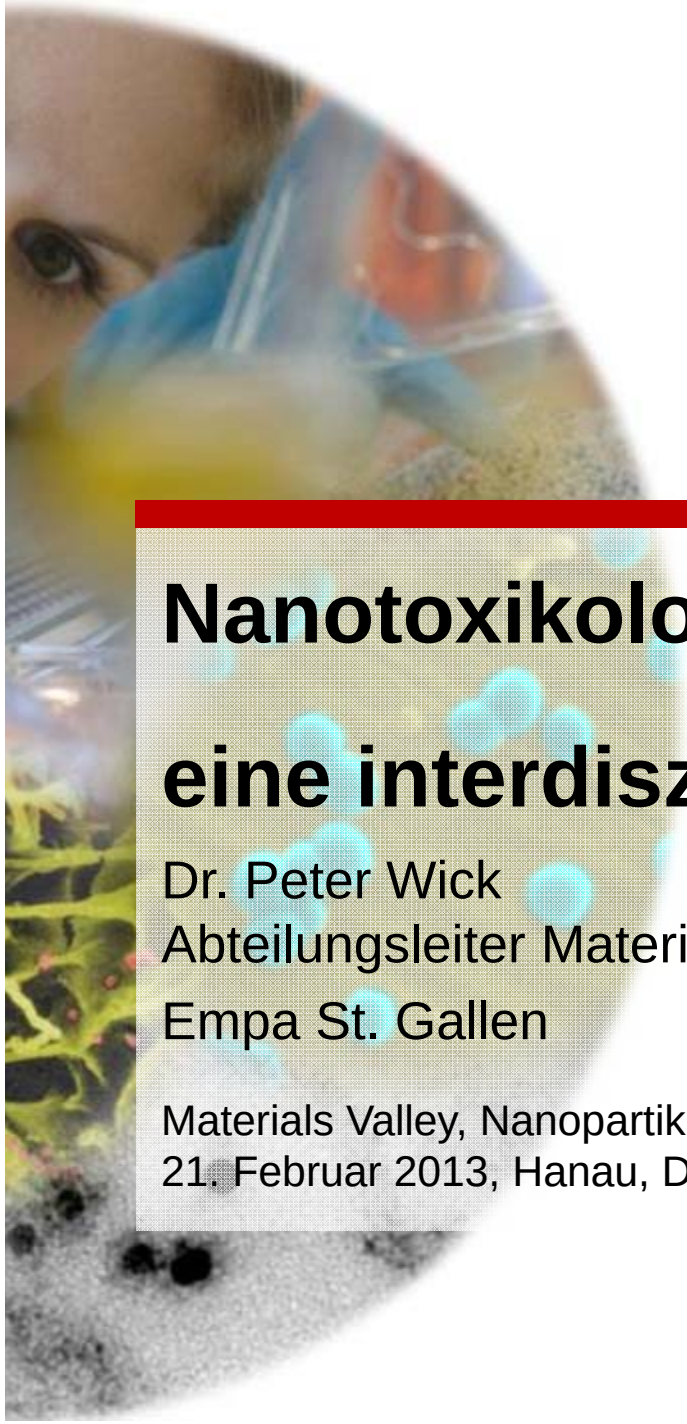

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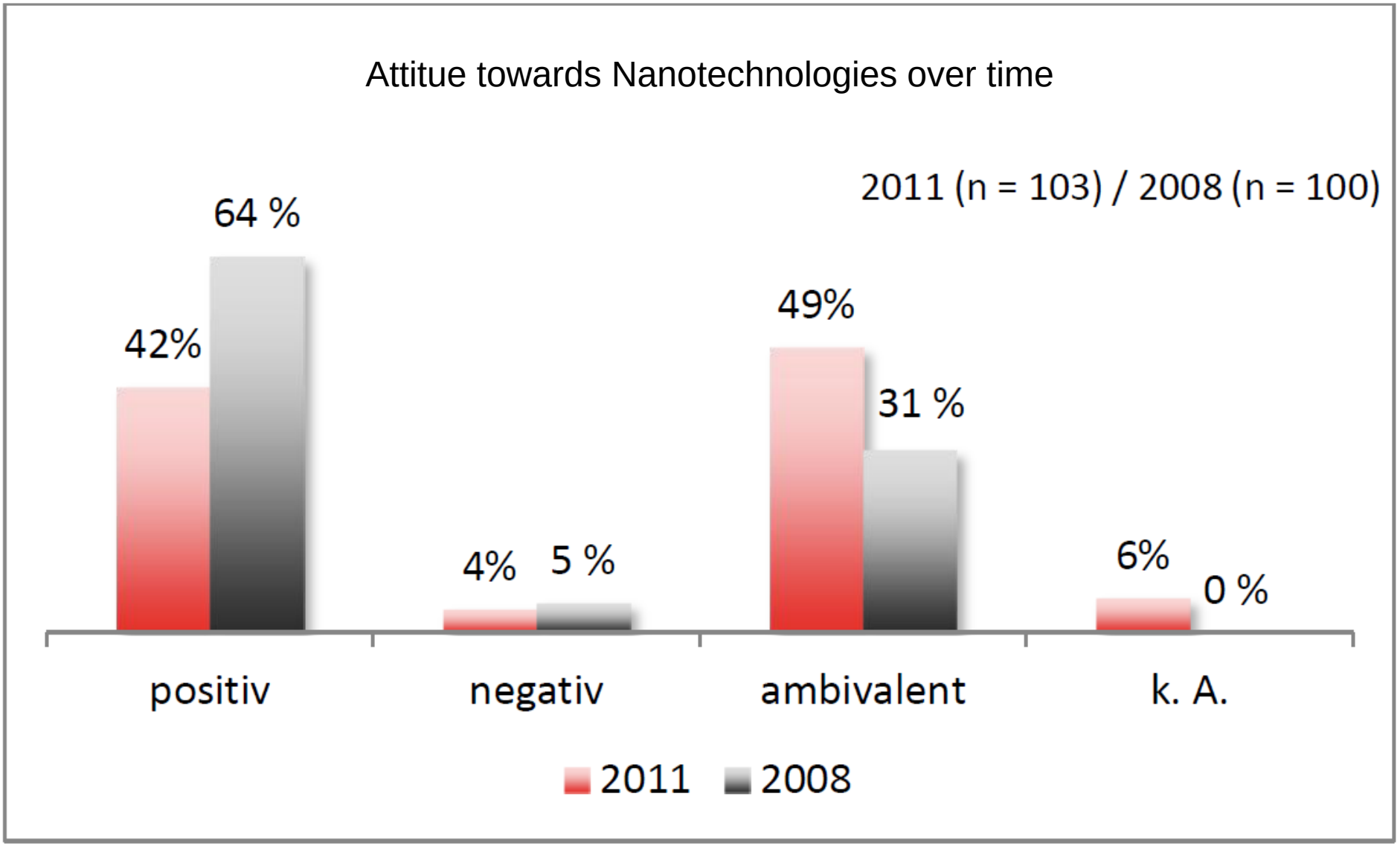
Nanotoxikologie:

eine interdisziplinäre Herausforderung

Dr. Peter Wick
Abteilungsleiter Materials-Biology Interactions,
Empa St. Gallen

Materials Valley, Nanopartikel – Einsatz in der Medizin, Chemie und Verfahrenstechnik
21. Februar 2013, Hanau, D

Opinion of public (Germany and Switzerland)



Antje Grobe, Mikko Rissanen, Philippe Funda, Joe De Beer, Uschi Jonas
Nanotechnologien aus der Sicht von Konsumenten (2012), Stiftung RISIKO-DIALOG

Variability of Nanomaterials

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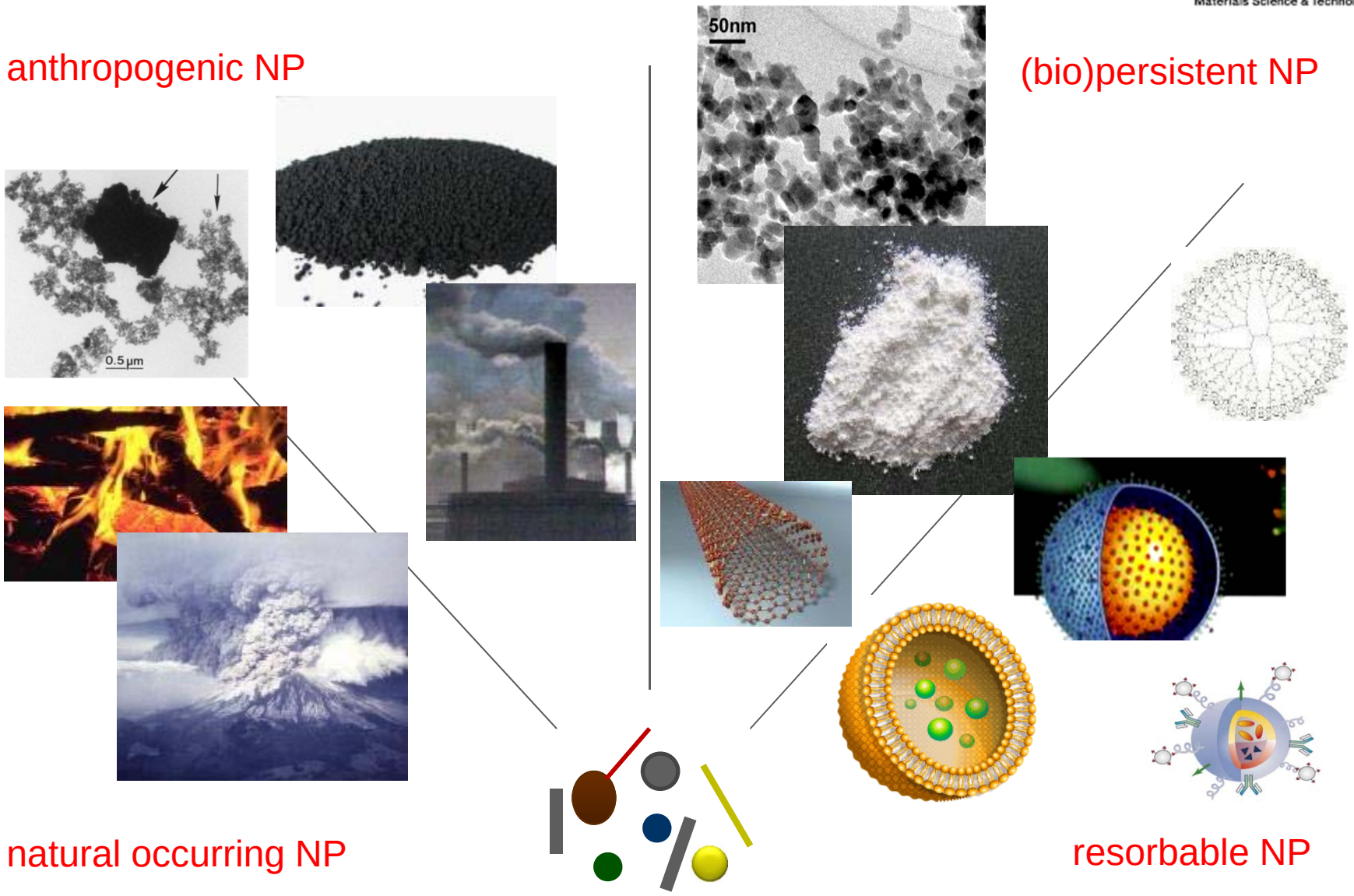
anthropogenic NP

(bio)persistent NP

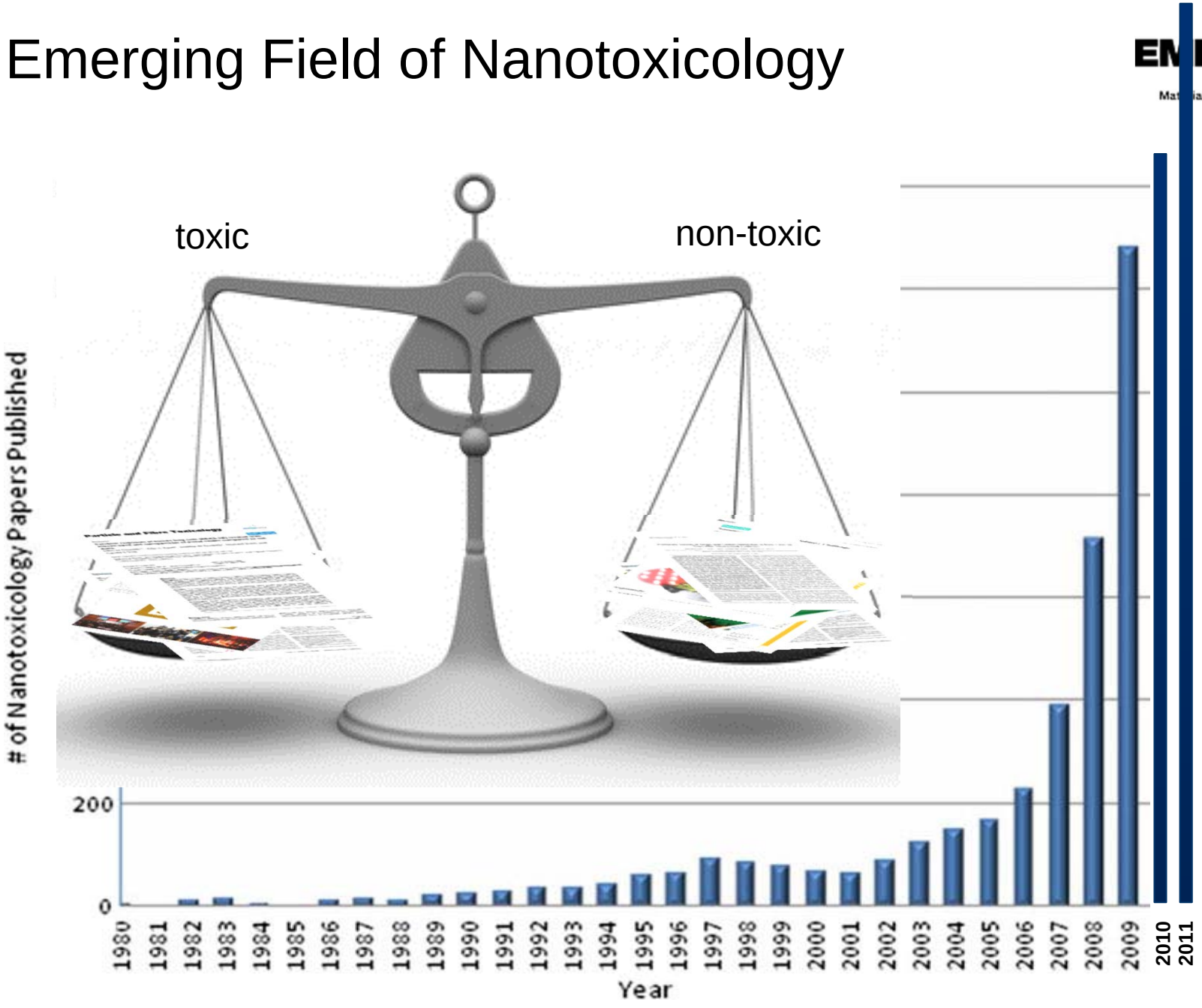


natural occurring NP

resorbable NP

Customized design

Emerging Field of Nanotoxicology



C.L.Haynes 2010

Motivation of the NanoSafety Research

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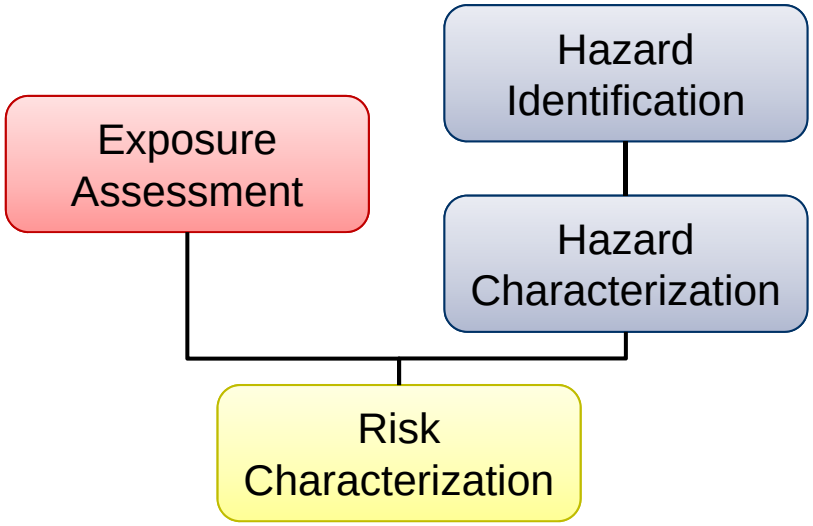
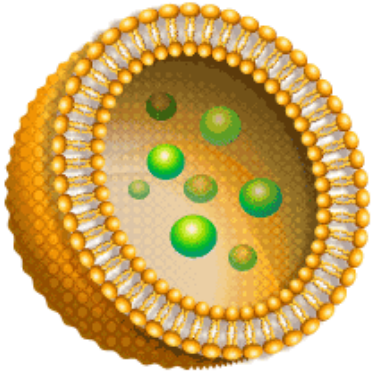
- Contribute to a safe development of nanotechnology
- Analyze possible adverse effects on humans and the environment as early as possible





Environmental Fate and Effects of Nanoparticles

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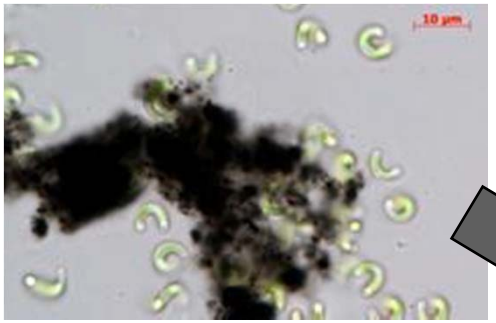
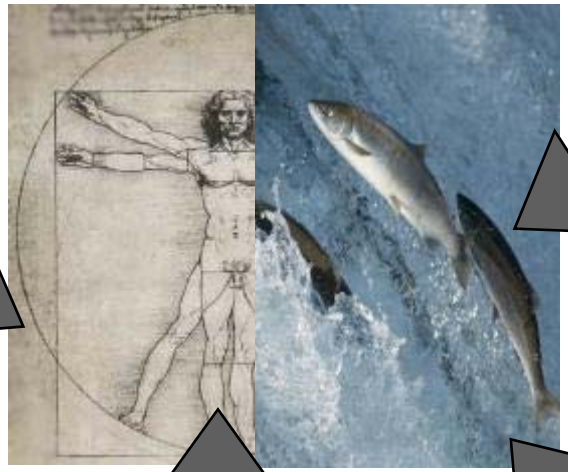
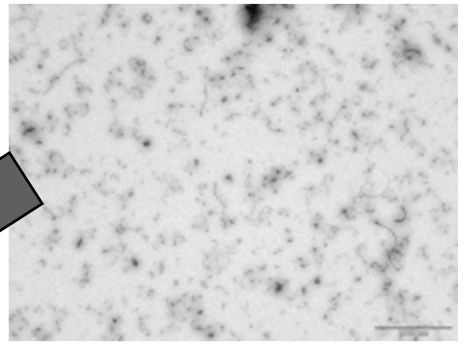


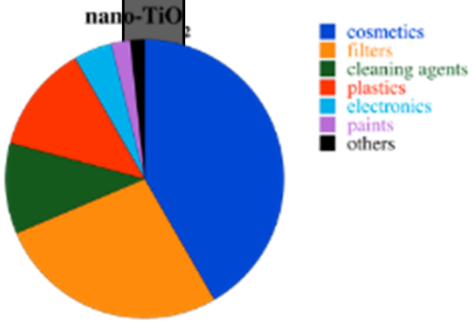
What are effects on organisms?





What is the form and concentration in the environment?

What is the behavior in the environment?



How much NP are used in what products?

How much is released from products, and in what form?

How to assess the safety of ‘Nano’?

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Exposure (E)

Hazard (H)

Risk (R)

$R = f_P \{E, H\}$

Risk Communication

Exposure scenario and biological effects of ENM

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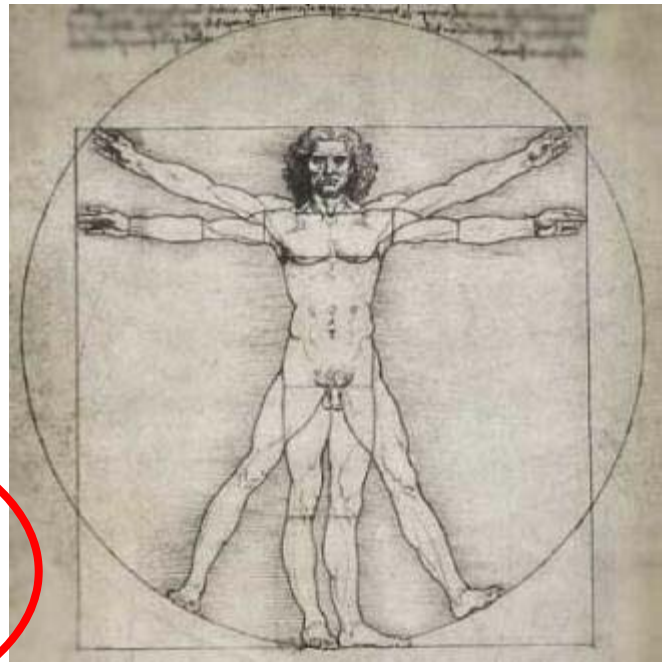
nose:
olfactoric nerve
bypass BBB



lung:
140 m^2
air / blood barrier
very thin < 2 µm

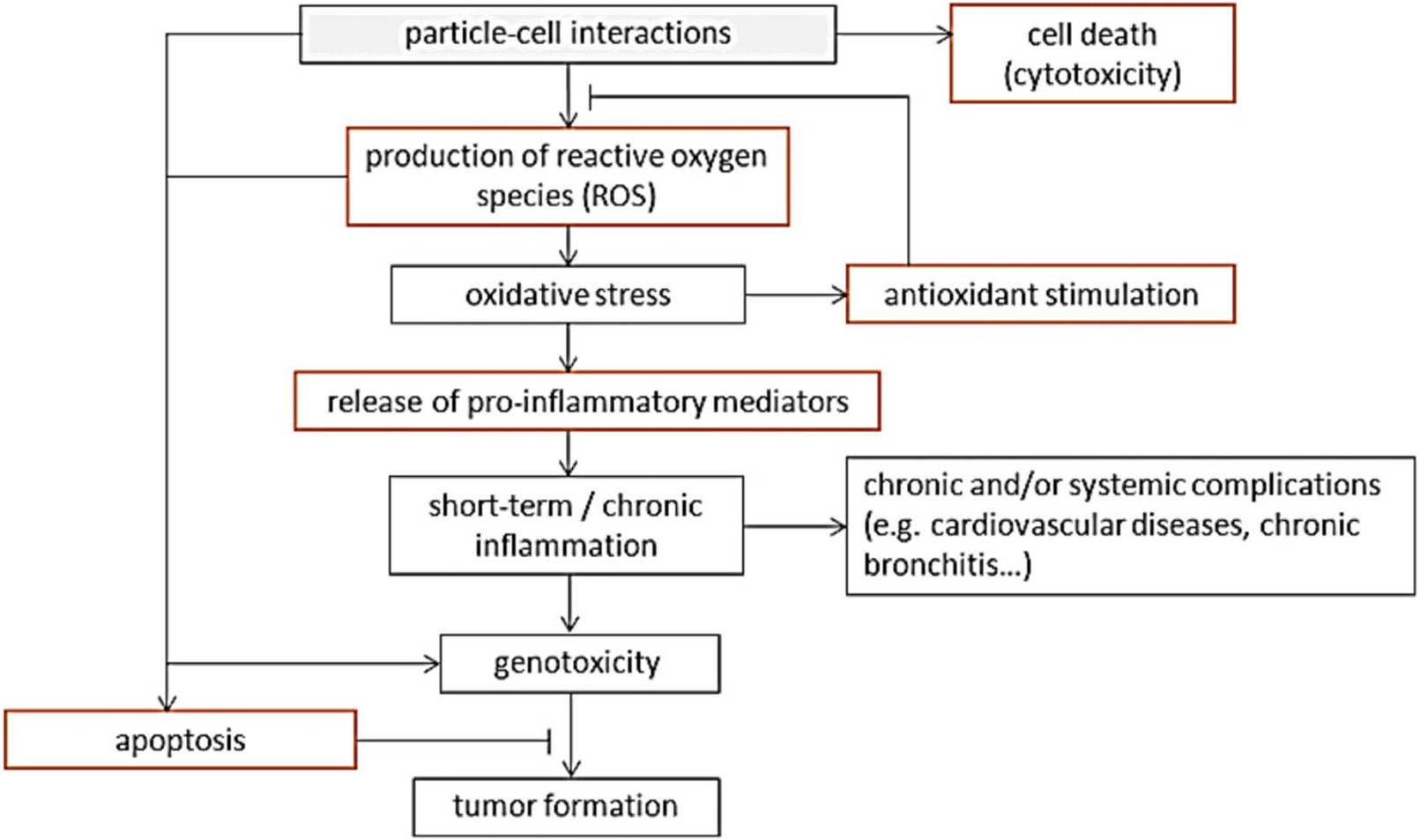
injection:
efficient distribution in the body (4 - 5l cardiac output per minute)

skin:
1.8 m^2
barrier **very thick**,
epidermis, horny skin

hair follicle	20/cm^2
respiratory glands	150/cm^2
sebaceous glands	15/cm^2

gastrointestinal tract:
surface: 2000m^2 incl Microvilli
pH 2, intestinal mucosa thick;
distance to blood vessels **big**

Oxidative stress paradigme for ENMs



Scheme adapted from: Donaldson et al. 2004, Occup Environ Med; Schins, Knaapen 2007,Inhal Toxicol; S. Steiner

3 Principles of Nanotoxicology

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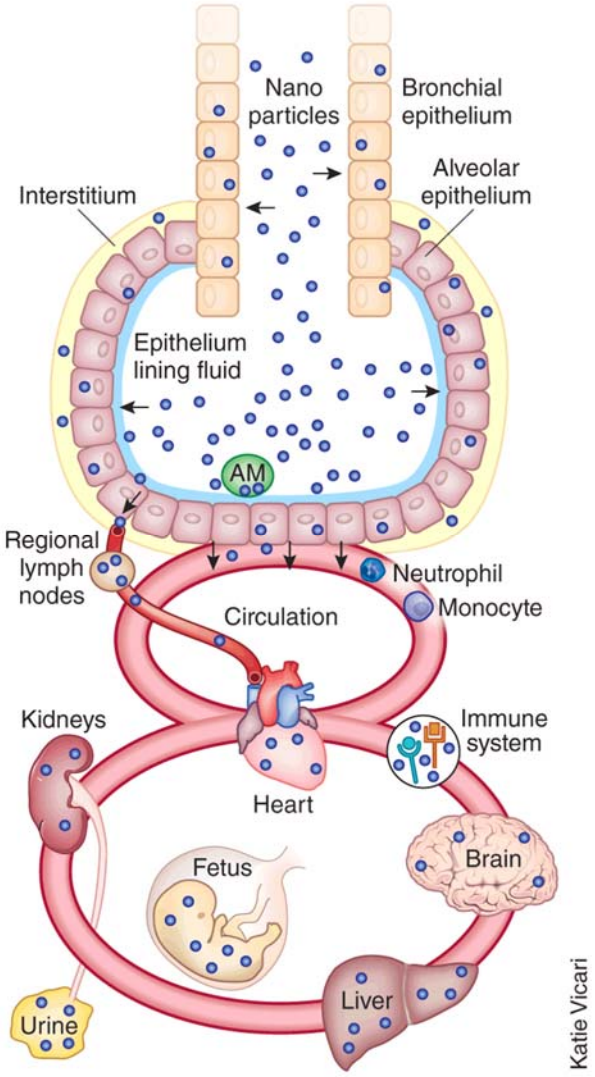
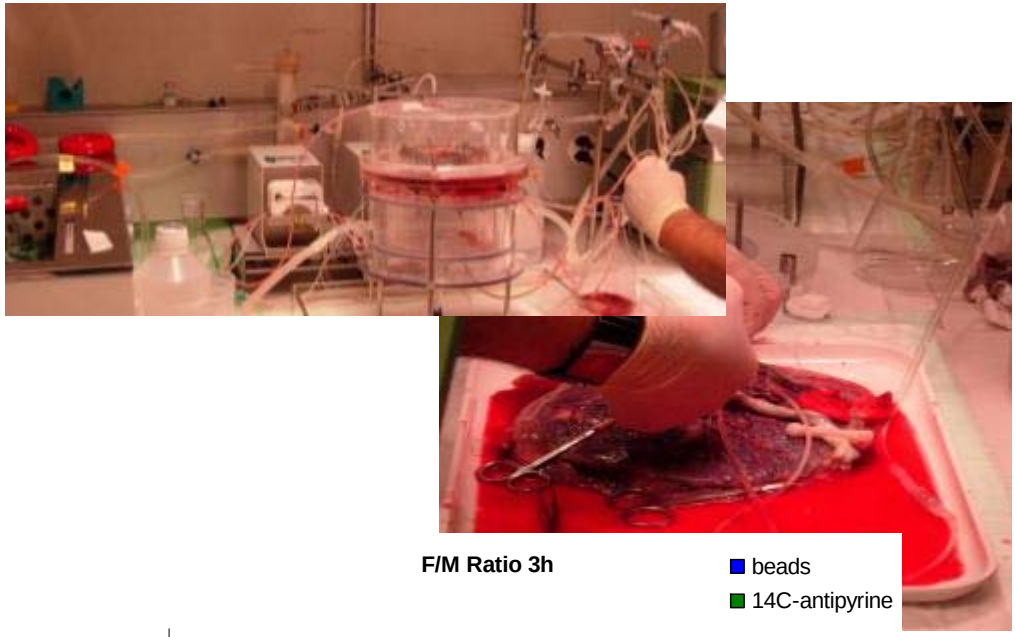
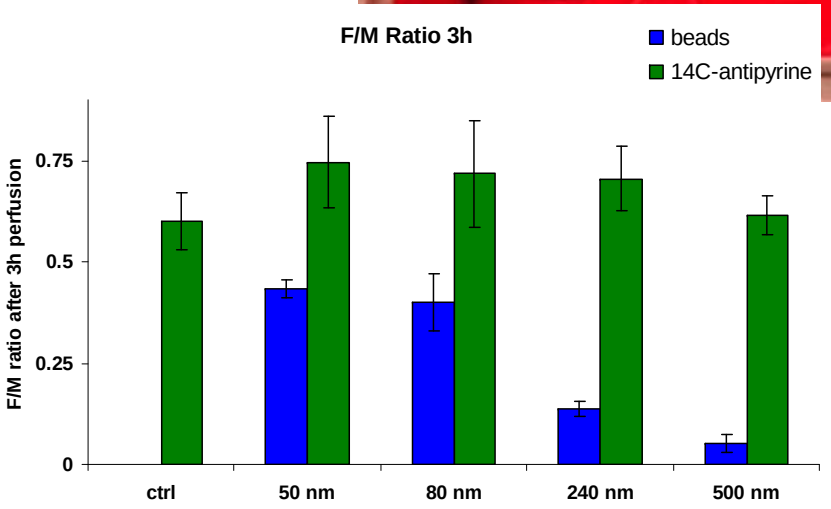
- uptake / transport principle
- surface principle
- material principle

1. Uptake / translocation: Size matters!



Semmler-Behnke et al 2008;
Kreyling et al 2010

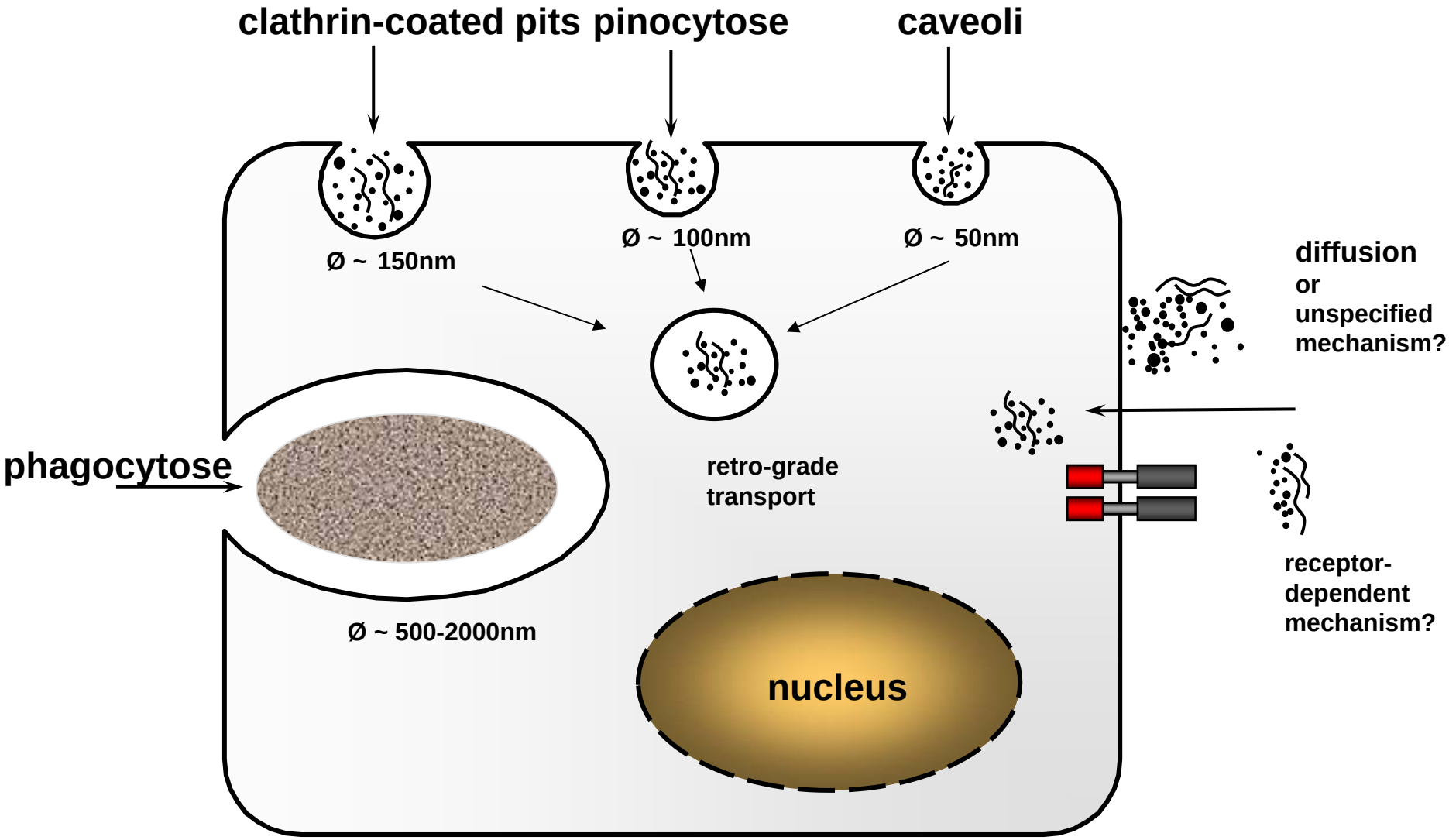




(at least n=4; mean ± S.E.M.)

Wick et al 2010

Intracellular uptake of nano-sized material



adapted from Conner SD et al., 2003; Geiser M et al., 2005, and Krug HF et al., 2006

Caveoli – nanoparticle shuttle

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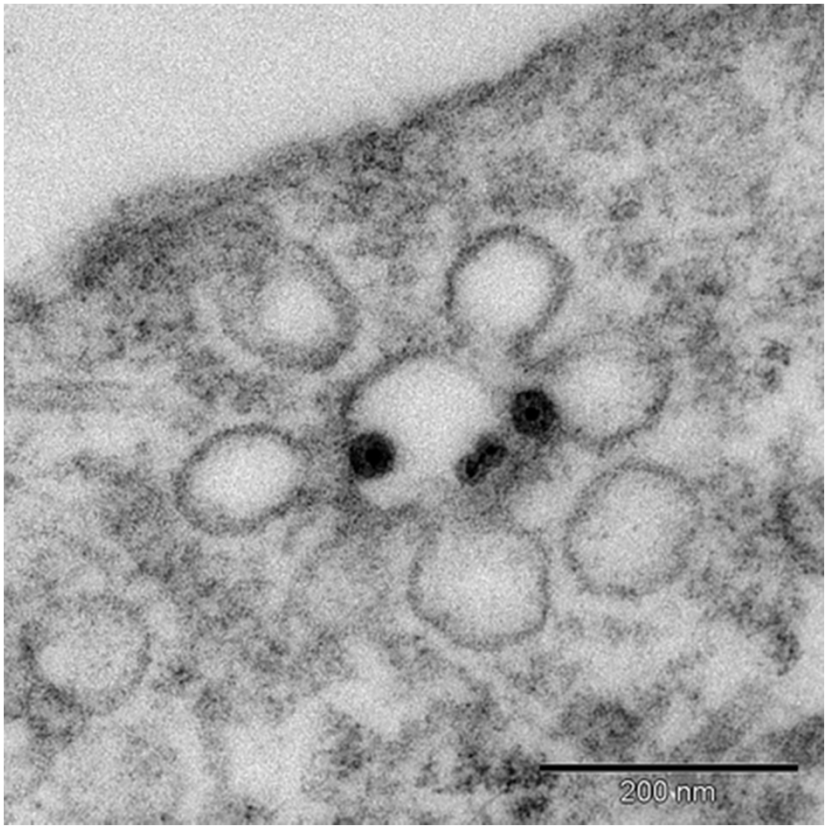
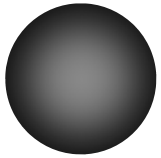
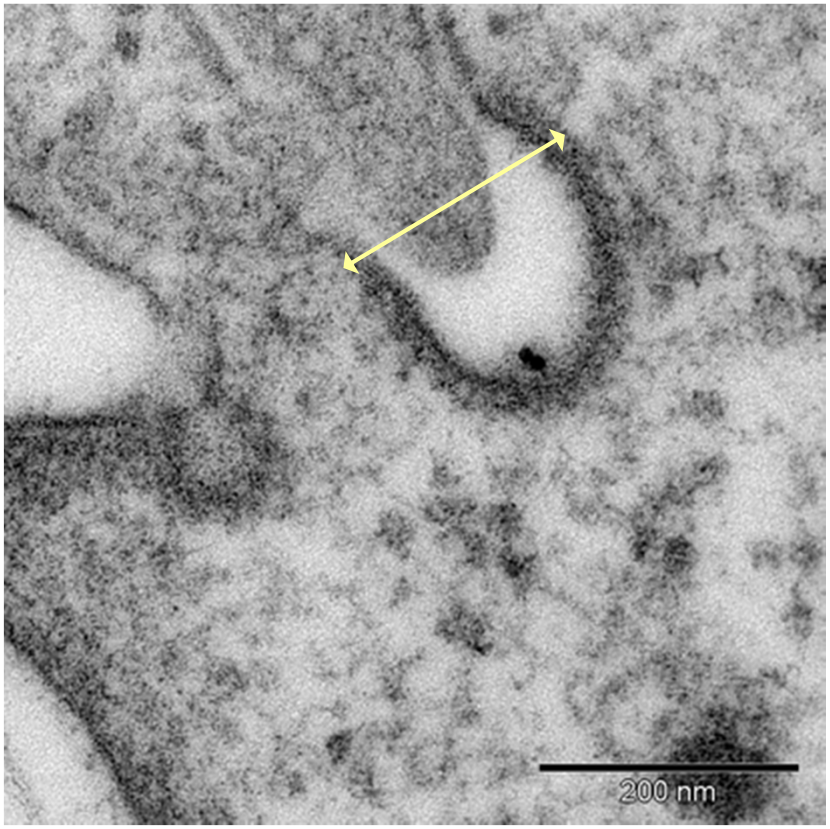


↔ 10 nm iron oxide core
⟷ 38 nm SiO_2 shell



↔ 10 nm iron oxide core
⟷ 22 nm SiO_2 shell



The Trojan Horse mechanism

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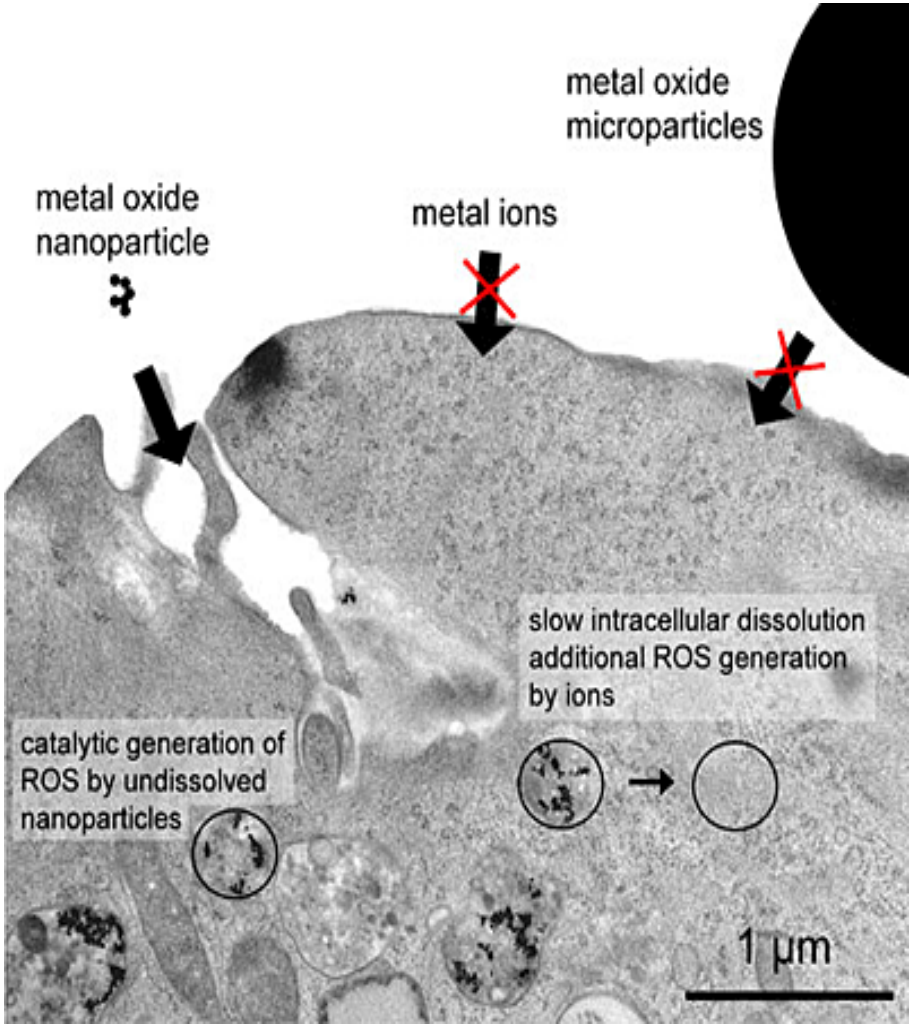
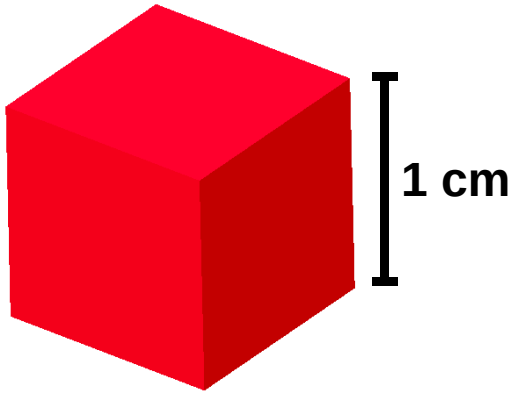
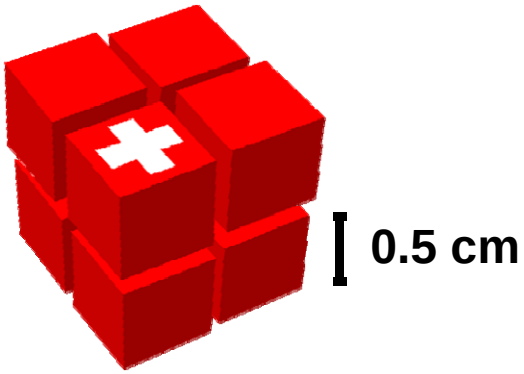
- Nanomaterials were taken up and may reach cells or tissues which were not affected when exposed to its bulk or ionic form
- Promising opportunity for pharmaceutical engineering
- Modulate the bioavailability of xenobiotic
- Understanding the underlying mechanism necessary for both the pharmaceutical as well as toxicological science



Brunner et al 2006
Limbach et al 2007

2. Surface / volume ratio of NPs

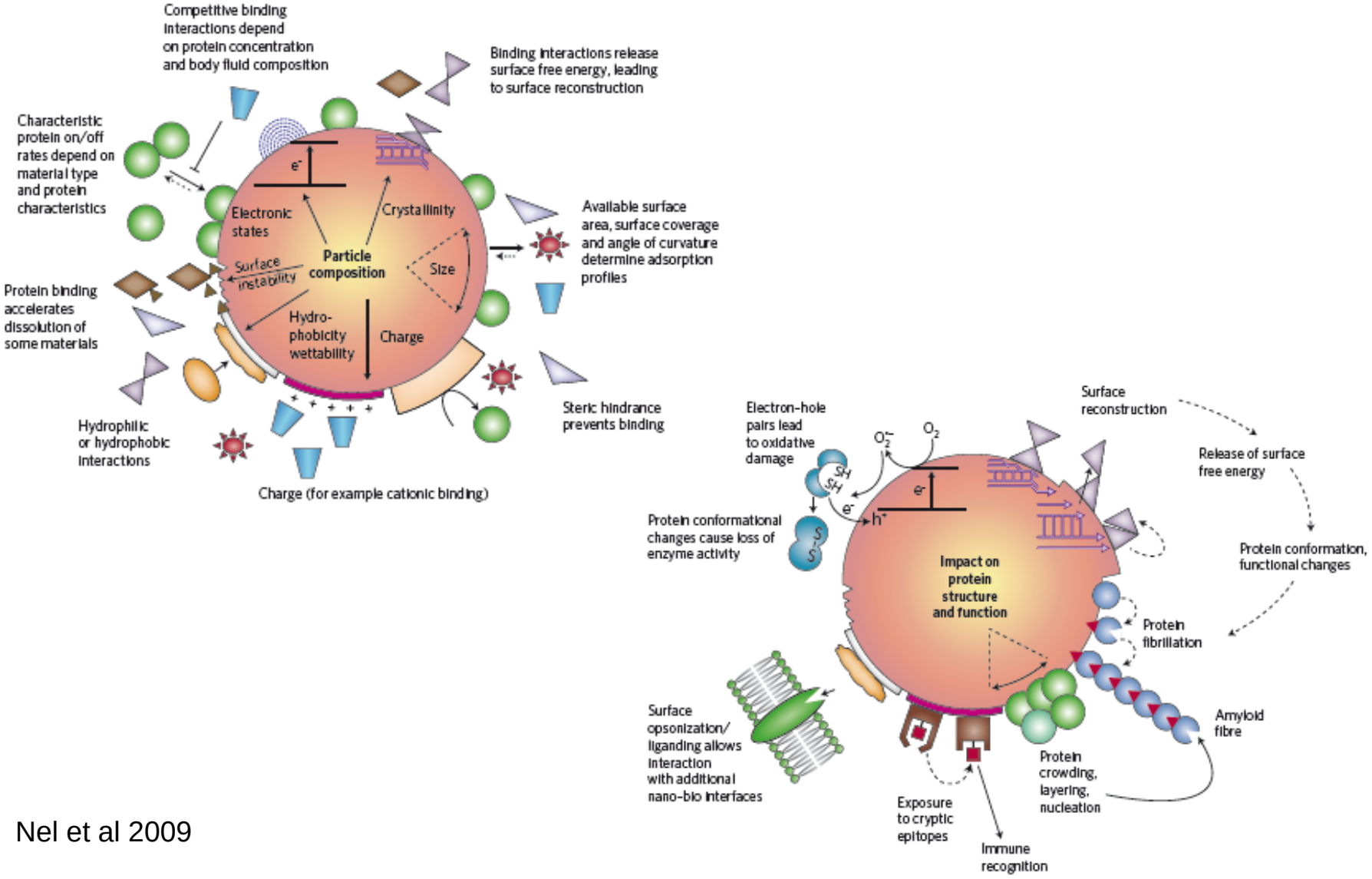




1 cube:	**1 cm^3**	**8 cubes:**	**1 cm^3**	**10^{21} cubes:**	**1 cm^3**
surface:	**6 cm^2**	**surface:**	**12 cm^2**	**surface:**	**6000 m^2**
mass:	**1g (density of 1)**	**mass:**	**1g (density of 1)**	**mass:**	**1g (density of 1)**

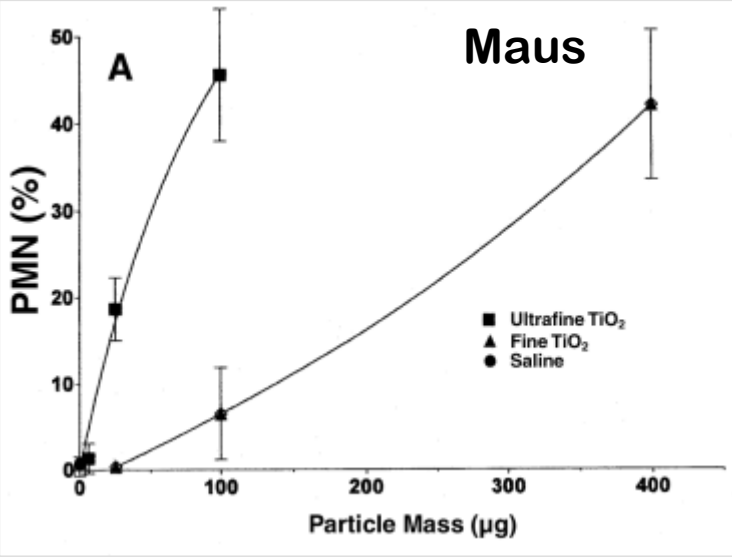
similar mass, but 10 Mio. larger surface

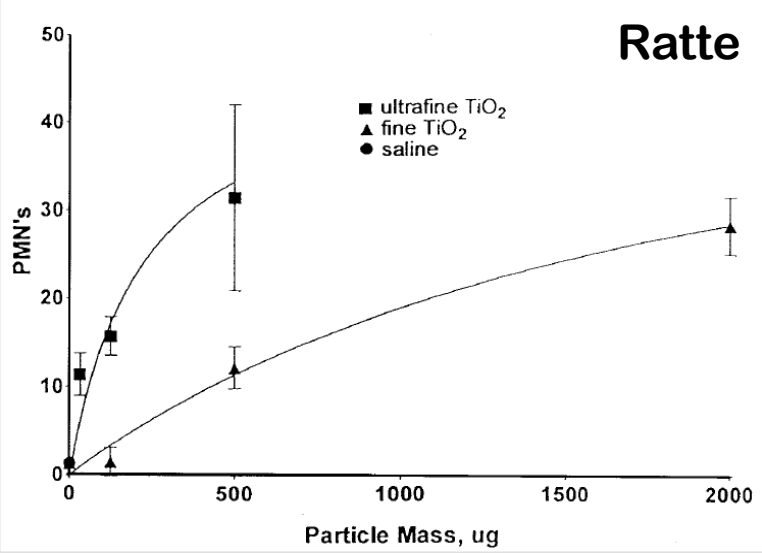
Surface effects: key element for NPs – cell interactions



Nel et al 2009

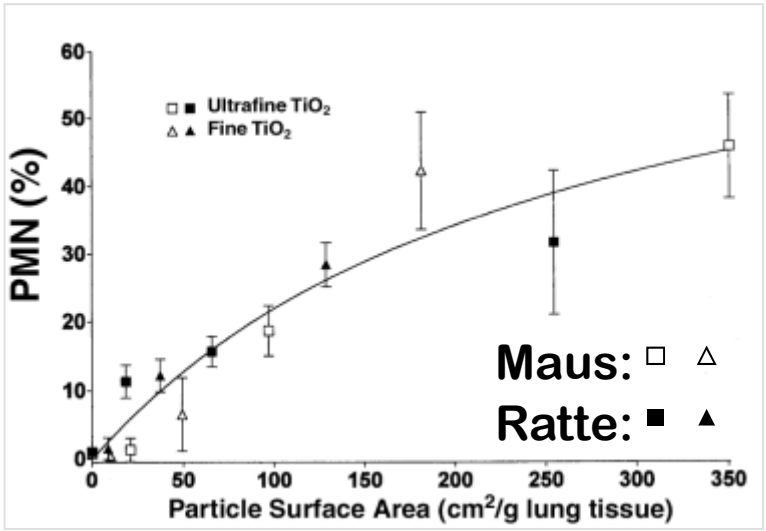
Acute effects of nanoparticles in the lung



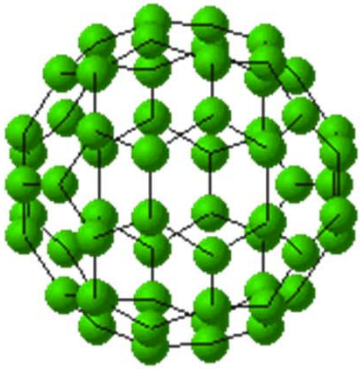


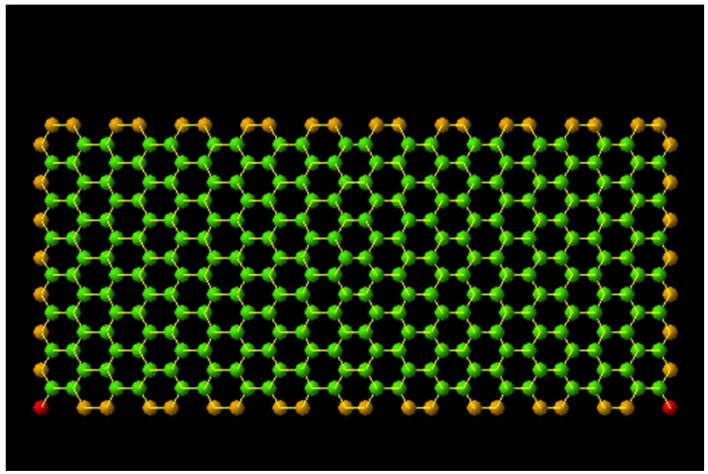
Inflammatory cell response in lung lavage (procent of Neutrophils) 24hr after intratracheal instillation of fine (~250 nm) or ultrafine (~20 nm) TiO_2 particles in rats and mice.

Oberdörster et al., 2000: HEI-Report 96
Oberdörster 2001: Int. Arch. Occup. Environ. Health, 74, 1-8

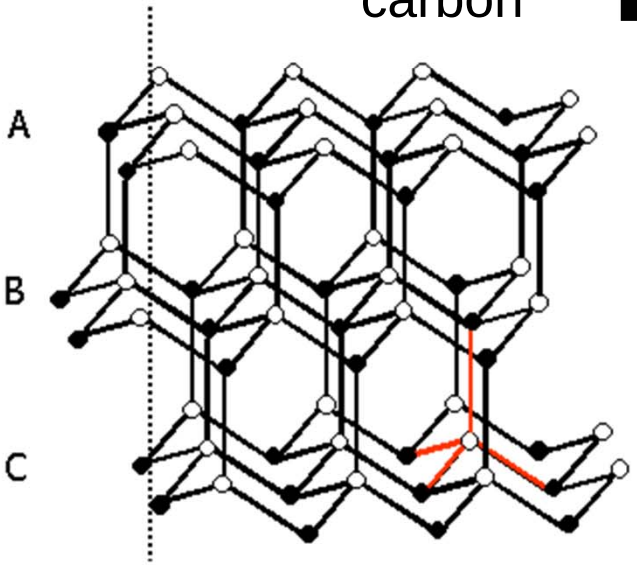


3. One Material – different appearance

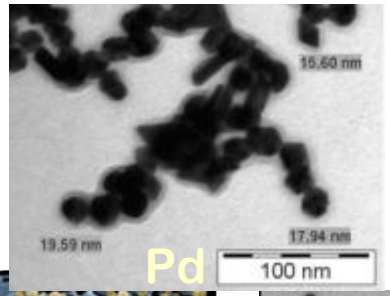


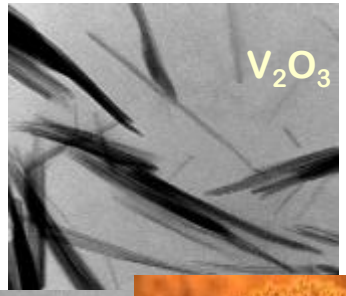


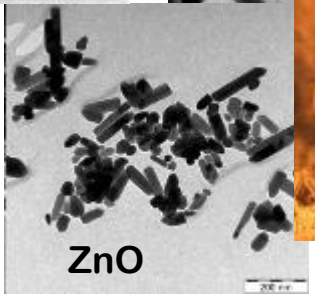
carbon



and others…







Fibre paradigma

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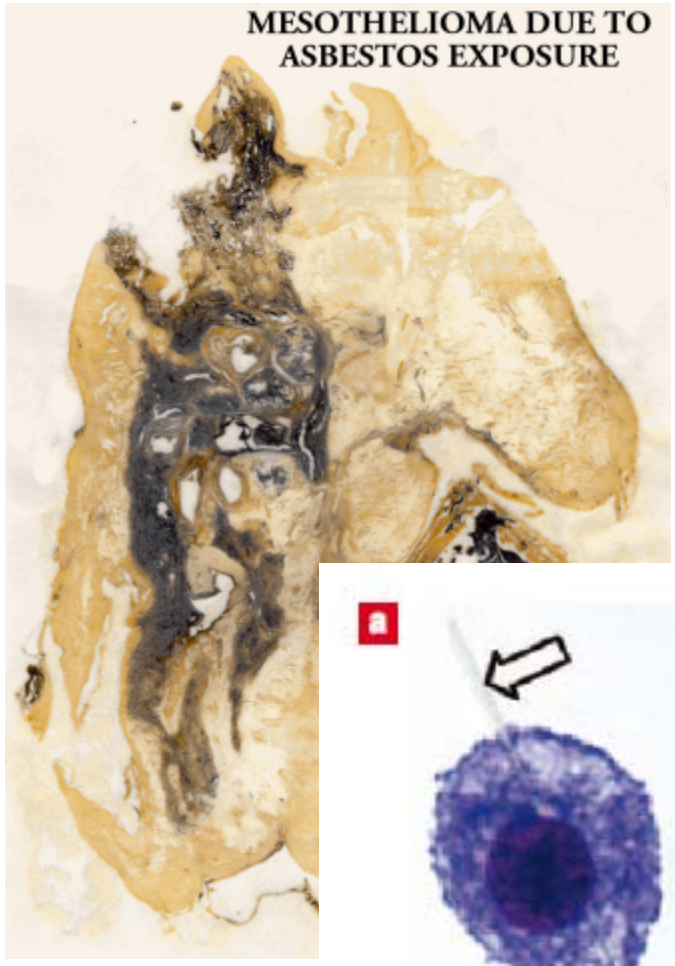


- > 50 µm in length
- rigid
- biopersistent

Donaldson et al. Particle and Fibre Toxicology 2010, 7:5
http://www.particleandfibretoxicology.com/content/7/1/5

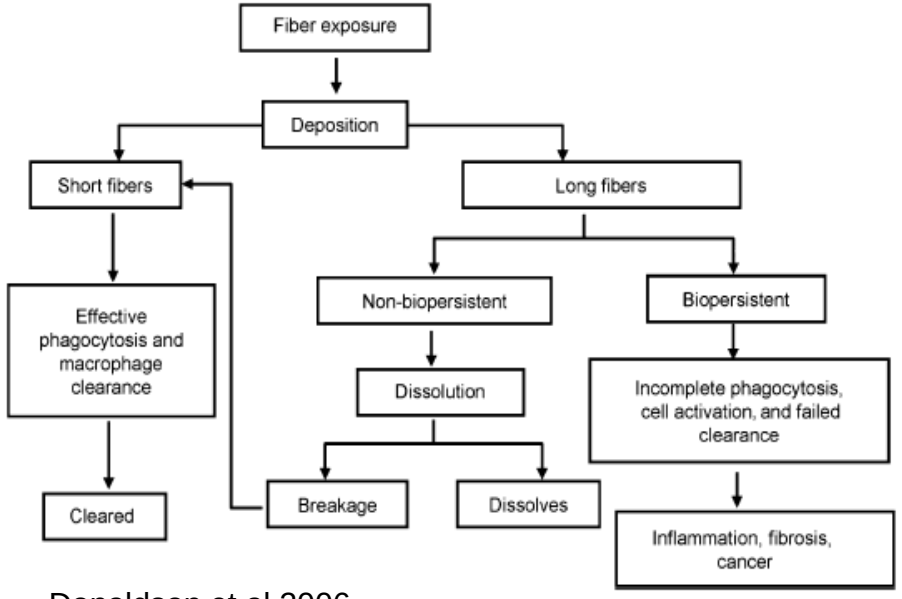
PARTICLE AND FIBRE TOXICOLOGY

REVIEW Open Access

Asbestos, carbon nanotubes and the pleural mesothelium: a review of the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma

Ken Donaldson*, Fiona A Murphy, Rodger Duffin, Craig A Poland

Donaldson *et al*. (2010) *Part. Fibre Toxicol, 7*, 5



Donaldson et al 2006

Comprehensive material characterization is necessary prior to any biological work

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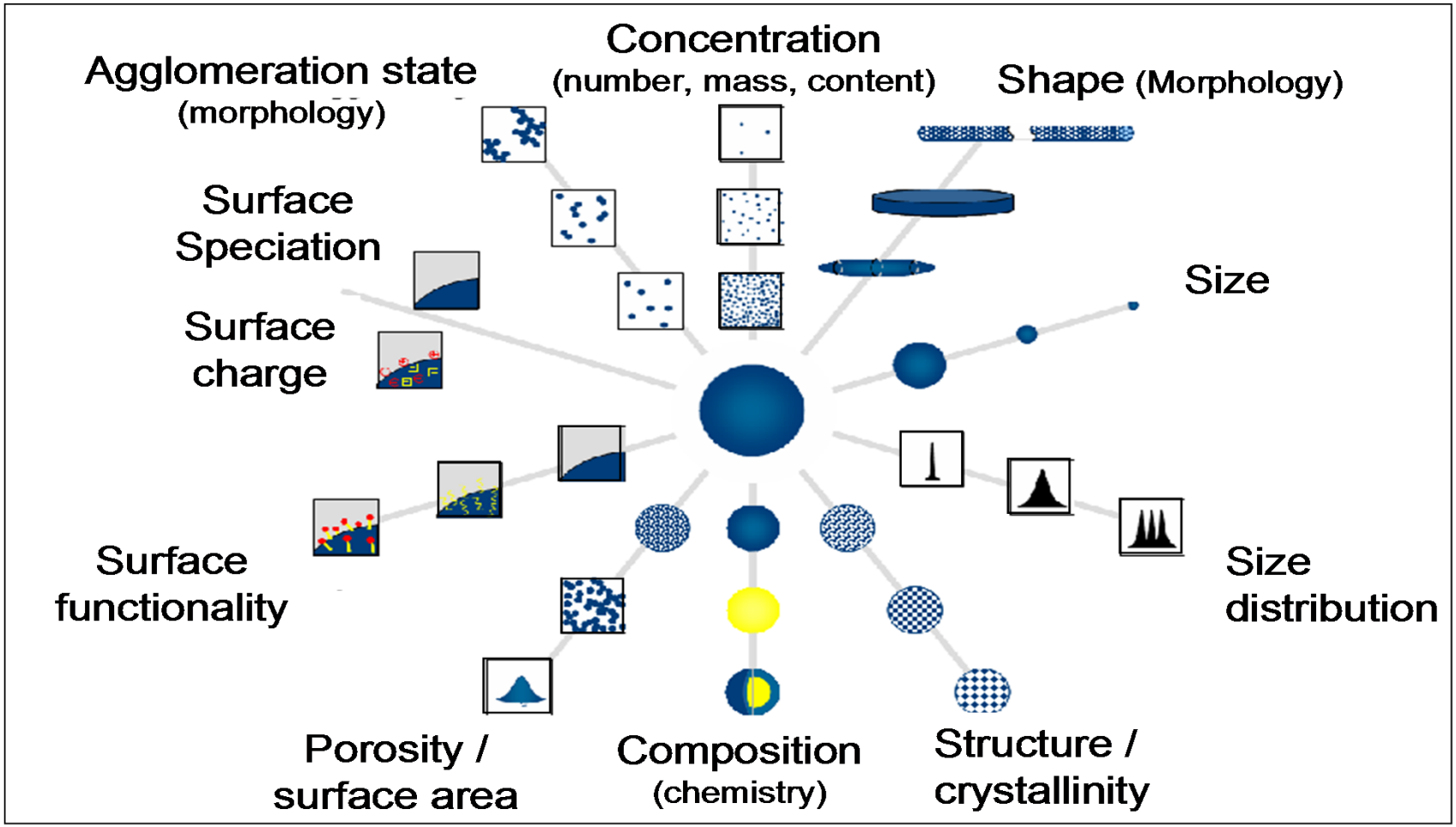
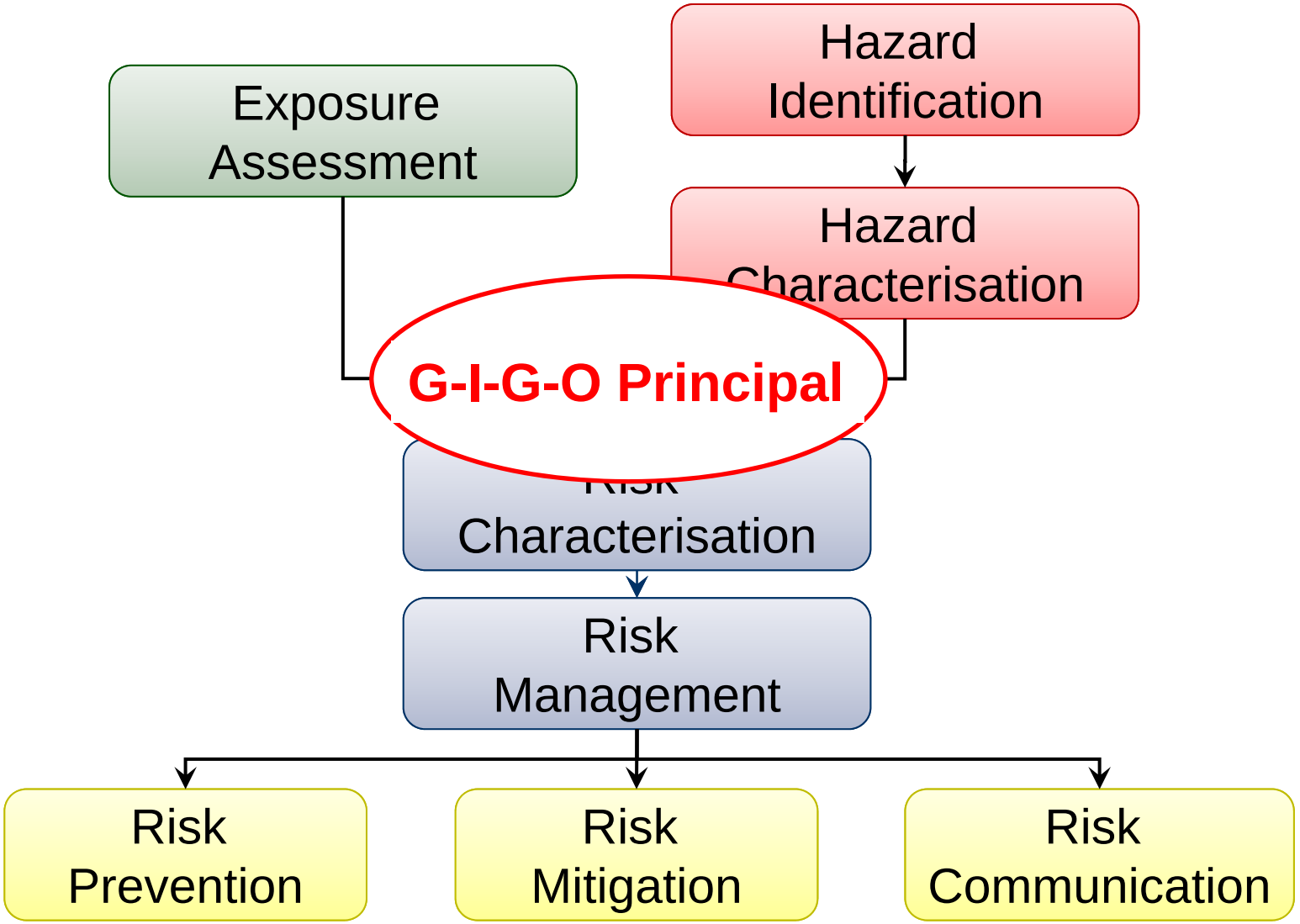


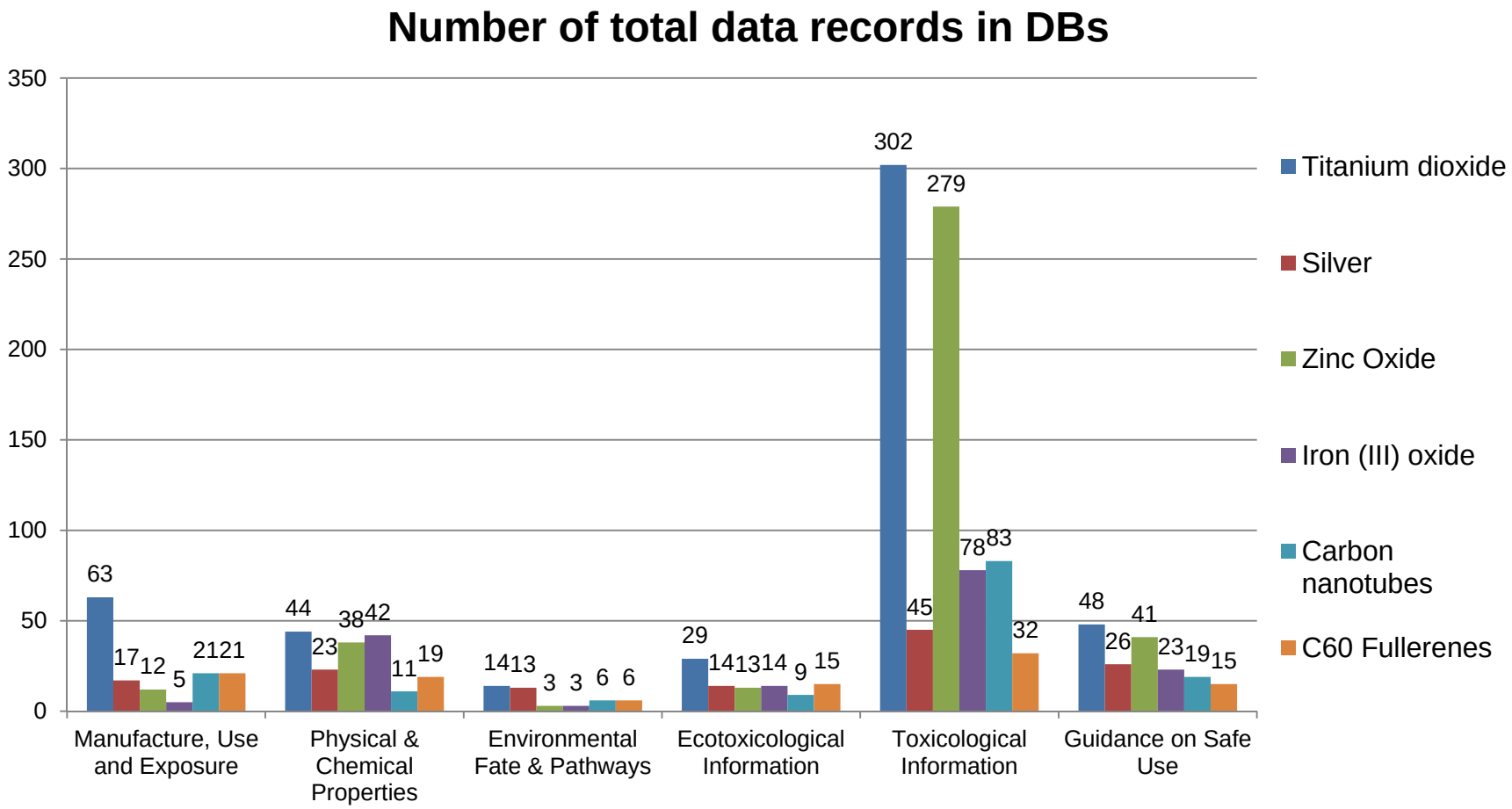
M. Hassellov, et al 2008

Risk Assessment is important



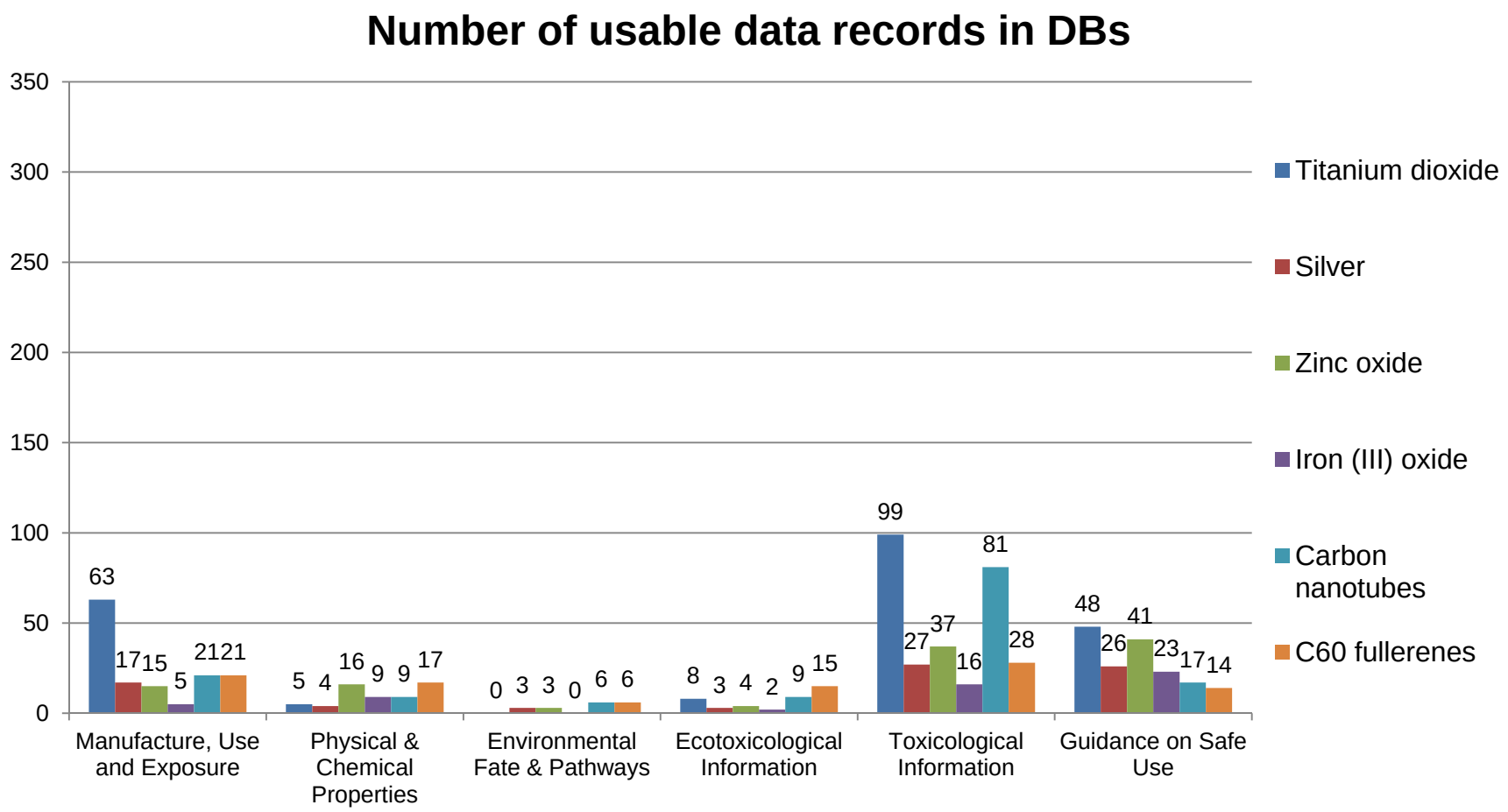
Krug and Wick 2011

Review of nano-EHS data availability



Hristozov et al., 2012

Review of nano-EHS data availability



Hristozov et al., 2012

Toxicology in the 21st Century for Nanomaterials

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HORIZONS

NATURE|Vol 460|9 July 2009

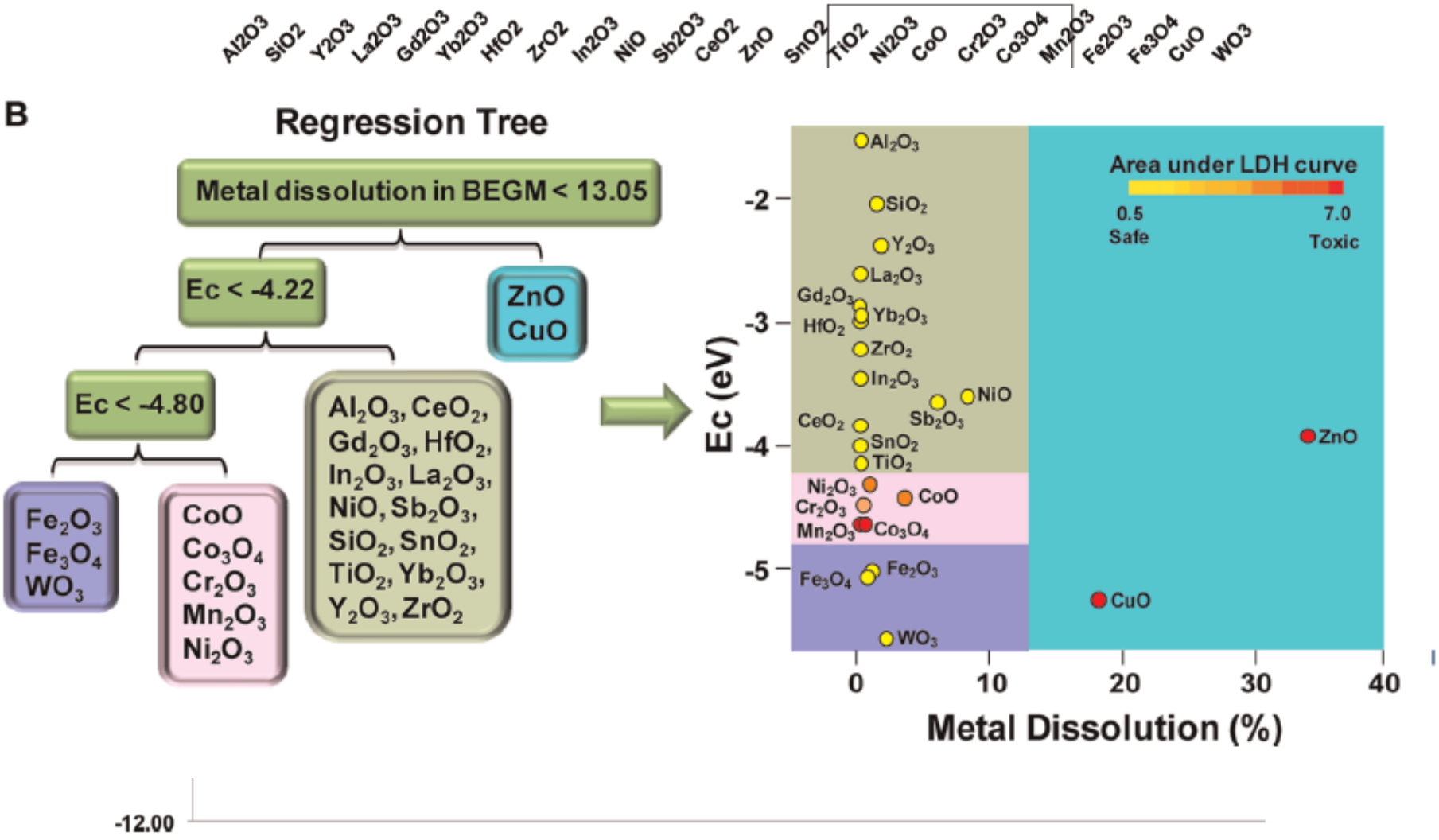
Toxicology for the twenty-first century

Thomas Hartung

The testing of substances for adverse effects on humans and the environment needs a radical overhaul if we are to meet the challenges of ensuring health and safety.

Hartung T (2009) Toxicology for the twenty-first century.
Nature 460: 208-212

QSAR for nanoparticles



QSAR = quantitative structure-activity relationship

Zhang et al 2012 ACS Nano

Reliable acute nano-tox testing strategy

NP properties may interfere with current used acute tox test system(s) and provoke false negative or positive results

Inter-laboratory differences in NP tox assessment

Insecurity not only by the consumer, but also NGOs, authorities, researchers and industries

Only sustainable and safe (nano-) technological products / applications will be successful on the market

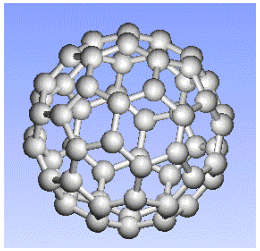
NANO LETTERS
2006
Vol. 6, No. 6
1261−1268

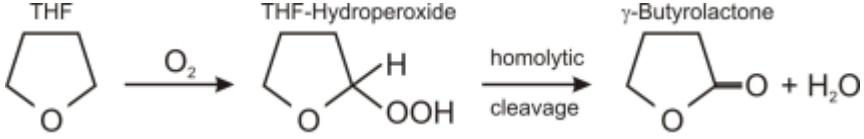
Oops They Did It Again! Carbon Nanotubes Hoax Scientists in Viability Assays

J. M. Worle-Knirsch, K. Pulskamp, and H. F. Krug*

The reliability and limits of the MTT reduction assay for carbon nanotubes–cell interaction

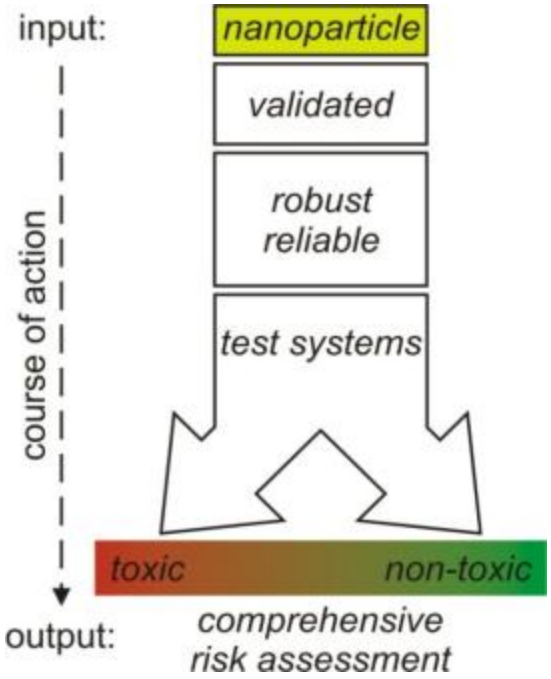
Larisa Belyanskaya, Pius Manser, Philipp Spohn, Arie Bruinink, Peter Wick *





Spohn et al 2009

Reduction of uncertainties by standardization



CCMX
Competence Centre for
Materials Science and Technology

FNSNF
Schweizerischer Nationalfonds zur
Förderung der wissenschaftlichen Forschung

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Bundesamt für Umwelt BAFU

Bundesamt für Gesundheit BAG

Industrial relevant nanomaterials: metals, metal-oxides, carbon based and polymers
According to the oxidative stress paradigm: 4 endpoints each at least 2 methods

Outcome: improved test methods for nanomaterials including quality control
data obtained will be compared with inter-laboratory round robins
test system knowledge will be available for industry
methods will be transferred to ISO and / or OECD guidelines
can be combined with other activities if desired

Risk assessment strategies

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ACCOUNTS
of chemical research

Toward the Development of Decision Supporting Tools That Can Be Used for Safe Production and Use of Nanomaterials

CLAUDIA SOM, BERND NOWACK, HARALD F. KRUG,*
AND PETER WICK

Empa, Swiss Laboratory for Materials Science and Technology, Lerchenfeldstrasse 5, 9014 St. Gallen, Switzerland

RECEIVED ON FEBRUARY 9, 2012

Summary and Conclusions

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- Motivation of nanosafety research is to support nanotechnology
- Nanosafety research is a real interdisciplinary field which combines material science, chemistry, physics, analytics, life sciences and toxicology
- 3 principles guide the nanosafety research
- Risk assessment demands quality management for data
  (standardized methods or reference materials should became standard for hazard ranking studies)
- Decrease the insecurity by consumer, industry, regulatory bodies and researcher
- Contribute to a fact based discussion about the chances and risks of nanomaterials

Rösslein et al 2011 Nanomedicine

Collaborations

Prof B. Rothen-Ruthishauser and team AMI
Prof B. Fadeel (Coordinator of FP 7 Nanommune) KI
Prof U. von Mandach and team USZ
Dr L. Tran (Coordinator of FP / MARINA) IOM
Prof W. Jochum and PD R. Hornung KSSG
Prof B. Yan St. Jude Children's Hospital Memphis
Dr J. Kelm and Dr W. Moritz Insphero
Prof Dr U. Graf-Hausner and team ZHAW
Prof W. Stark and team ETHZ
Prof H. Hofmann and team EPFL
Prof Dr J. Huwyler and team UniBasel
Dr M. Salit and team NIST
Prof Dr. K Savolinen FIOH

Thank you for your attention

Upcoming workshop

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