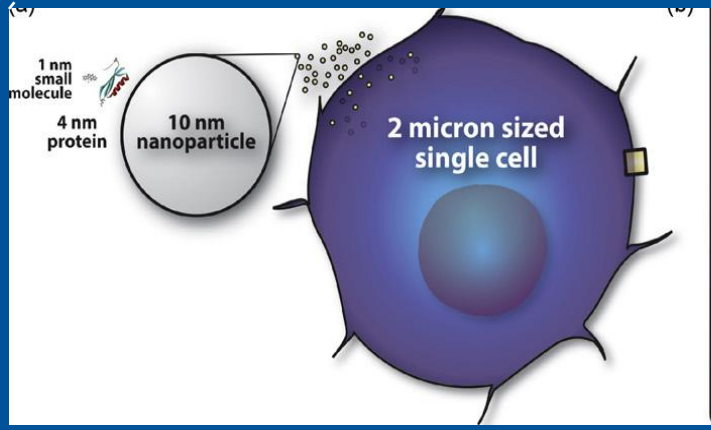
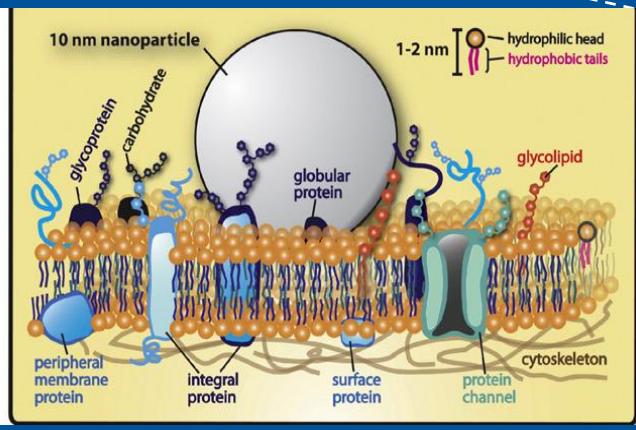
Ultrafine particles: particles- with aerodynamic diameter lower than 100 nm

Engineered nanoparticles- with at least one dimension lower than 100 nm.







Suh et al. (in press)

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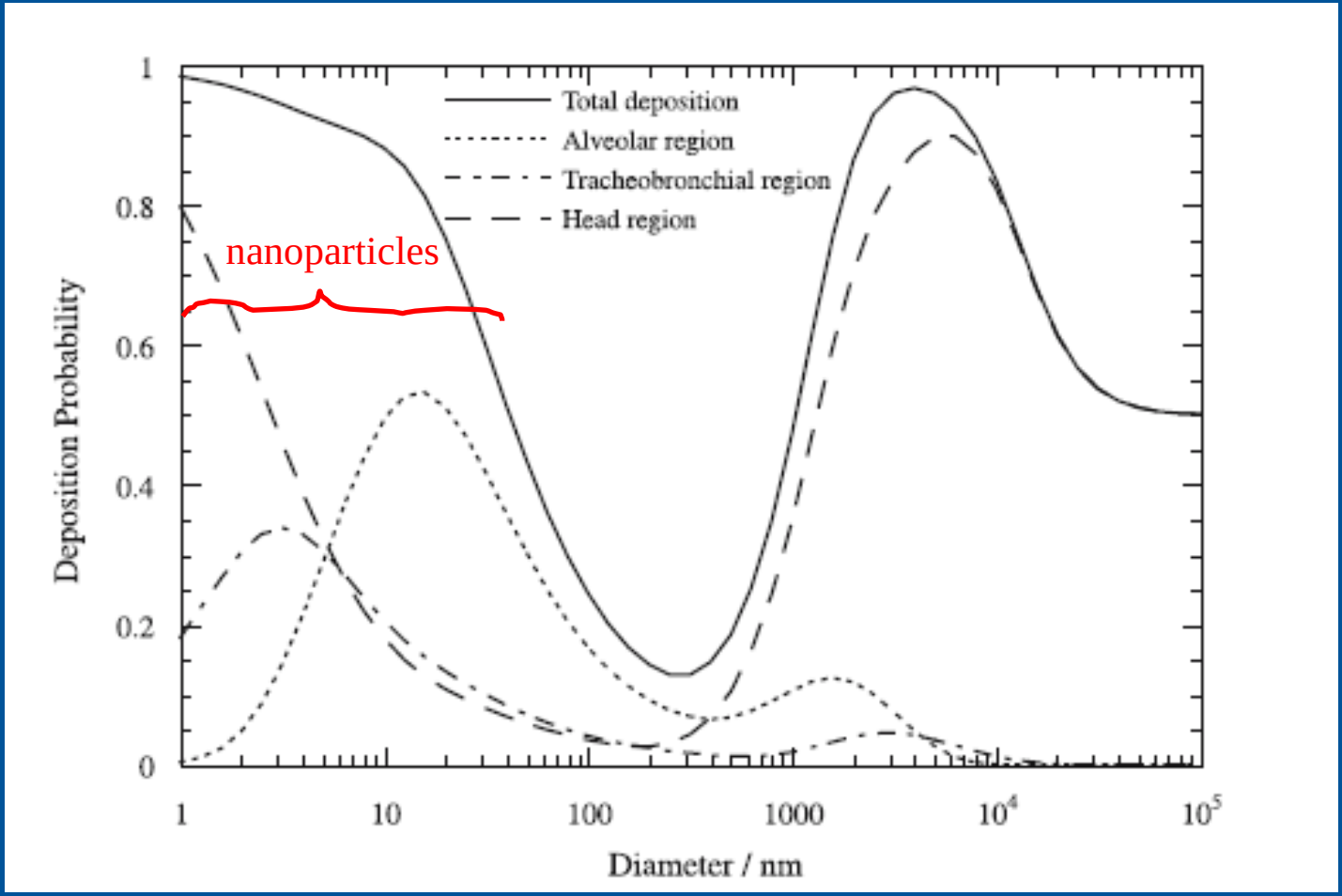
Deposition of nanoparticles in the respiratory system



NPs in lung: different deposition according to particles dimension

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Other particle characteristics important for adverse health effects

- Biopersistence in the lung
- Surface area/ reactivity
- Shape (fiber)
- Binding of proteins in the lining fluids of the lung
- Agglomeration/ aggregation properties

No single particle characteristic as a hallmark indicator for fate and pulmonary toxicity has been identified

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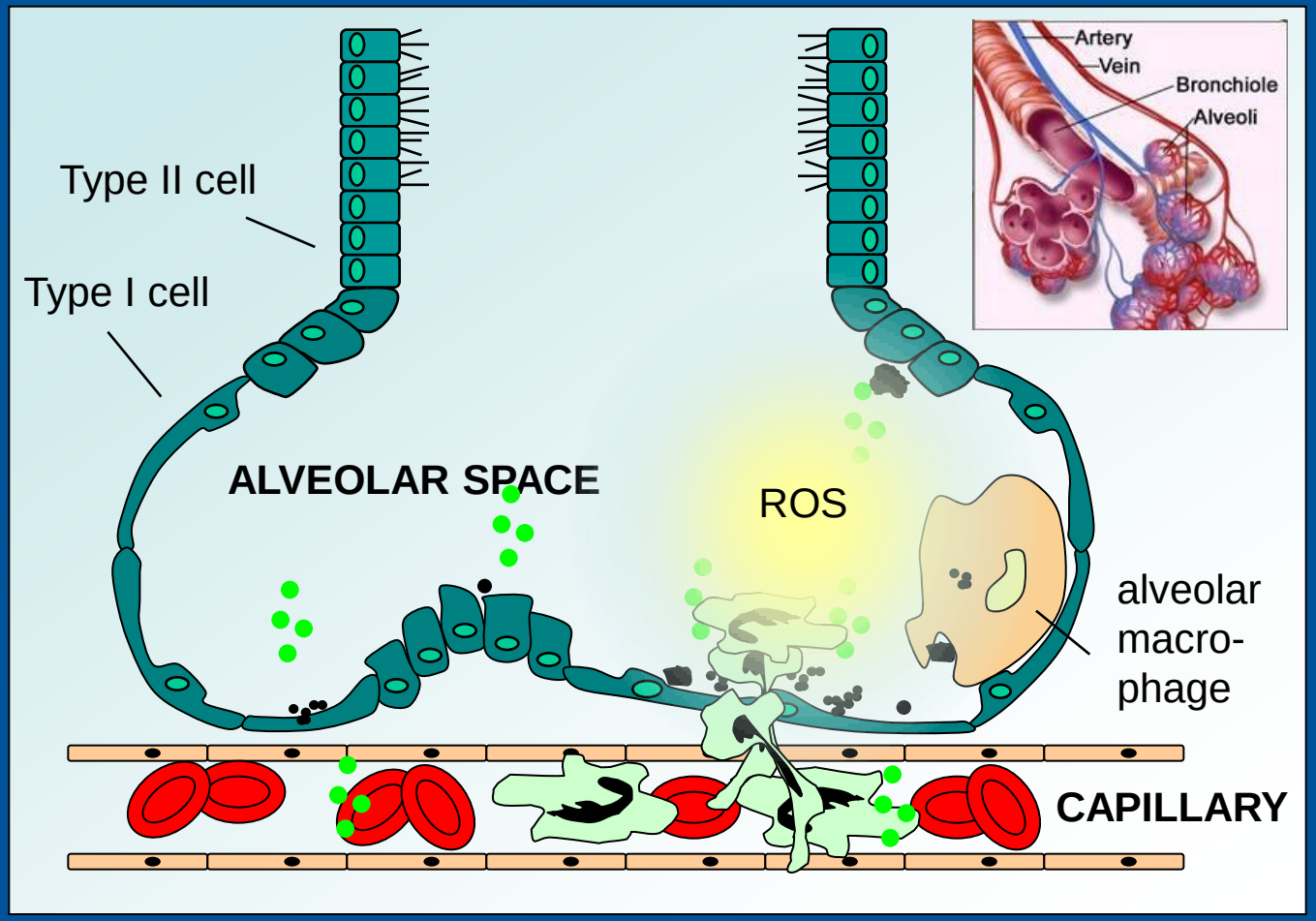
Inflammation
–Crucial for health effects induced by particles



Release of inflammatoric mediators (eg IL-6)

Dilatation & leakage from capillaries

Attraction of immune cells

Production of reactive oxygen species (ROS)

Development of tissue damage

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Lung inflammation

- Lung inflammation plays a key role in development and aggravation of lung diseases such as asthma, chronic obstructive pulmonary disease, silicosis/fibrosis and during lung infections
- Barrier disruption with increased particle translocation

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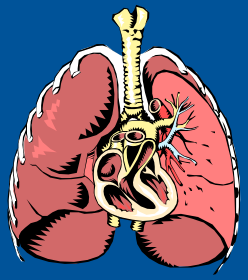
Mechanisms of disease and death induced by particulate matter

Particles

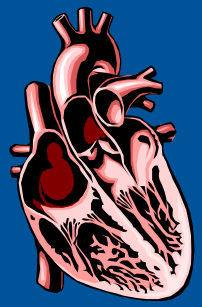


Particles and components enter the circulation

Release of inflammatory mediators to the circulation

Inflammation responses in lung

Lung disease



- Stress responses
- Remodulation of the heart
- Changes of heart rate variability
- Blood coagulation
- Atherosclerosis

Cardiovascular diseases

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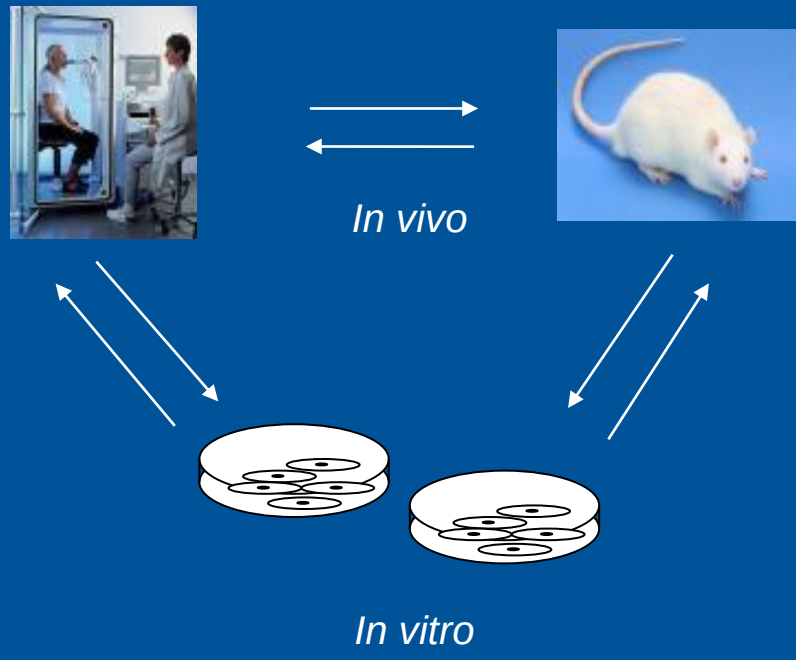
Lung exposure to nanoparticles

- Human inhalation chambers
  - Mainly diesel exhaust particles
- Animal inhalation studies (acute, subacute, subchronic, chronic)
- Intratracheal instillation
  - Similar effects as with inhalation studies
- Use of lung cells culture (*in vitro*)



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Human inhalation chamber

- Diesel exhaust
  - High level of nanoparticles
  - Short term changes of lung and systemic inflammation, thrombogenesis, vascular function and brain activity
  - Uncertainty about which diesel exhaust component that is responsible
- Ultrafine carbon particles
  - Subtle effects on vascular endothelial function
  - Effects on heart rate variability
- Zinc oxide nanoparticles
  - No acute systemic effects in healthy subjects

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Animal inhalation studies

- ***Acute***
  - Nanosilver (18-20 nm): No significant effects (750 µg/m^3) (*Sung et al 2011*)
  - Nickel nanoparticles: Endotelial distruption and impaired vasorelaxation from 100 µg/m^3 (*Cuevas et al. 2010*)
- ***Subacute*** (OECD 412)
  - Amorphous silica (38 nm): Pulmonary and cardiovascular alterations in old rats (*Chen et al. 2008*)
  - Nanosilver (~10 nm): Minimal inflammatory response and cytotoxicity (*Stebounova et al. 2011)*
- ***Subchronic*** (OECD 413)
  - Ultrafine TiO_2 (21 nm): Prolongation of lung retention and acute inflammatory response (*Ferin et al. 1992)*
  - Ultrafine TiO_2: Rats developed a more severe inflammatory response than mice and hamsters (*Bermudez et al. 2004***)**
  - Nanosilver (18-19 nm): Lesions in rat lung and liver, NOAEL 100 µg/m^3 (*Sung et al 2009*)
  - Gold nanoparticles (4-5 nm): Small changes in lung histopathology and fuction in high-dose rats, NOAEL 0.38 µg/m^3 (*Sung et al 2011*)

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Higher lung inflammatory response after exposure to TiO_2-D (21 nm) than TiO_2-F(250 nm)

TABLE 4

*Polymorphonuclear leukocytes in lavage fluid during and after 3 mo of inhalation**

Time from Start of Exposure (wk)	Control		TiO_2-D		TiO_2-F	
	No. × 10^{-5}	95% CI	No. × 10^{-5}	95% CI	No. × 10^{-5}	95% CI
4	0.92 ± 0.3	(0.65, 1.19)	3.59 ± 1.0	(2.74, 4.45)	1.54 ± 0.9	(0.80, 2.27)
8	0.61 ± 0.3	(0.39, 0.83)	47.16 ± 8.5	(40.08, 52.25)	1.10 ± 0.6	(0.58, 1.62)
12	0.68 ± 0.3	(0.40, 0.95)	87.38 ± 19.2	(71.3, 103.45)	4.03 ± 3.1	(1.41, 6.66)
41	0.82 ± 0.3	(0.61, 1.04)	12.84 ± 5.7	(8.1, 17.6)	2.58 ± 1.2	(1.50, 3.66)
64	1.01 ± 0.3	(0.51, 1.43)	2.63 ± 1.7	(0.5, 4.7)	1.93 ± 0.6	(1.21, 2.65)

Definition of abbreviation: CI = confidence interval.
* Values are mean ± SD; n = 5 to 8 per group.

Ferin et al.1992, Am J Respir Cell Mol Biol

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Subchronic inhalation of gold NPs (4-5 nm)

Table 11 Histopathologic observations for female rats.

GROUP:					Control		Low		Middle		High	
Number of Animals					10		10		10		10	
					N	%	N	%	N	%	N	%
Liver	No microscopic findings				9/10	90	9/10	90	8/10	80	7/10	70
	Abnormality				1/10	10	1/10	10	2/10	20	3/10	30
		Inflammation	Focal	minimum	0/10	0	1/10	10	0/10	0	0/10	0
				mild	1/10	10	0/10	0	0/10	0	0/10	0
	Sign	Necrosis	Focal	minimum	0/10	0	0/10	0	1/10	10	1/10	10
		Vacuolization	Hepatocellular	minimum	0/10	0	0/10	0	1/10	10	2/10	20
				mild	0/10	0	0/10	0	0/10	0	1/10	10
Lungs	No microscopic findings				10/10	100	10/10	100	9/10	90	3/10	30
	Abnormality**				0/10	0	0/10	0	1/10	10	7/10	70
	Sign	Inflammation**	Focal	minimum	0/10	0	0/10	0	1/10	10	6/10	60
				mild	0/10	0	0/10	0	0/10	0	1/10	10

**, $p < 0.01$, compared with control. Abnormality" refers to such changes as inflammation, vacuolization and necrosis upon histopathological examination. One abnormality is counted even if inflammation and necrosis are present simultaneously

Sung et al 2011, PFT

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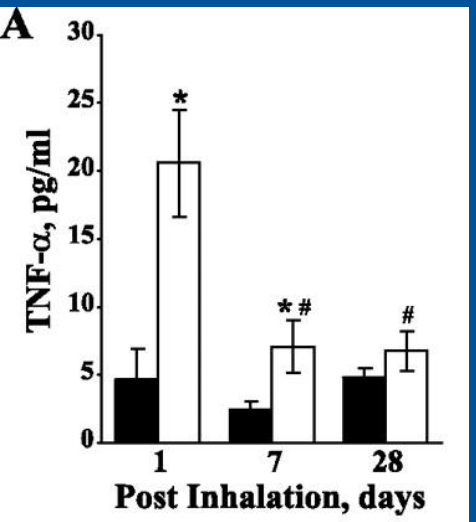
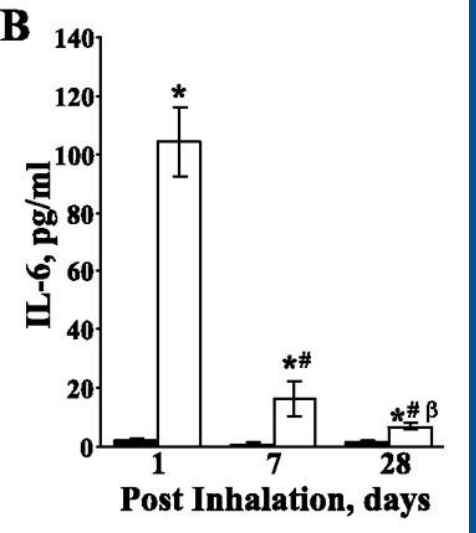
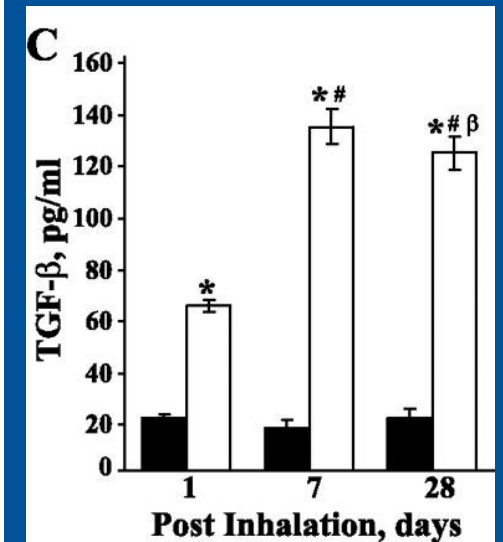
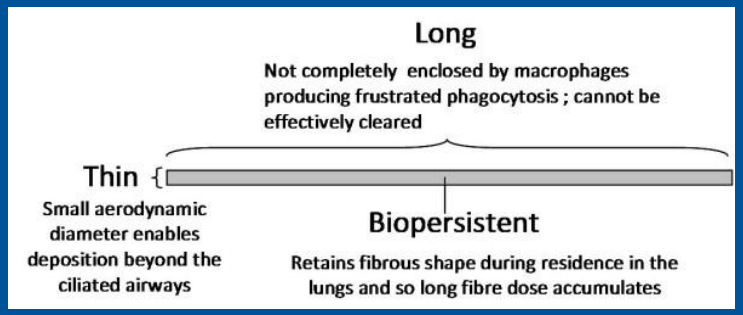
Inhalation of carbon nanotubes (SWCNT) induced both pro-inflammatory and fibrogenic responses









Donaldson et al. 2010 PFT

- Do carbon nanotube have hazards similar to asbestos?
- Asbestos causes fibrosis and mesothelioma (cancer in the pleural mesothelia)

Shedova et al. 2008, Am J Phys Lung Cell Phys

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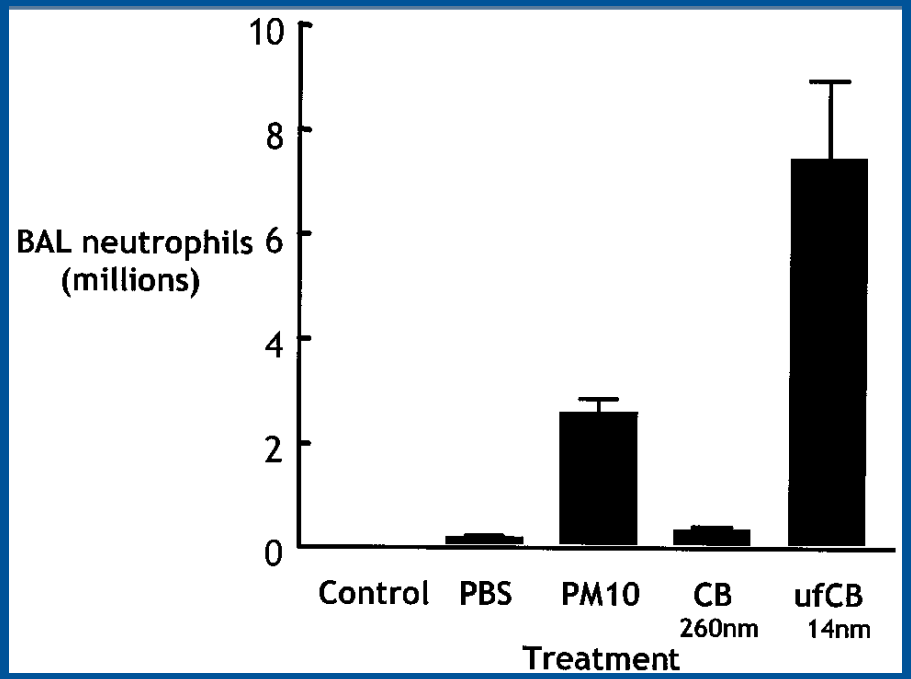
Instillation of particles

- Much used surrogate for inhalation route
- Predict the potential for inhaled particles to produce lung hazard effects
- Similar effects as with inhalation studies



Donaldson et al. 2002, J Aero Med

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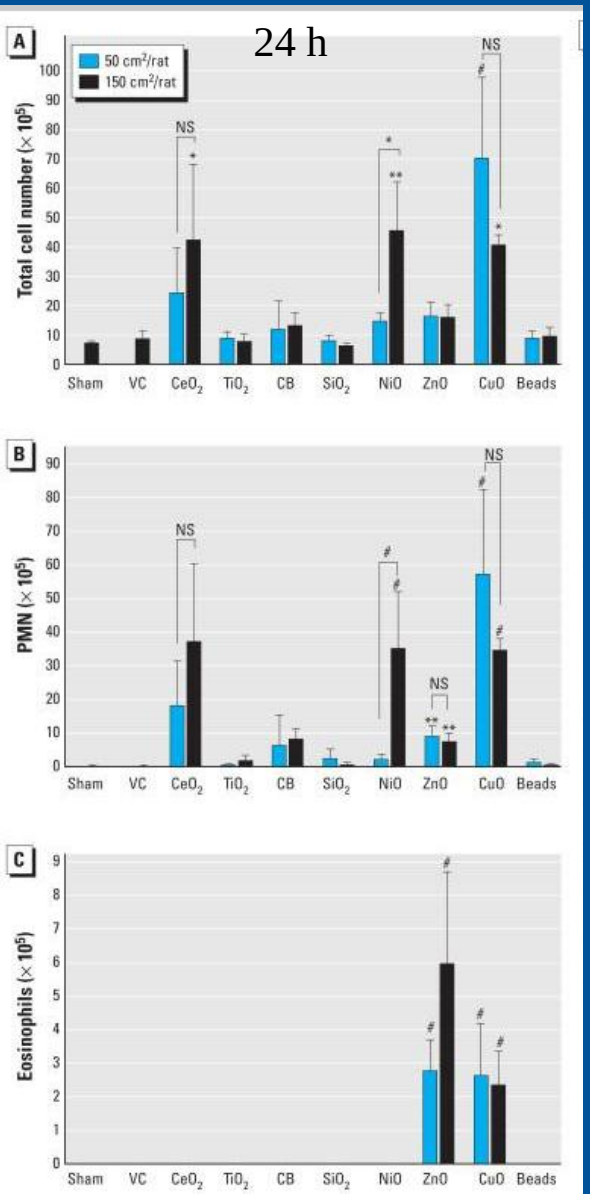
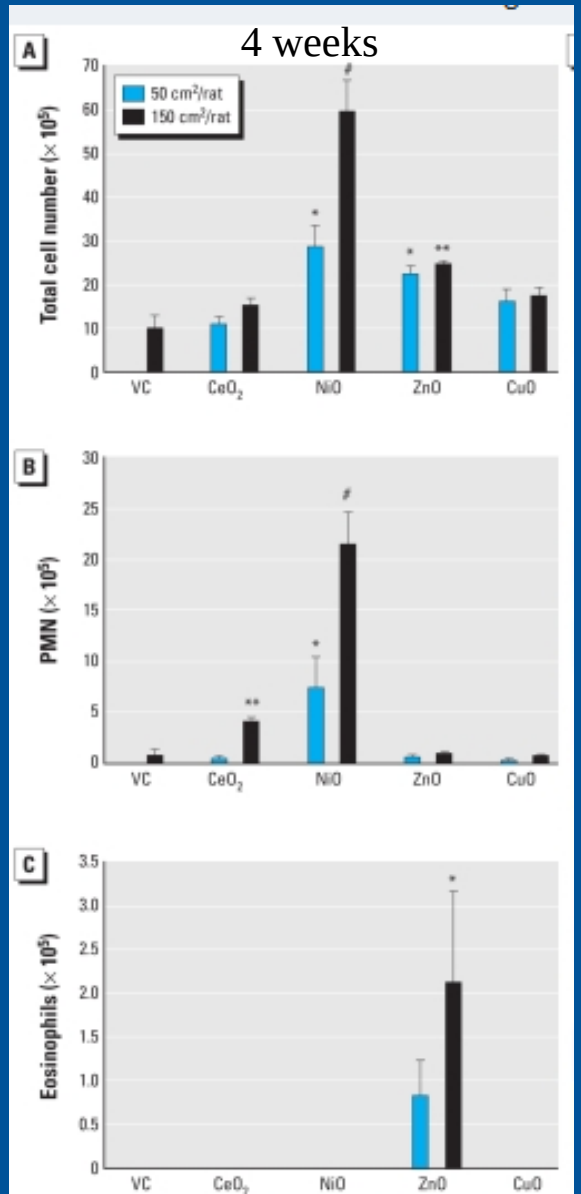
Instillation of metal oxide nanoparticles





- Equal- surface-area doses
- The different NPs have different types of inflammation
- NPs can not be viewed as a single hazard entity

CHO et al 2010, EHP

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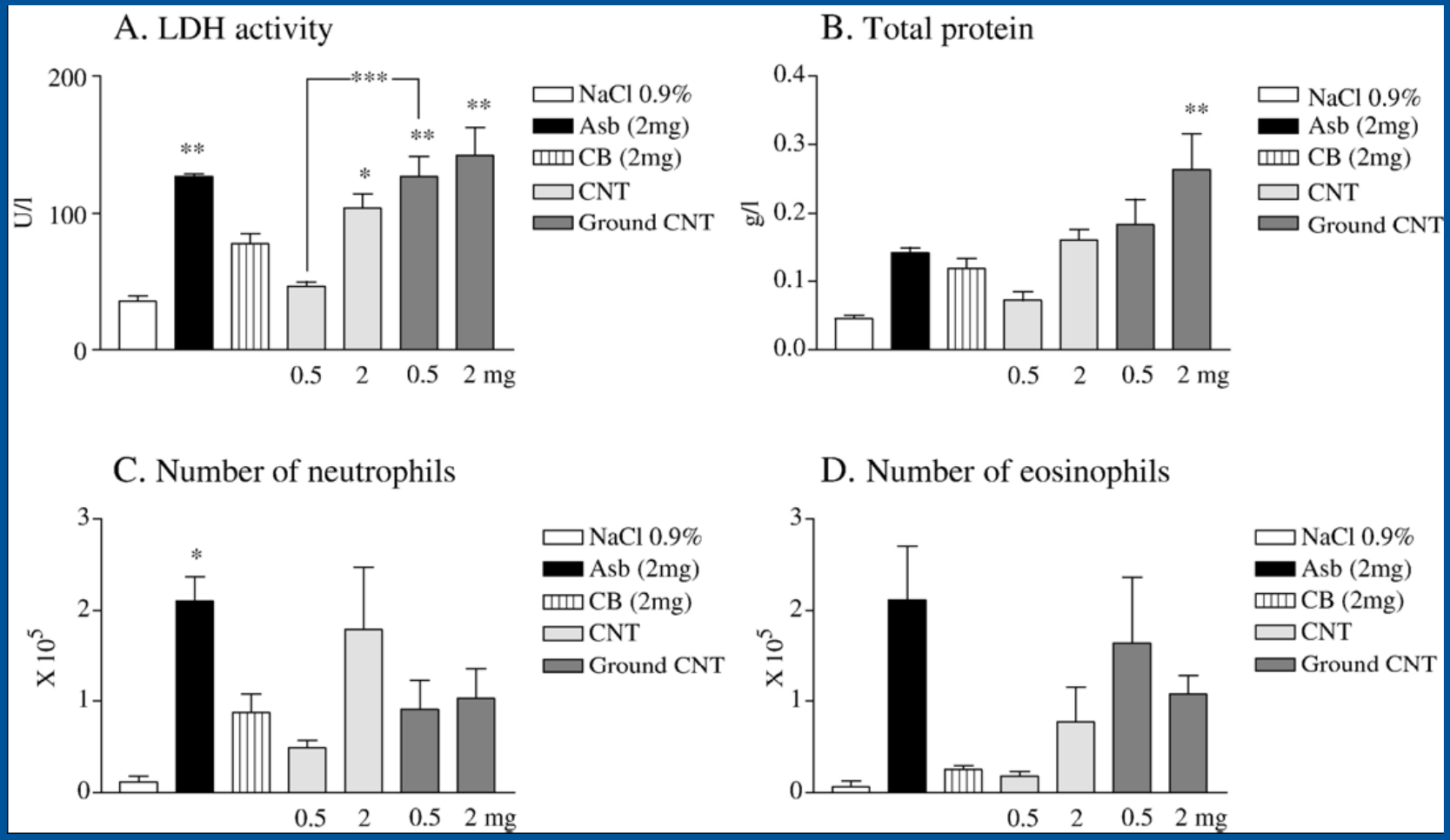
Instillation of carbon nanotubes (MWCNT)



Muller et al 2005, Tox Appl Pharm

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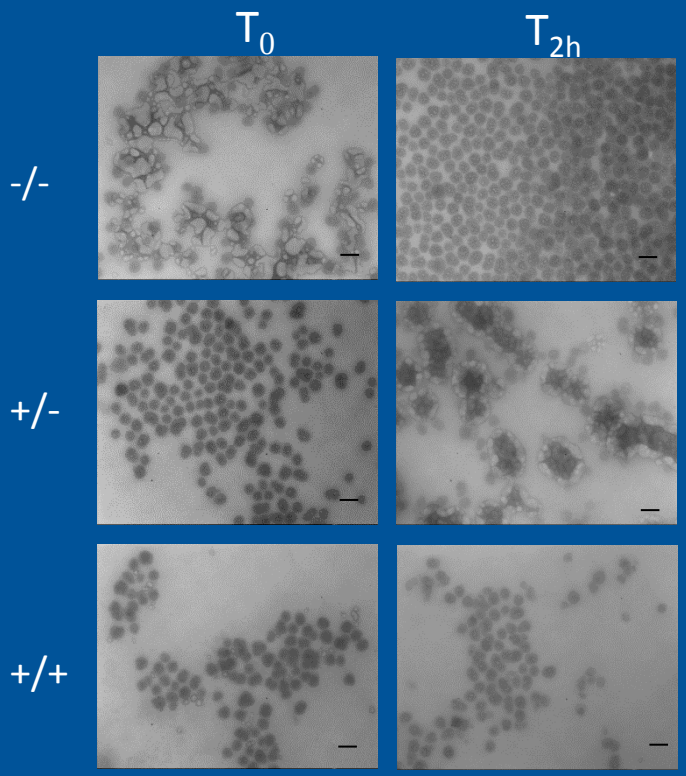
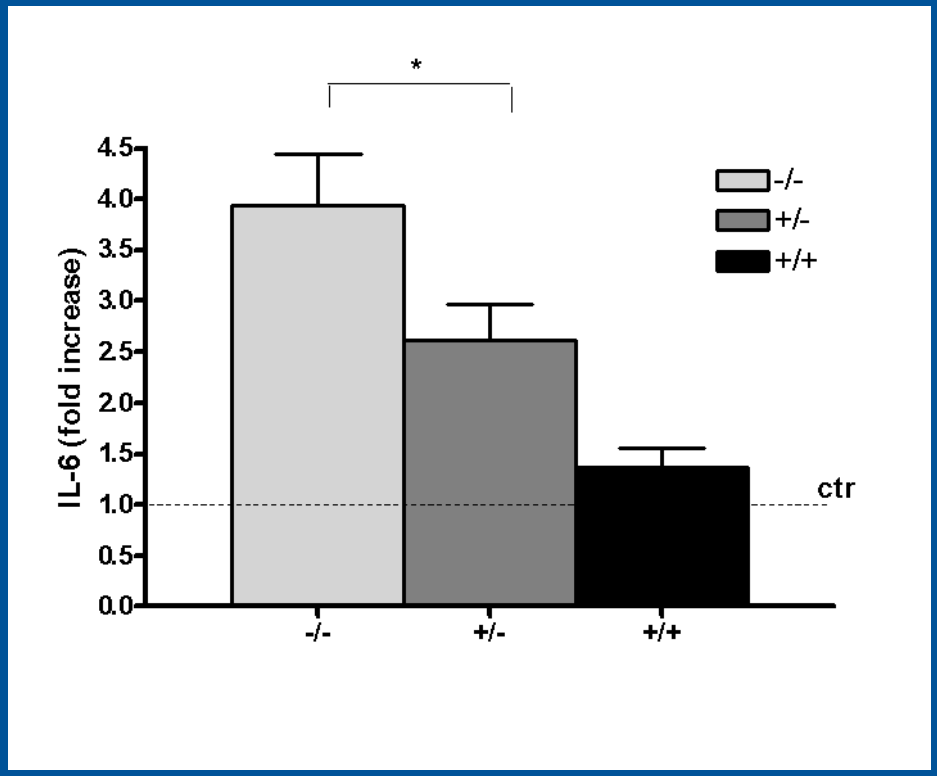
Silica nanoparticles 30 nm in a epithelial lung culture





-/- without BSA in both stock solution and in media
+/- BSA in stock solution, not in media
+/+ BSA in stock solution and in media (0.1%)

Gualtieri M et al 2011, Nanotox

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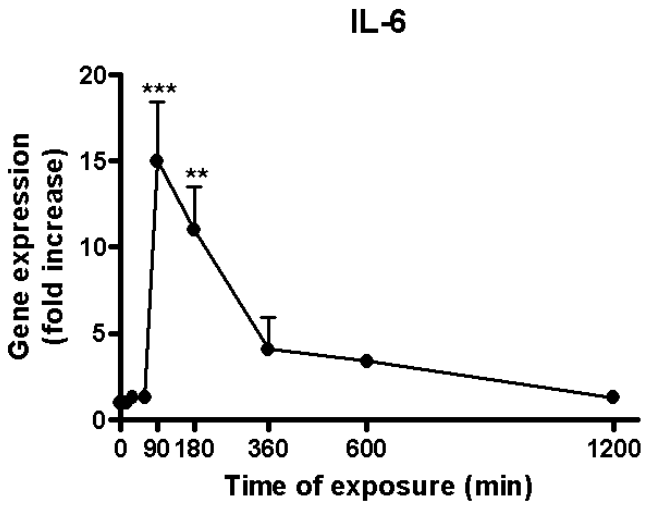
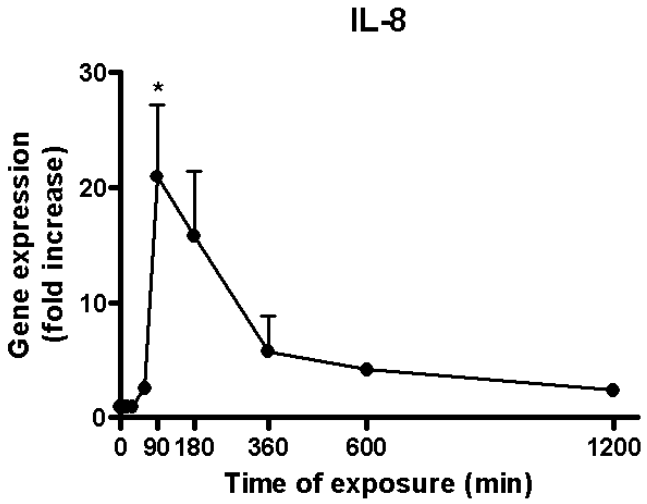
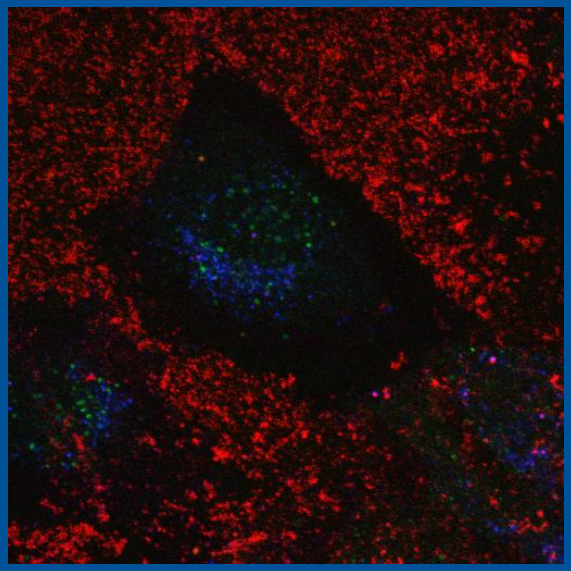
Cytokine responses without uptake of silica nanoparticles (50 nm labelled with rhodamine)





Confocal microscopy



3 hours

Gualtieri M et al 2011, Nanotox

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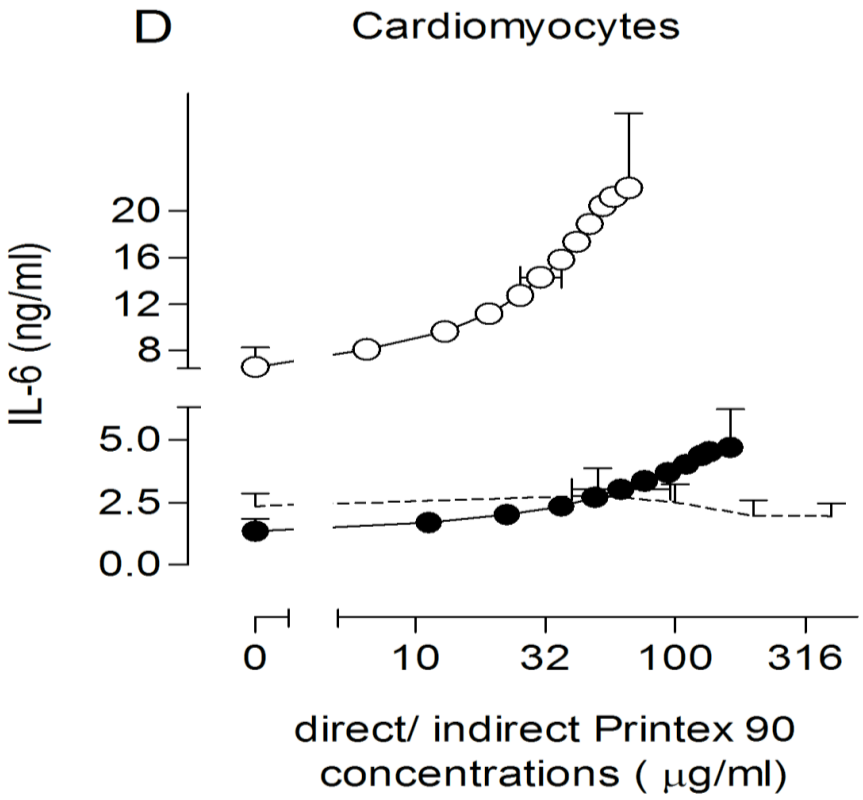
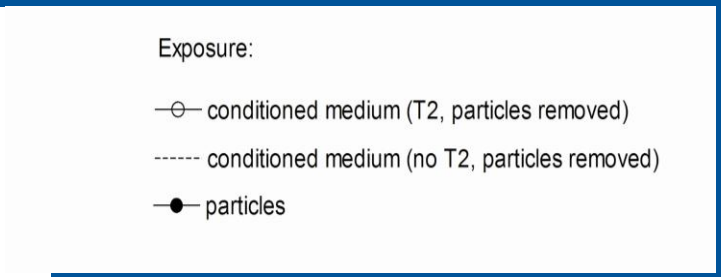
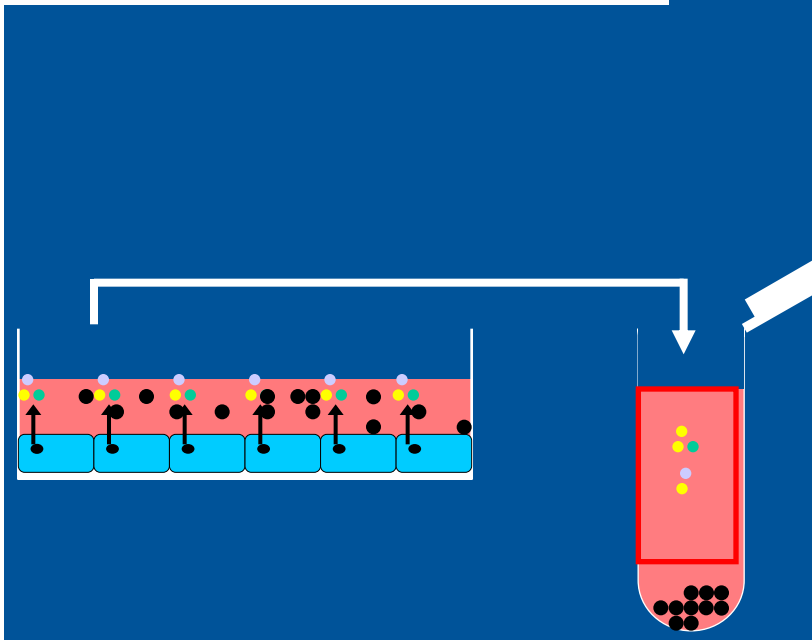
Inflammatory responses by carbon nanoparticles in lung cell culture enhanced effects in cardiac cell culture







Totlandsdal et al 2008 Tox Sci

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Potentiating effects of NPs on ongoing inflammatory processes?

- Adverse health effects of urban particles (PM) effects are primarily seen in individuals with pre-disposing factors, such as asthma, COPD, atherosclerosis - diseases known to involve inflammatory processes

- How is potentiating effects of NPs with such pre-disposing factors?
  - Allergy-elicited lung inflammation?

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Effect of carbon black NPs on antigen (OVA)-related airway inflammation: Cellular profile in BAL fluid

Group	Animals (n)	Total Cells (× 10^4/total BAL)	Macrophages (× 10^4/total BAL)	Eosinophils (× 10^4/total BAL)	Neutrophils (× 10^4/total BAL)
vehicle	16	36.88 ± 3.56	36.74 ± 3.53	0 ± 0	0.12 ± 0.05
14 nm	13	111.69 ± 9.27**	83.79 ± 6.03**	0.332 ± 0.176	27.04 ± 4.98**
56 nm	14	97.36 ± 16.06**	88.64 ± 15.34**	0.331 ± 0.177	8.09 ± 2.49*
OVA	16	85.06 ± 12.63**	81.91 ± 12.4**	0.705 ± 0.255	2.2 ± 0.62
OVA + 14 nm	16	193.69 ± 18.33** ## $$	141.86 ± 14.97** ## $	13.667 ± 4.731** ## $	36.9 ± 3.67** ## $
OVA + 56 nm	17	102.65 ± 11.64**	90.7 ± 10.12**	3.984 ± 2.669	7.79 ± 2.29*

Intratracheal administration of ovalbumin (1 µg every 2 week for 6 weeks), carbon black (50 µg every week for 6 weeks);

Inoue et al 2005

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Conclusions/ considerations

- Nanoparticles have without doubt a potential to induce health effects and inflammation seems to be crucial
- Nanoparticles have to be assessed separately in the hazard identification
- However, the experimental studies have been performed with high concentrations of NPs
- The exposure levels are critical for the human health risk assessment
- Different nanoparticles may augment lung inflammation related to pre-existing lung diseases such as allergy, which may induce inflammatory response at lower concentrations of NPs than in ”healthy” individuals - more relevant in relationship to exposure levels?

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