6. BfR-Forum Verbraucherschutz: Nanotechnologie
Berlin, 10. November 2008

Biokinetik und Toxikologie inhalierter Nanopartikel

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Nanotechnologien -
Basis für zukünftige Wissenschaft + Technologien

Per se nachhaltig:

Ressourcen + Energie sparend

Welche Risiken?

Paradigma der Risikoanalyse für NP

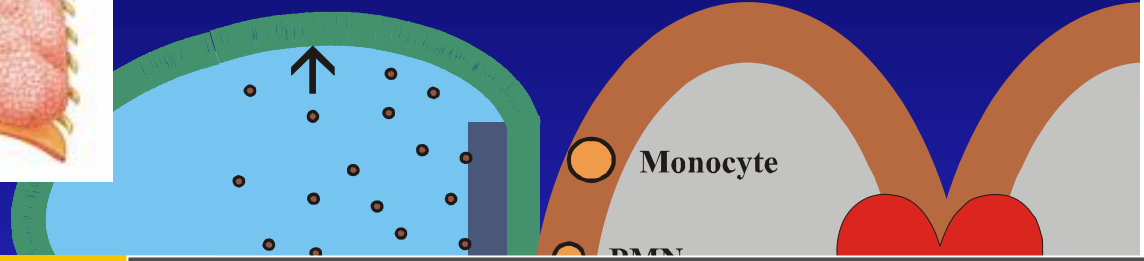
exposure assessment — hazard identification

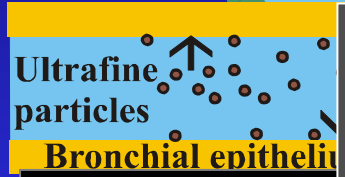
hazard characterization — risk characterization

NP Dosimetrie

Toxikologische Reaktionen auf NP

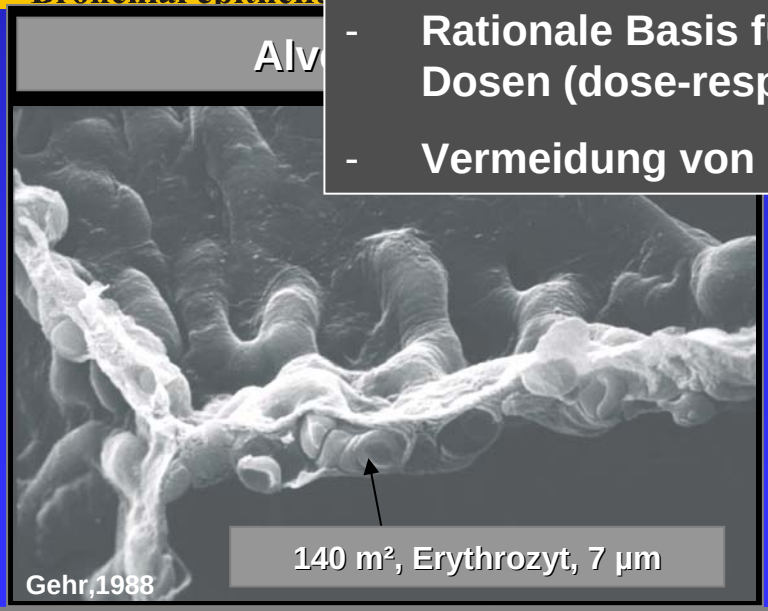
Nanoparticles (NP): Access to blood circulation

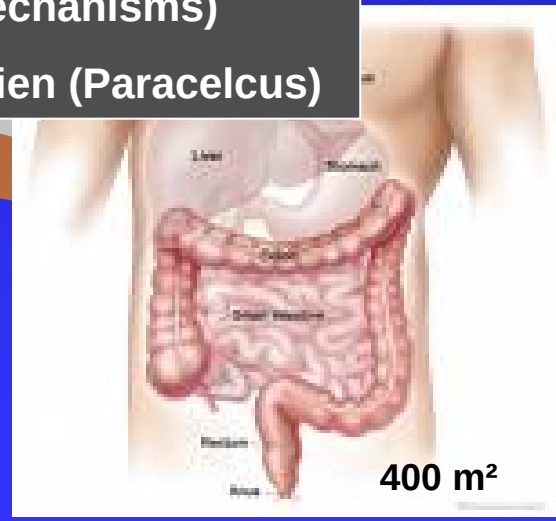




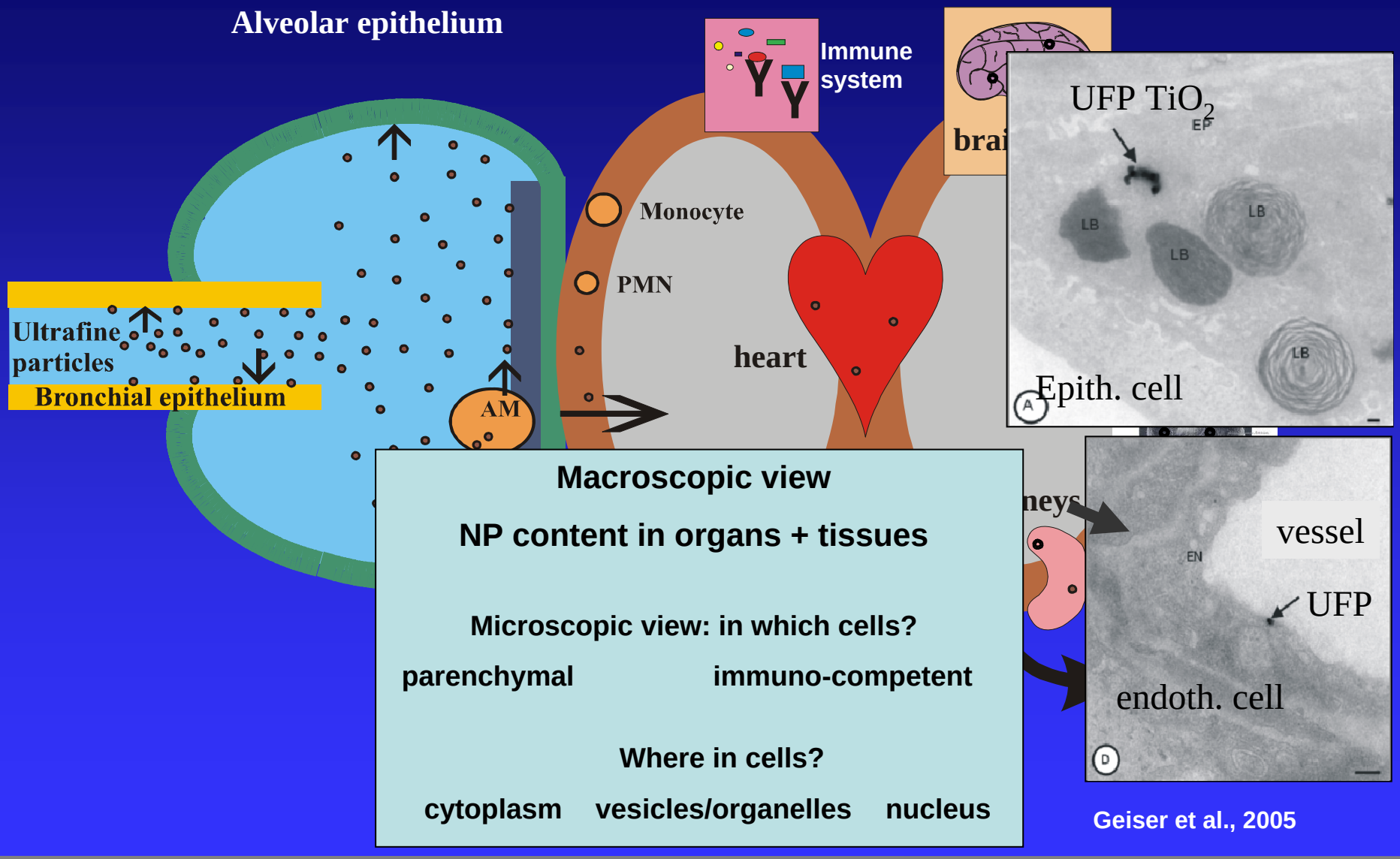
Daher liefern Biokinetikstudien mit inkorporierten NP:

- Fundierte Dosisabschätzung für jedes Organ
- Rationale Basis für toxikologische Studien mit relevanten Dosen (dose-response, modes of action, mechanisms)
- Vermeidung von unsinnigen Überdosisstudien (Paracelcus)





Nanoparticle (NP) translocation into circulation



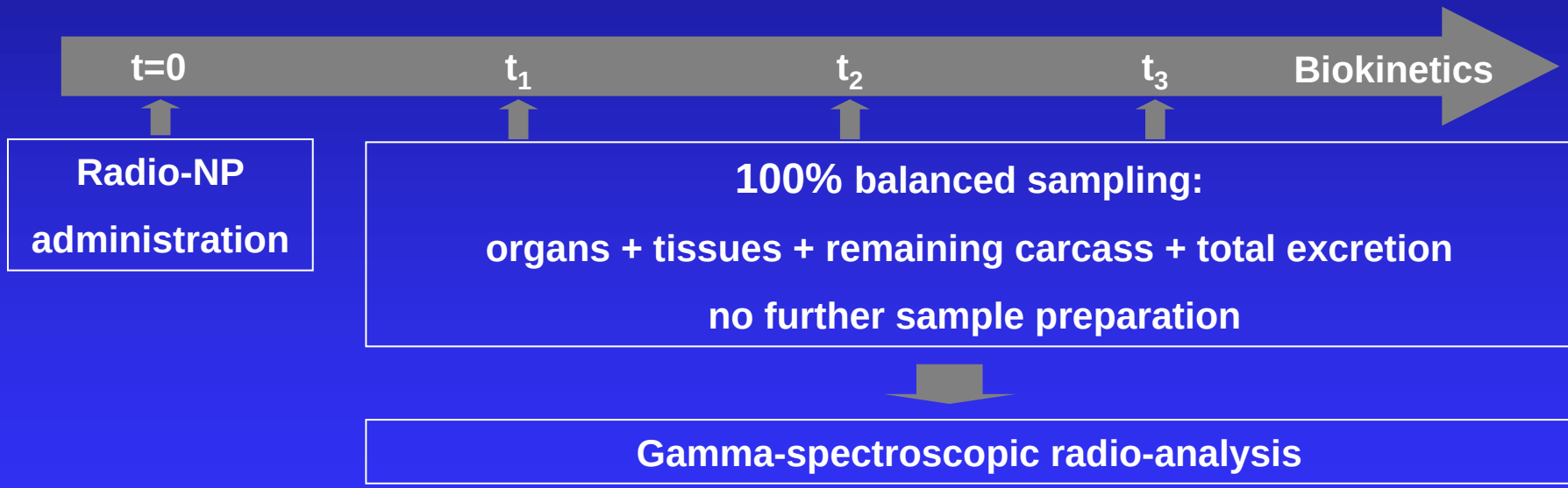
Geiser et al., 2005

Application + analysis of radio-labeled NP

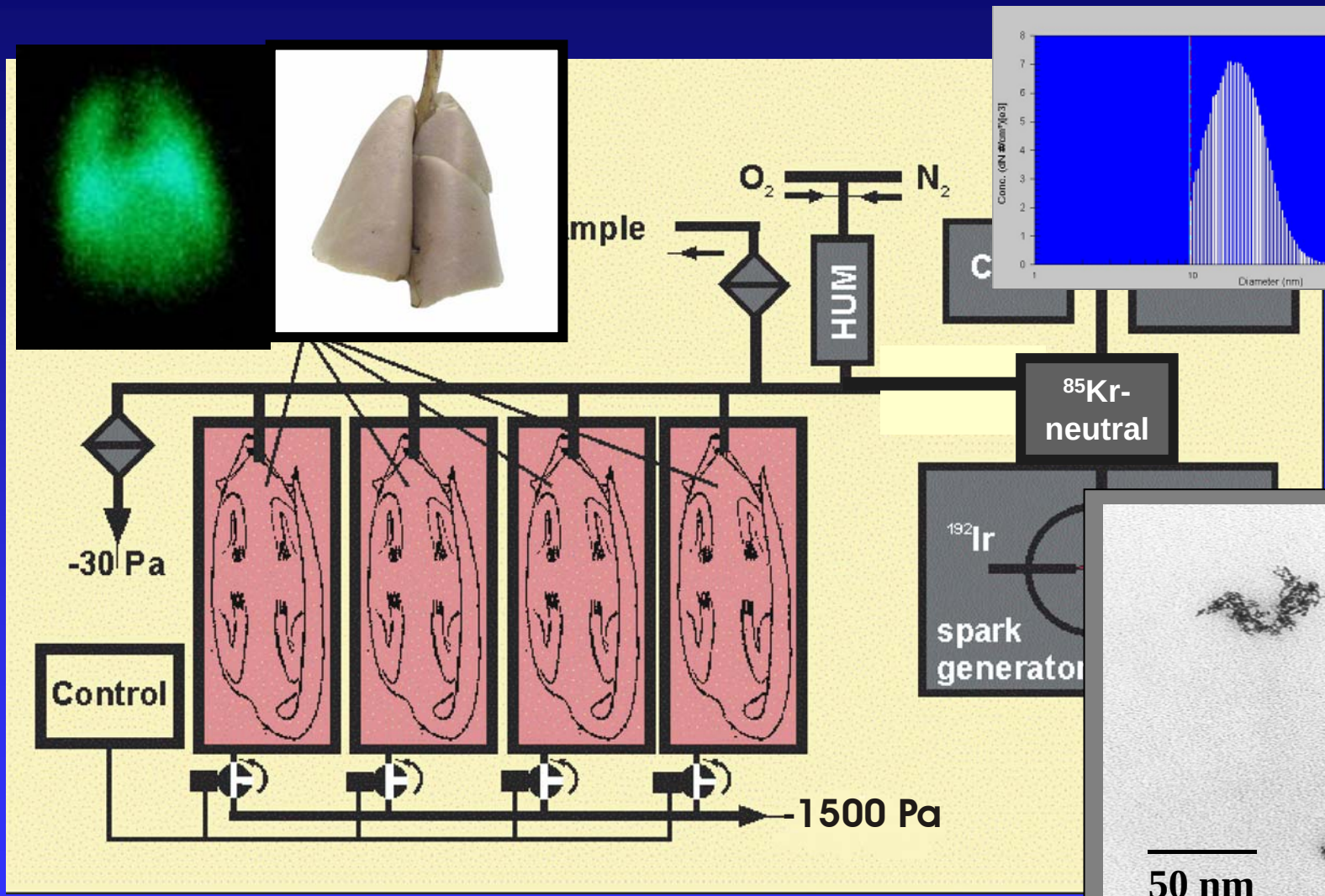
Inhalation (INH)

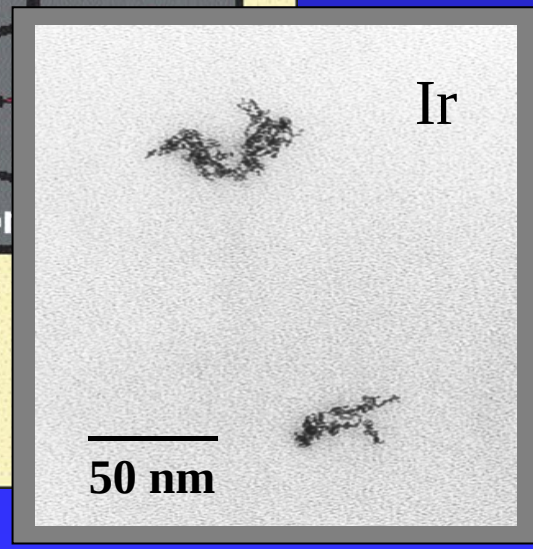
Intra-tracheal instillation (IT)

Intravenous (IV) injection



Intratracheal intubation-ventilation of Ir-NP



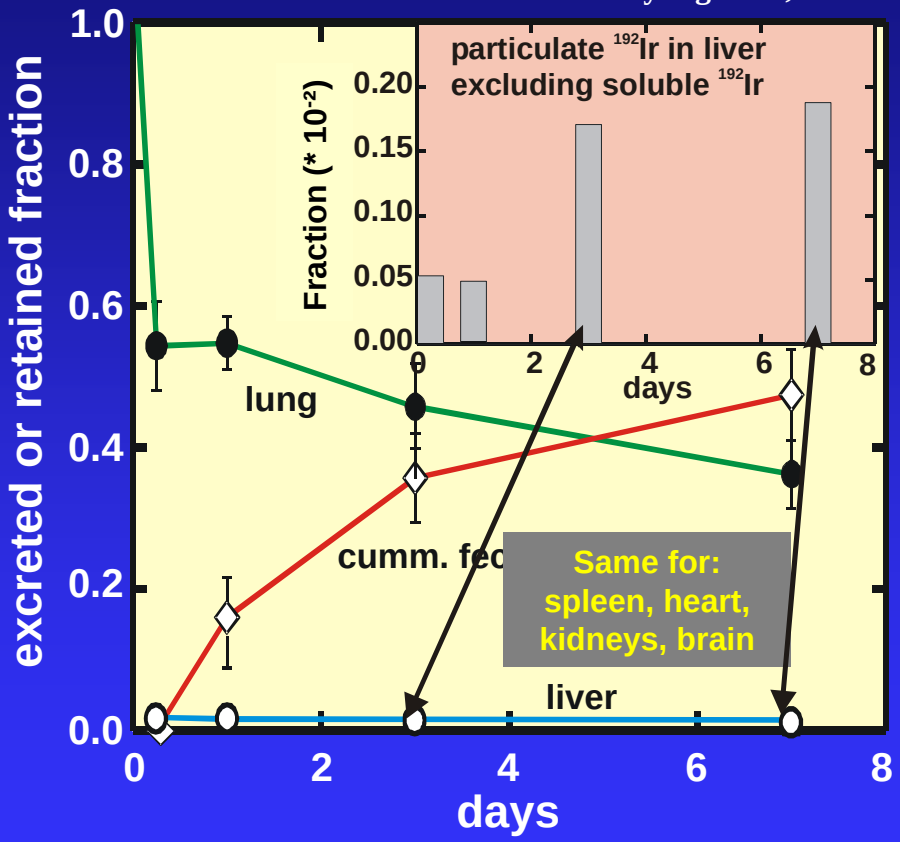


Kreyling et al.,2002

Systemic translocation of Ir NP towards 2nd target organs

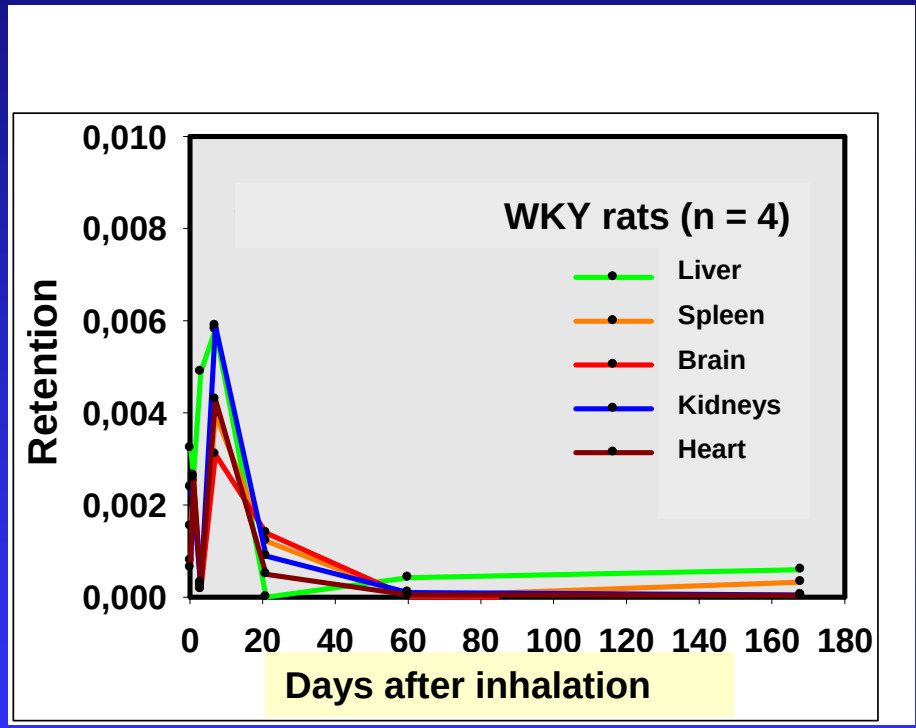
WKY rat, ^{192}Ir NP, 1 hr exposure
15 nm CMD, 10^7 cm^{-3}, 0.2 mg/m^3

Kreyling et al., 2002



Long-term translocation kinetics
same exposure

Semmler et al., 2004

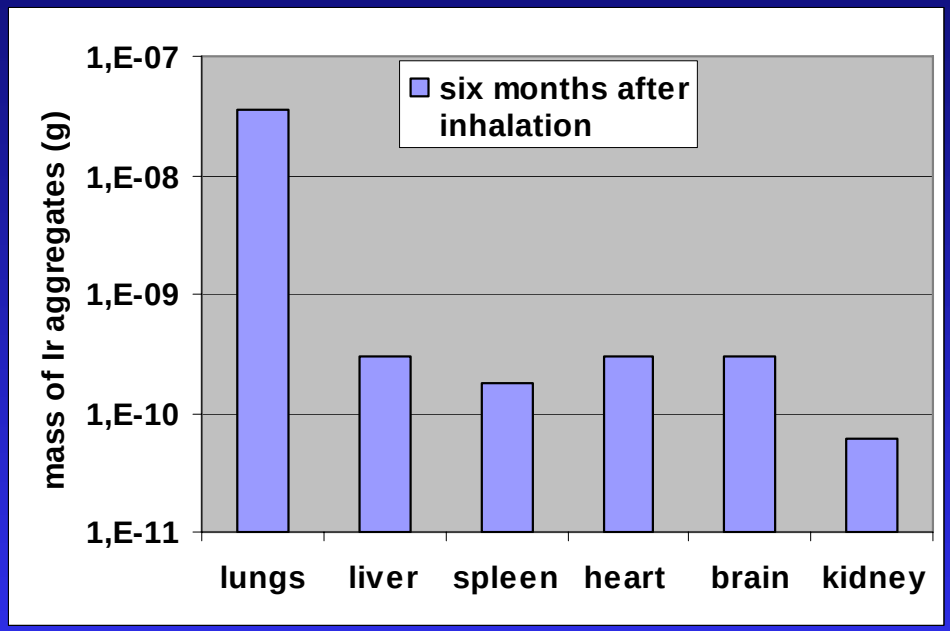


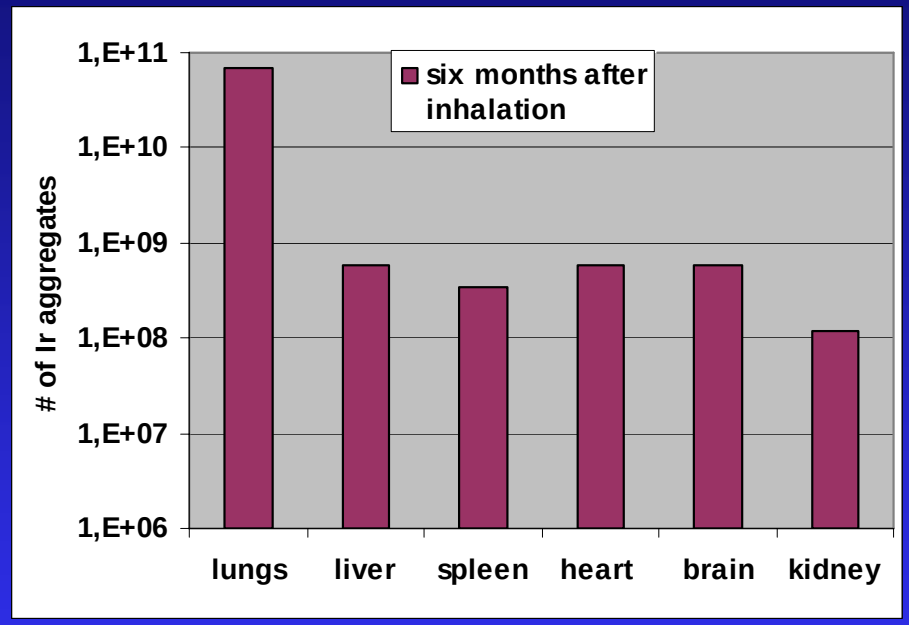
There is little but persistent accumulation of Ir-NP in secondary target organs

Ir NP mass < 1 ng, but number > 10^8 NP per organ

Systemic translocation of nanoparticles towards secondary target organs

WKY rat, ^{192}Ir NP, 1 hr exposure
15 nm CMD, 10^7 cm^{-3}, 0.2 mg/m^3





Primary particles	~ 2 nm
Specific surface area	1200 m^2 / cm^3
Zeta potential	- 20 mV
SIMS-TOF surface analysis	IrO_2

Unexpected high NP numbers in secondary target organs including heart and brain after six months which are not considered to be exposed to particulate foreign bodies.

Do these many NP cause harm?

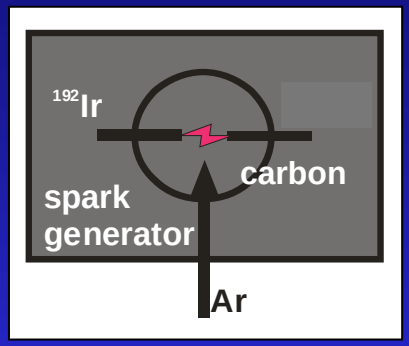
Systemic translocation of nanoparticles towards secondary target organs

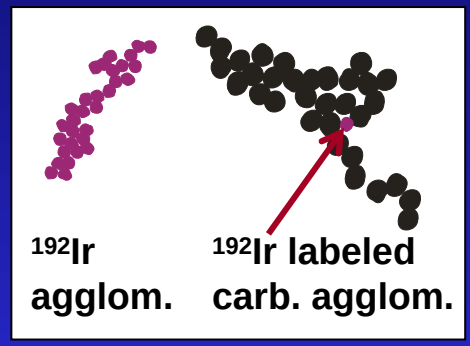
Human dose estimate during continuous exposure applying rat translocation dynamics determined for Ir UFP:

NC (UFP) (3 10^4 p/cm^3)	3 10^{10} p/m^3
Daily inhaled volume	10 m^3
Deposition fraction	0.3
Insoluble UFP fraction	0.1
Translocated fraction to brain, heart	0.001 (of lung deposit)
Retained UFP number in brain, heart	**~3 10^9 UFP / year**

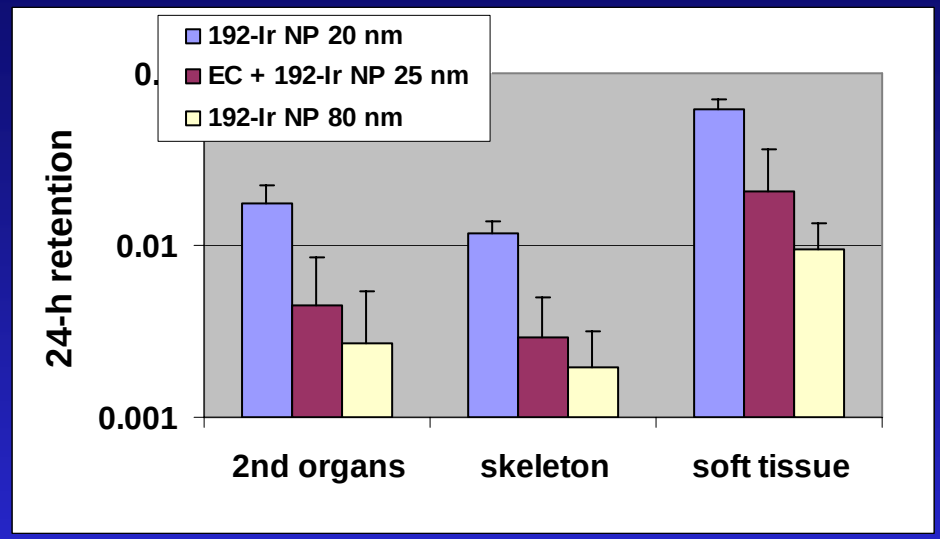
Translocation of iridium + carbon NP towards 2nd target organs

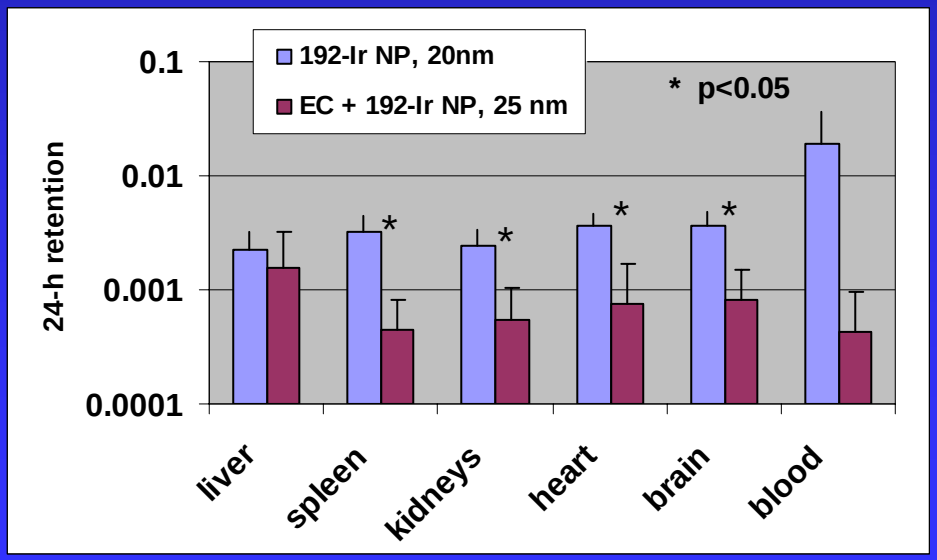
WKY rat, Ir or carbon UFP + ^{192}Ir label,
1-hr inhalation exposure
20 or 80 nm CMD, 10^7 cm^{-3}, 0.1 mg/m^3





Szymczak et al. 2006

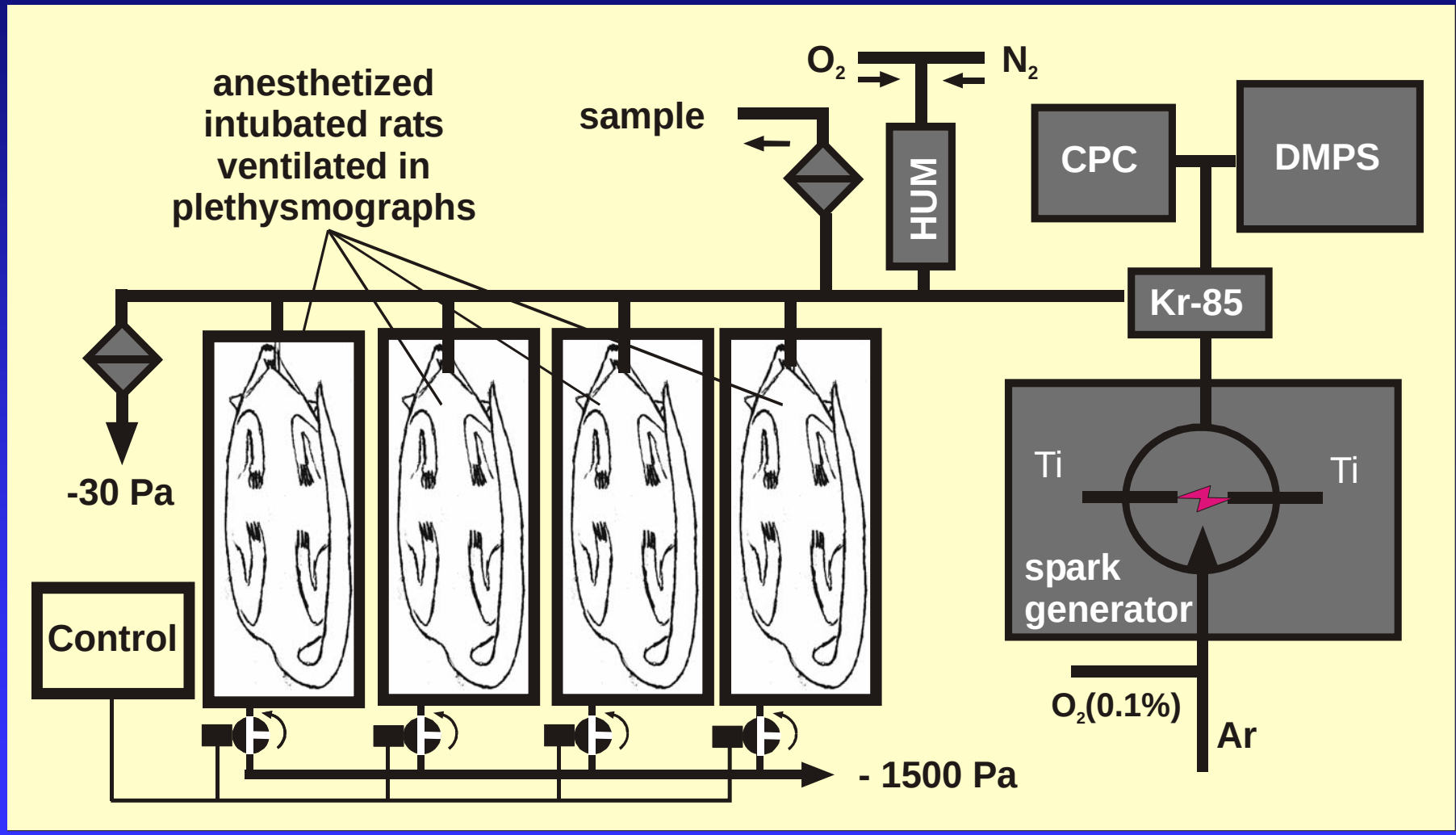




- Strong dependency of translocation on NP material: iridium vs. carbon NP of same size
- Size dependency of translocation of iridium NP (20 vs. 80 nm)

Ventilation-inhalation system of TiO_2 NP

Morphological characterisation of NP distribution in the lungs



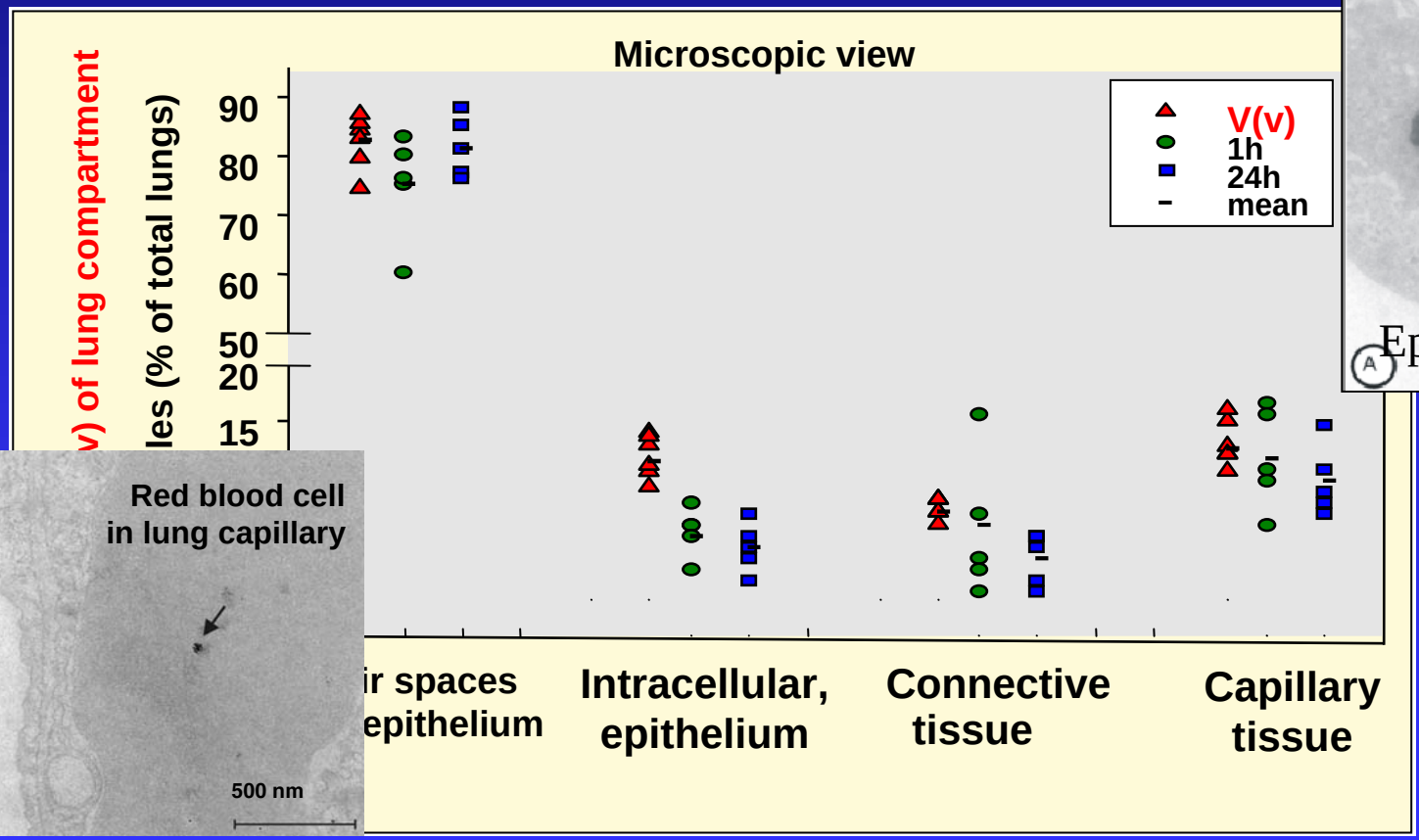
Morphometry of inhaled TiO_2 nanoparticles in rat lungs

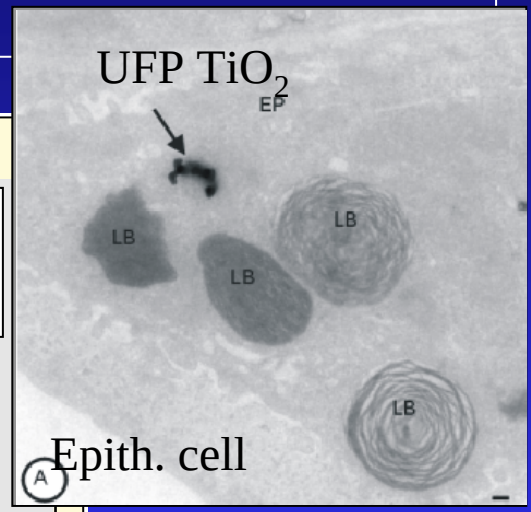
Intubated ventilated WKY rat,
TiO_2 NP, 1 hr exposure
22 nm CMD, 10^7 cm^{-3}, 0.1 mg/m^3
morphometry 0 + 24 h after inhalation

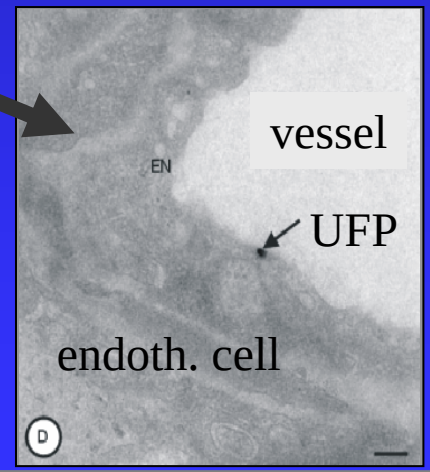
➔ Rapid translocation of ~ 20% NP fraction

➔ Volume proportional re-distribution: by which mechanism?

M. Geiser et al., EHP 2005

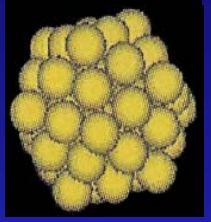






Translocation of gold nanoparticles: Effect of particle size

^{198}Au55 cluster 1.4 nm



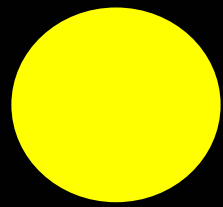
Intratracheal instillation or intravenous injection in WKY rats

1-10 µg ^{198}Au particles in 50 µL saline, negative ionic surface charge

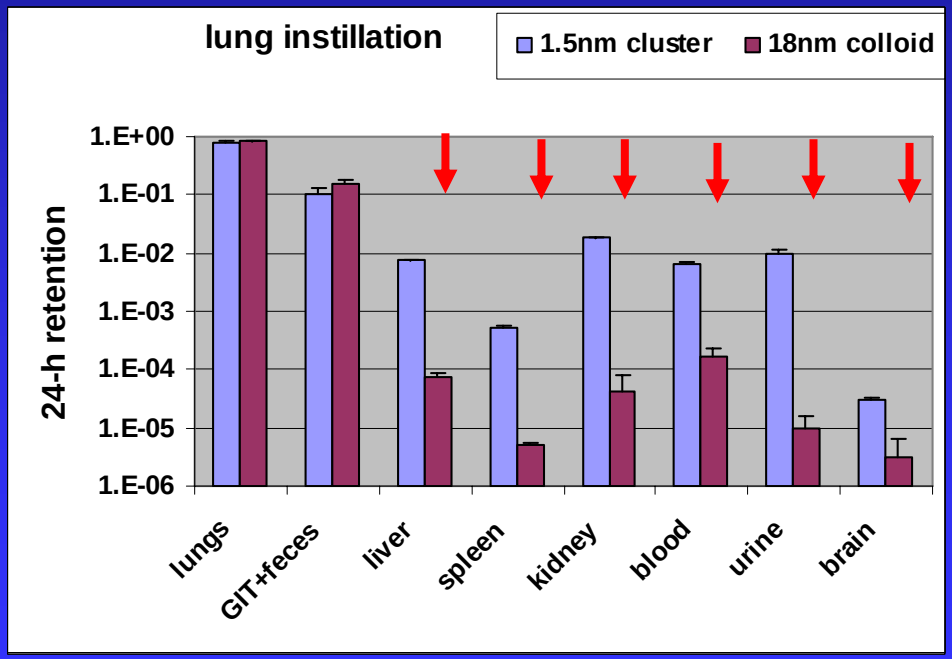
# of particles: 1 10^{14} (1.5 nm cluster) 2 10^{11} (18 nm colloid)

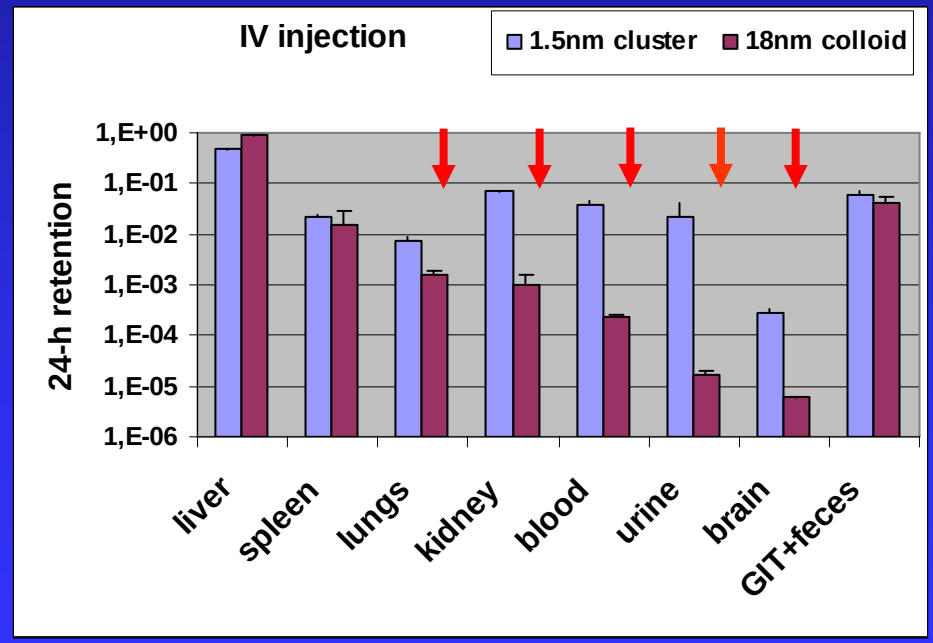
G. Schmid, Univ of Essen, Germany

^{198}Au colloid 18 nm



➢ **Mass fractions of gold nanoparticles in different organs after 24 h**

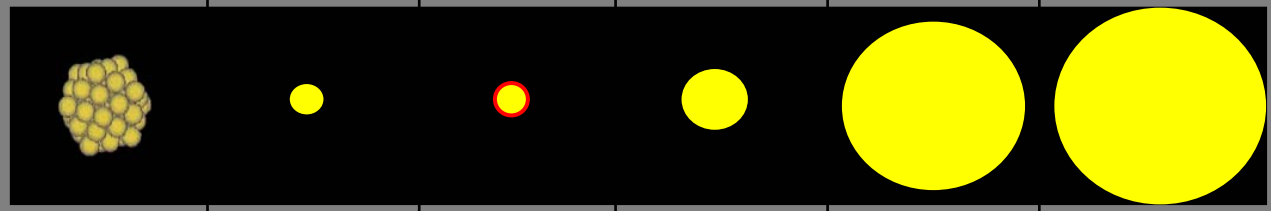




Indeed, size matters!!

Semmler-Behnke, Small, 2008

Administered Gold NP

							
		^{198}Au55 cluster	^{198}Au cluster	^{198}Au cluster	^{198}Au colloid	^{198}Au colloid	^{198}Au-colloid
diameter	(nm)	1.4	2.5	2.5	5	18	80 + 200
ligand		phosphine	carboxyl	amino	phosphine	phosphine	phosphine
		ionic	ionic	ionic	ionic	ionic	ionic
surface charge		negative	negative	positive	negative	negative	negative
admin. suspension vol.	(µL)	50	50	50	50	50	50
NP mass admin.	(µg)	2	1	1	10	5	2
NP number admin.		10^{14}	10^{13}	10^{13}	10^{13}	10^{11}	$10^{9} + 10^{8}$
NP surface admin.	(cm^2)	5	2	2	7	1	0.1 + 0.01

All gold NP were neutron activated prior to administration to achieve ^{198}Au radio-label

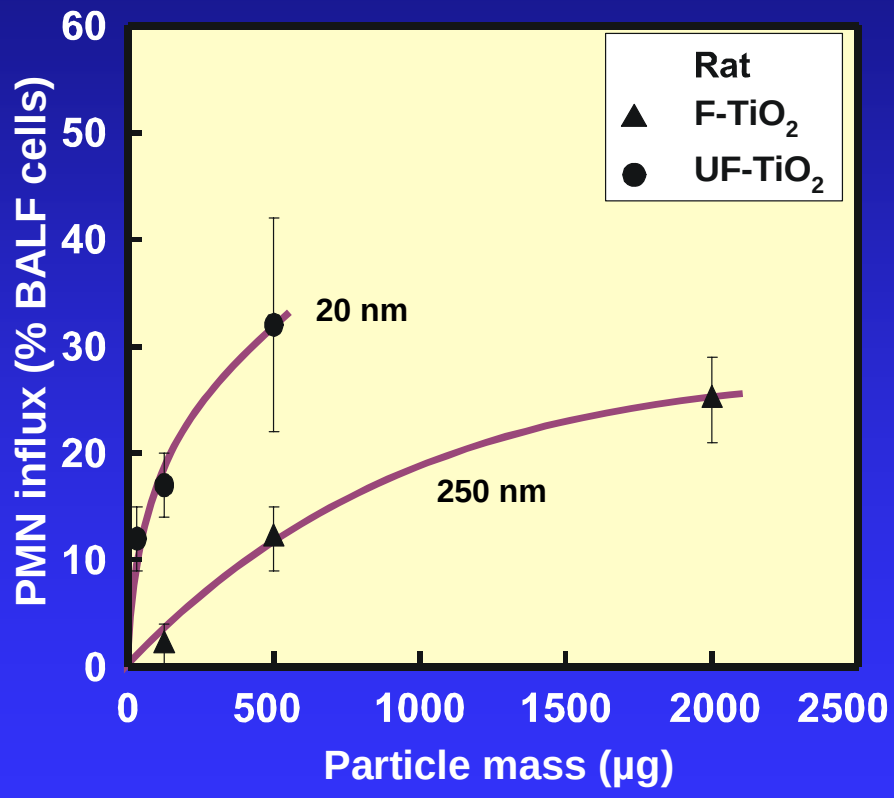
Toxikologische Reaktionen auf NP:

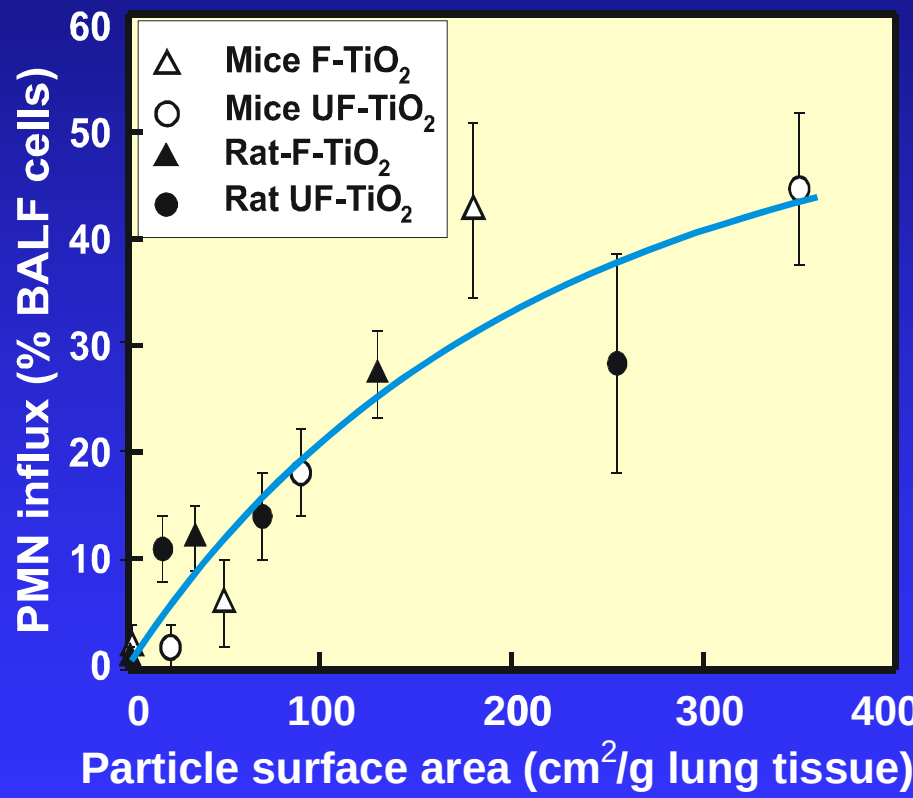
Rolle verschiedener NP Parameter

Surface area of NP is associated with inflammatory response

Influx of neutrophils (PMN) : indicator of inflammation

Instillation of ultrafine UF-TiO_2 (20 nm) or fine F-TiO_2 (250 nm) into rat lungs

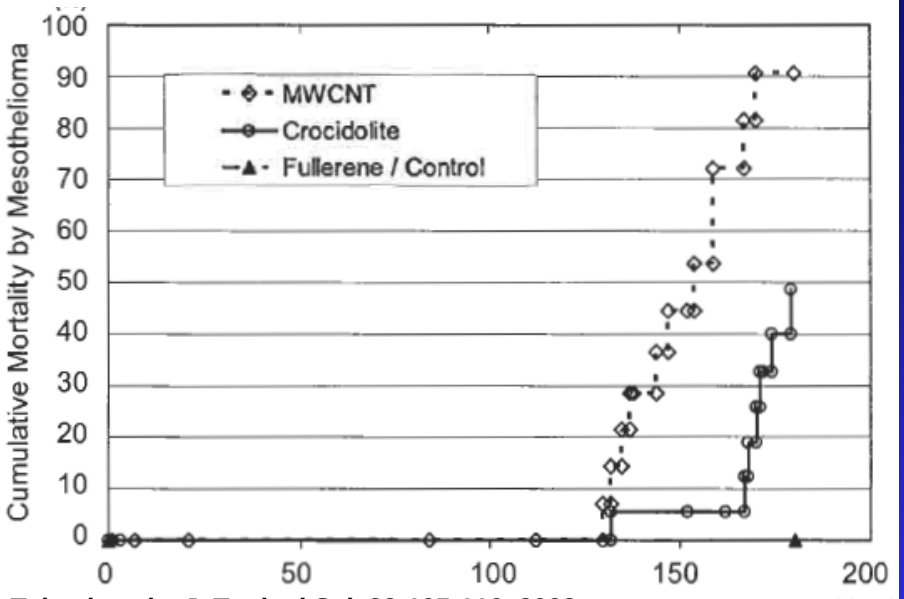




Oberdörster et al., HEI 2000

Long, biopersistent carbon nanotubes (CNT) lead to similar pathogenesise as asbestos fibers

Life shortening by mesothelioma



Takagi et al., J. Toxicol Sci. 33:105-116, 2008

Formation of granuloma :

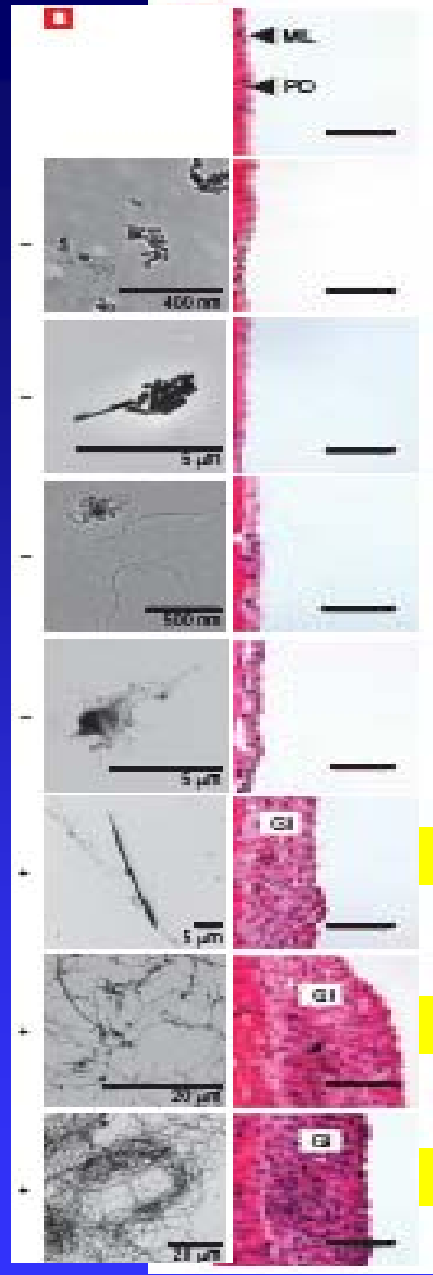
only Asbest$_{lang}$ und CNT$_{long1+2}$

Inflammatory parameters only Asbest$_{long}$ und CNT$_{long1+2}$:

Neutrophil cell influx

increased total protein

Alv. Macroph: frustrierte Phagocytose von CNT$_{lang}$



contr.

Nanopart. carbon black

Asbes$_{short}$

CNT$_{tang1}$

CNT$_{tang1}$

Asbest$_{long}$

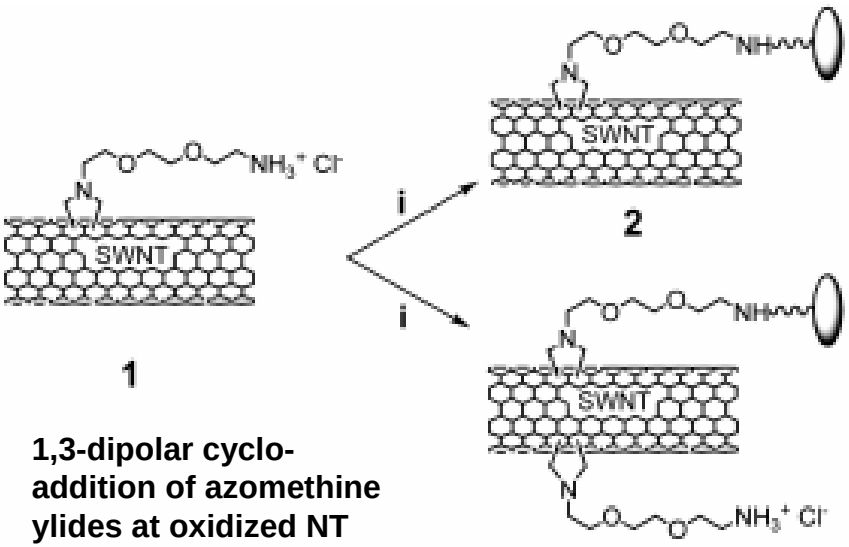
CNT$_{long1}$

CNTo$_{ang2}$

Poland et al. Nature Nanotechnology, 2008

Less toxicity of functionalized nanotubes

Functionalized SWNT & MWNT lead to high solubilization + no toxic response



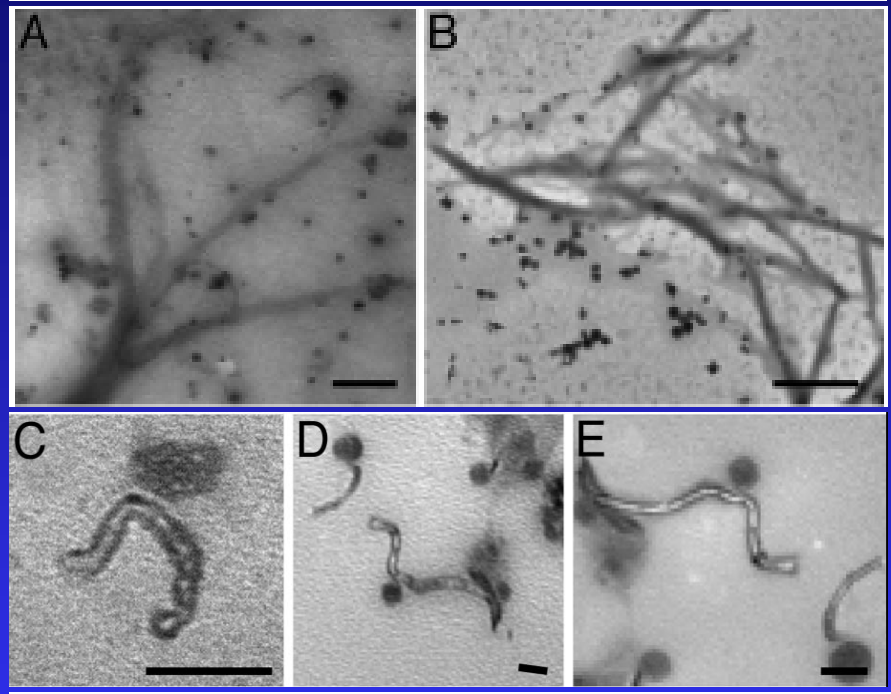
1

2

1,3-dipolar cyclo-addition of azomethine ylides at oxidized NT sides

Singh et al. PNAS (2006)

SWNT in urinary supernatant



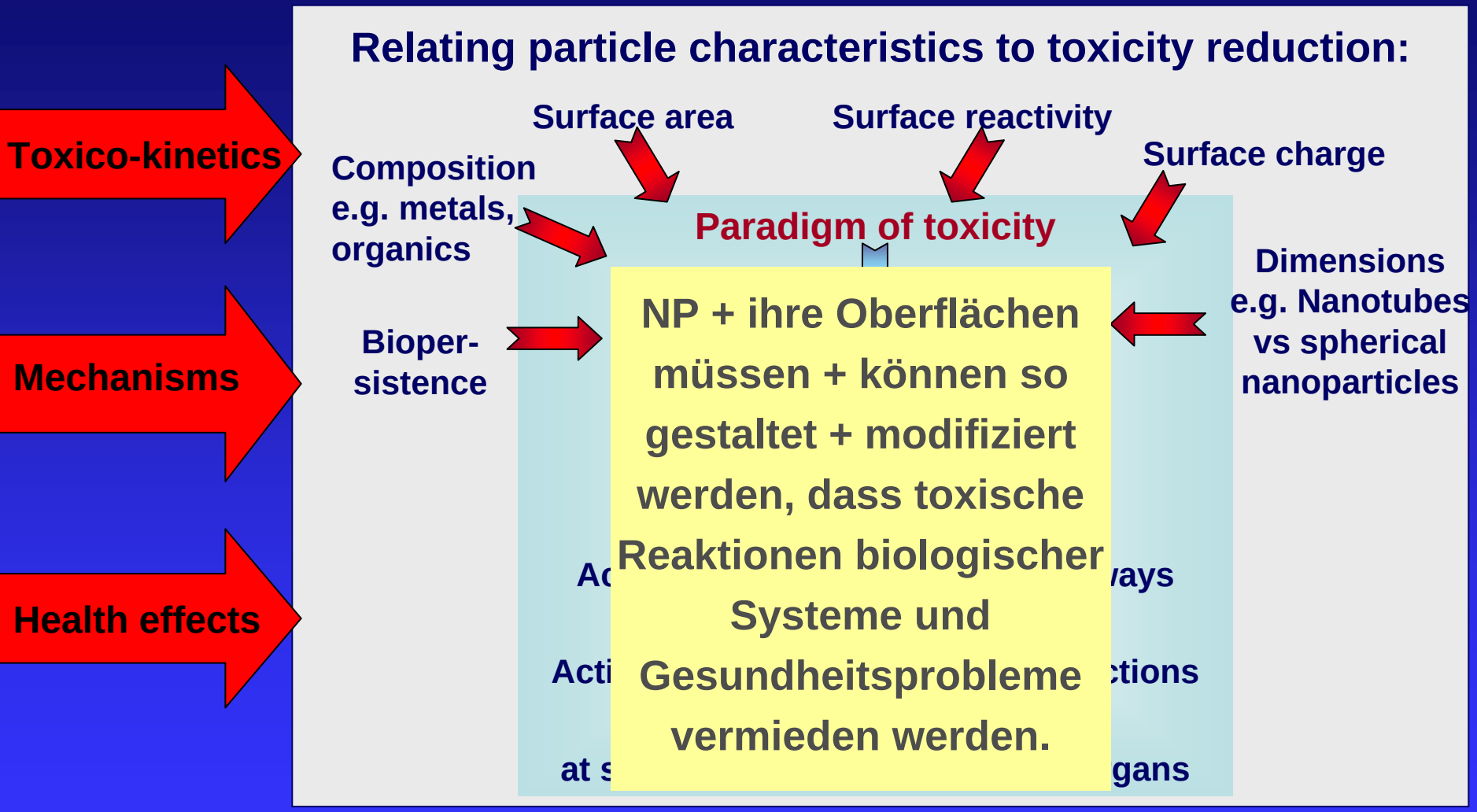
MWNT in urinary supernatant

Virtually no organ & tissue retention after 3 hours

➔ No signs of inflammation

Original SWNT and MWNT were not excreted in urine and showed inflammatory responses

Search for Safe Nanomaterials



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