



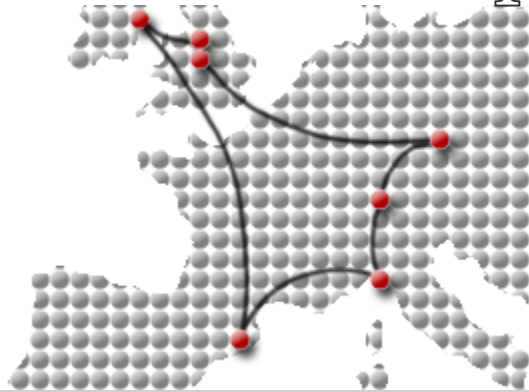
RESEARCH & INNOVATION  
Marie Curie Actions

# Kick off meeting

Barcelona

23-24 February 2013

# MagNETic FUN



## Nanotoxicology

Robert N. Grass

ETH Zurich, Switzerland

TurboBeads GmbH, Zurich, Switzerland

# The problem with nanotoxicology - generalization

## Penetration of Intact Skin by Quantum Dots with Diverse Physicochemical Properties

Jessica P. Ryman-Rasmussen, Jim E. Riviere, and Nancy A. Monteiro-Riviere<sup>1</sup>

*Center for Chemical Toxicology Research and Pharmacokinetics, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina 27606*

Test of 1 spherical QD (4.6 nm) and 1 ellipsoid QD (6x12 nm) with 3 surface coatings

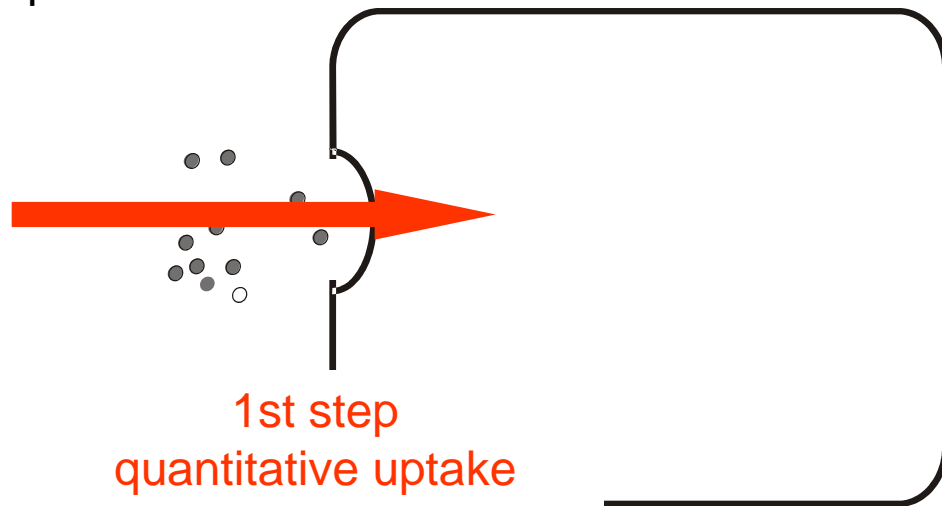
# The problem with nanotoxicology

“The penetration of QD through skin was addressed by the Monteiro-Riviere research group employing an ex vivo porcine skin model. Their **initial results found that**, with 8 and 24 h of exposure to QD, porcine skin exhibited **QD penetration throughout the epidermis** and deep into the dermis in some cases. In a more **recent follow-up study, they** reported **contrasting results** in that minimal penetration of QD through ex vivo porcine skin was found, with the bulk of the QD remaining in the stratum corneum. Reasons for this discrepancy remain unclear, however, **other researchers** have examined the question of skin penetration employing different NP types (metals, polymers) using ex vivo skin models, **and again contrasting** results of both high and low levels of NP penetration are reported.”

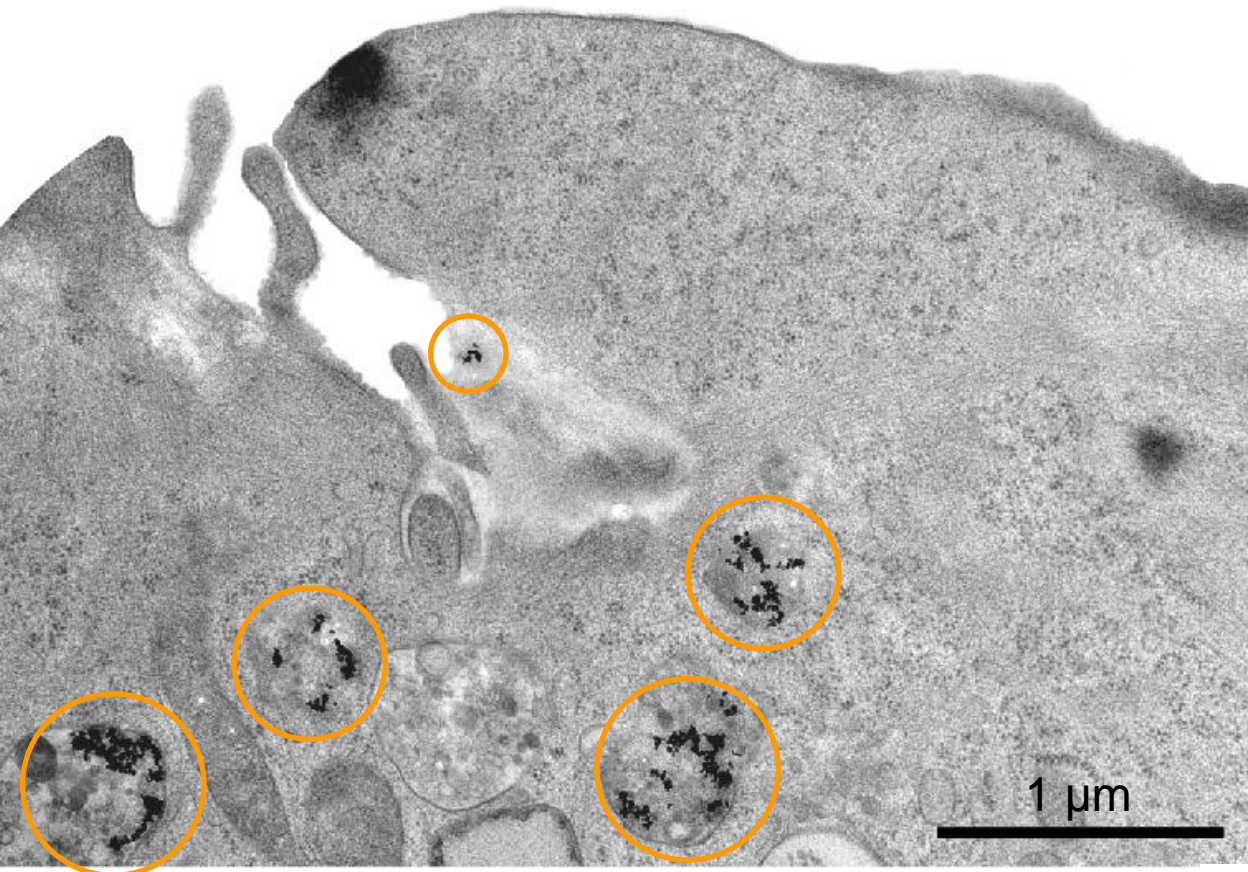
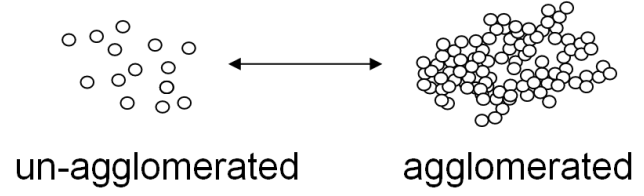
**NANO LETTERS**  
**2008 Vol. 8, No. 9 2779-2787**

# Why we are afraid: Nanoparticle in living cells?

uptake of nanoparticles



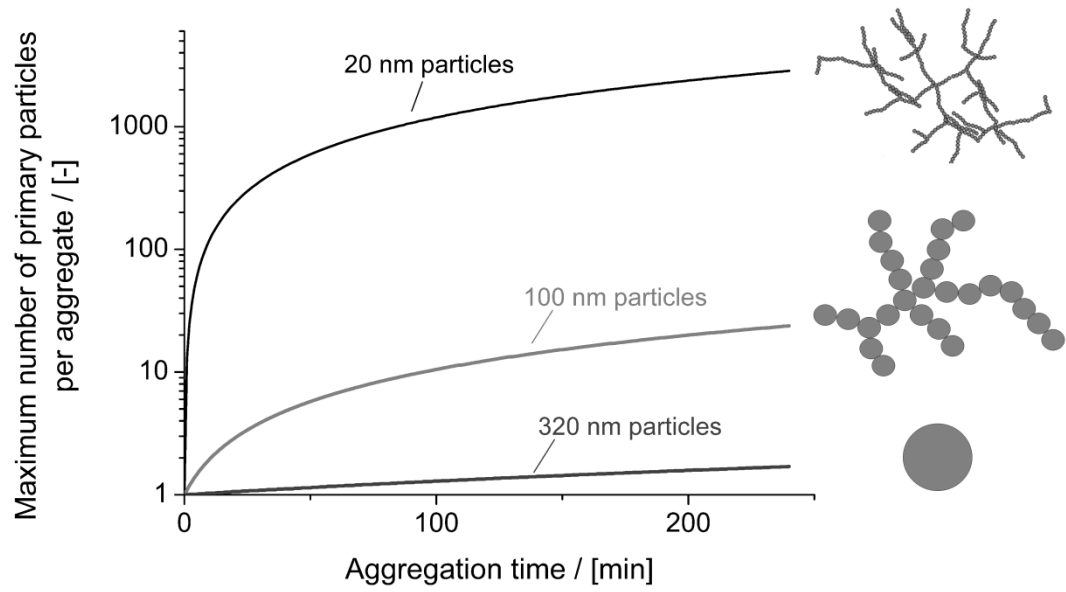
# quantitative uptake of nanoparticles in cells



$$\frac{dn_t}{dt} = -\frac{1}{2} \frac{\beta}{W} n_t^2$$

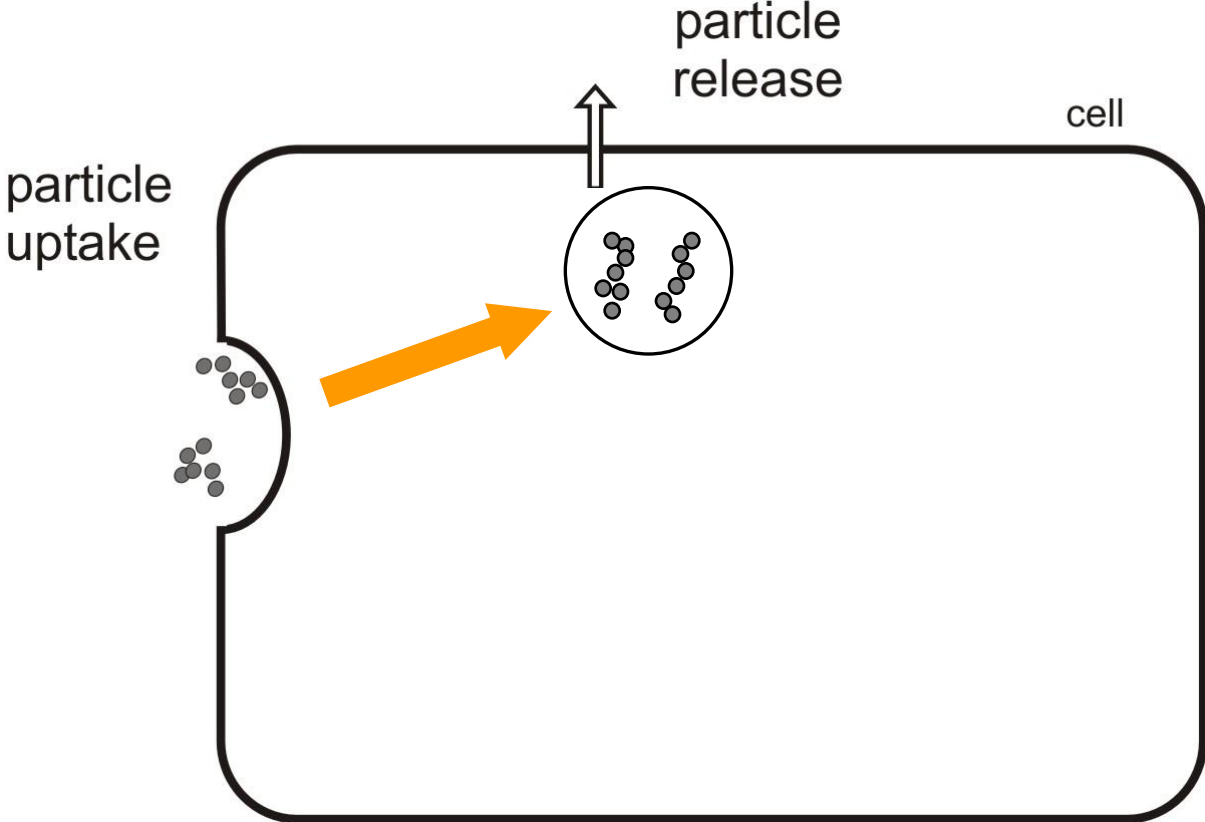
Friedlander (1953), Smoke, Dust and Haze

# agglomeration – same mass concentration different size

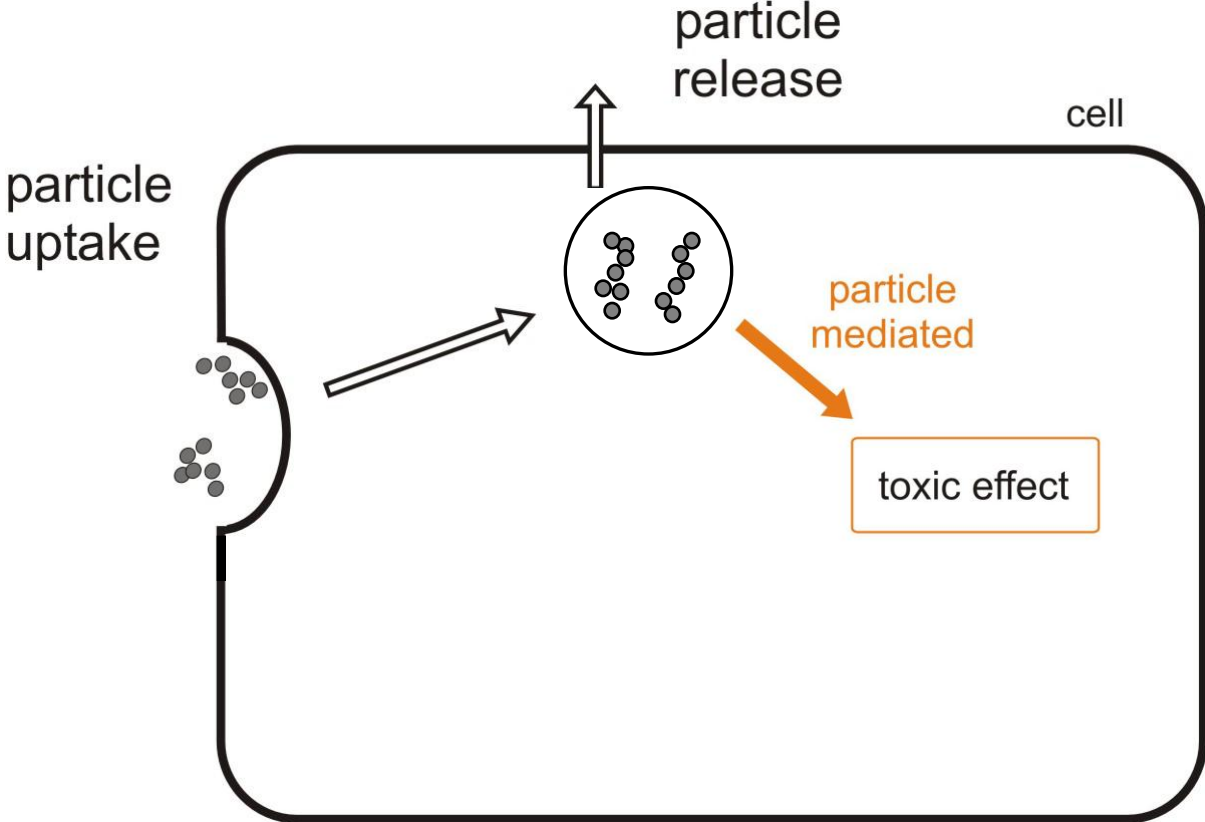


Biodistribution = f (time, concentration)

# Schematic diagram



# Schematic diagram





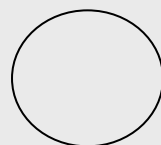
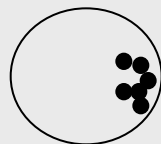
# Trojan horse mechanism



ZnO-nanoparticle



pH = 5.5



Intracellular dissolution  
additional damage through ions

Zn<sup>2+</sup>-ions



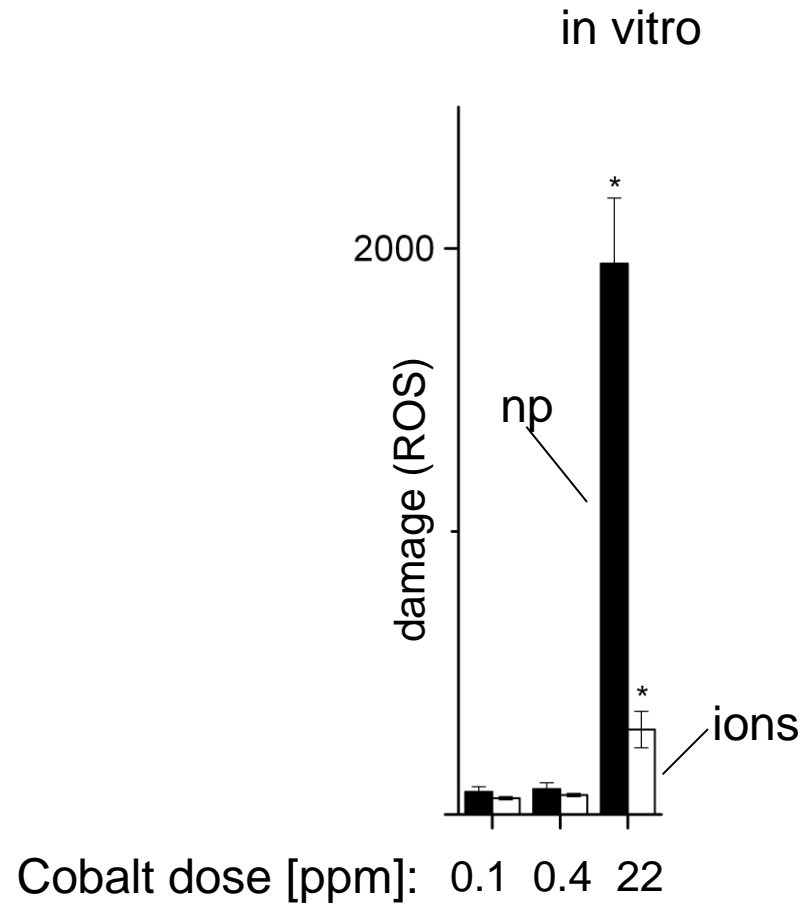
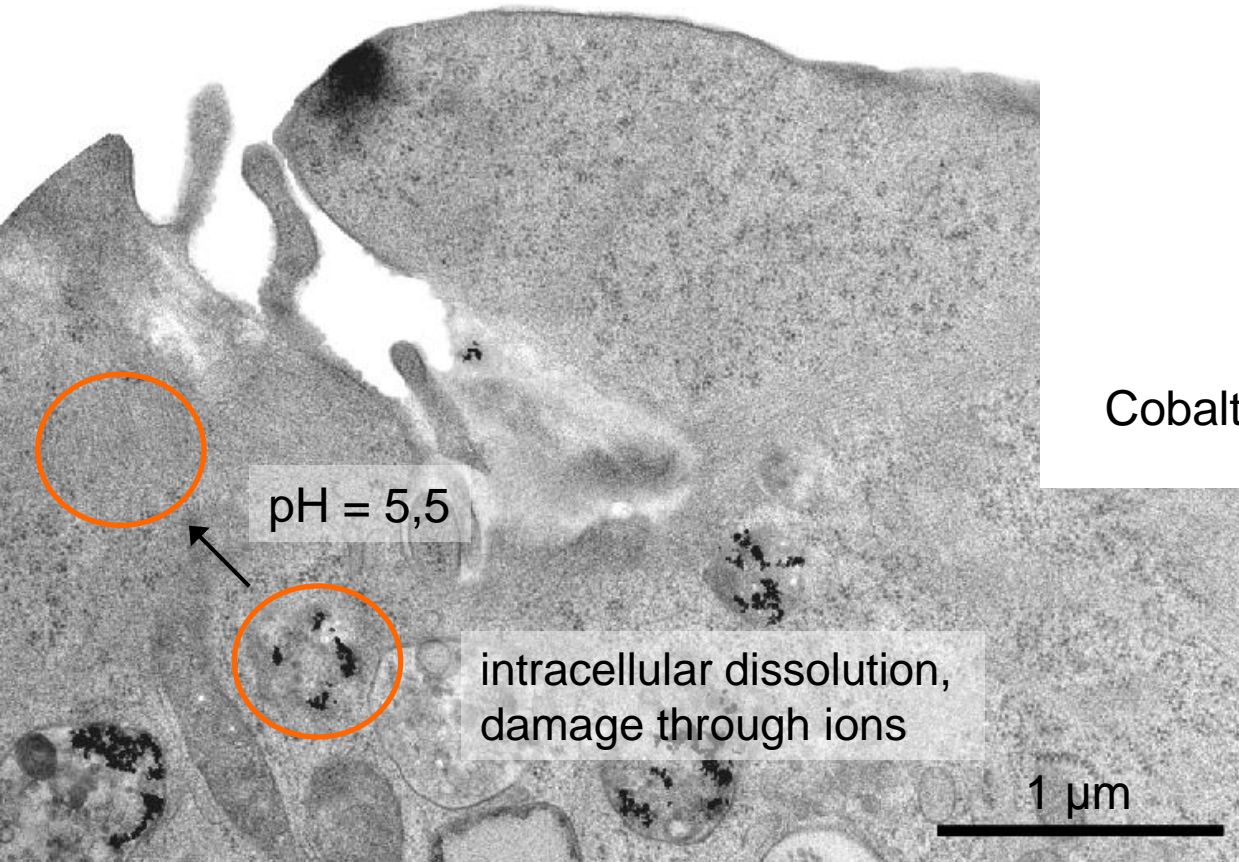
ZnO-microparticle



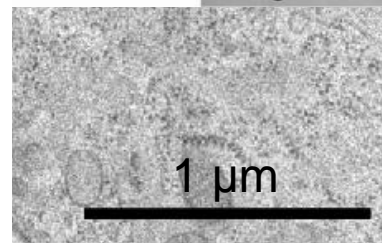
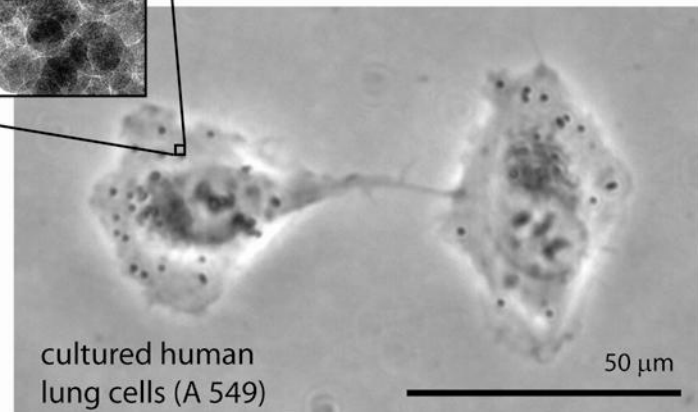
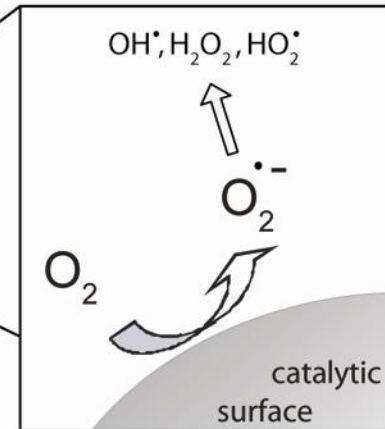
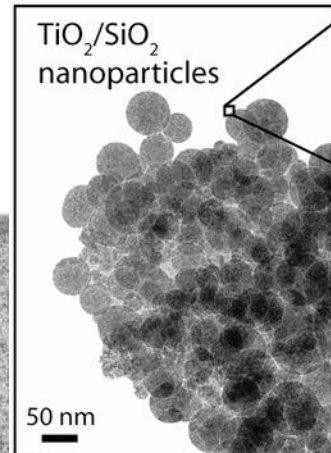
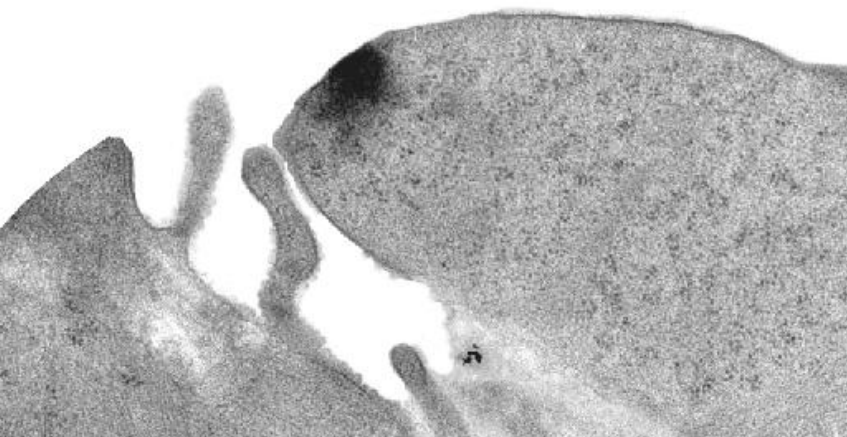
cell



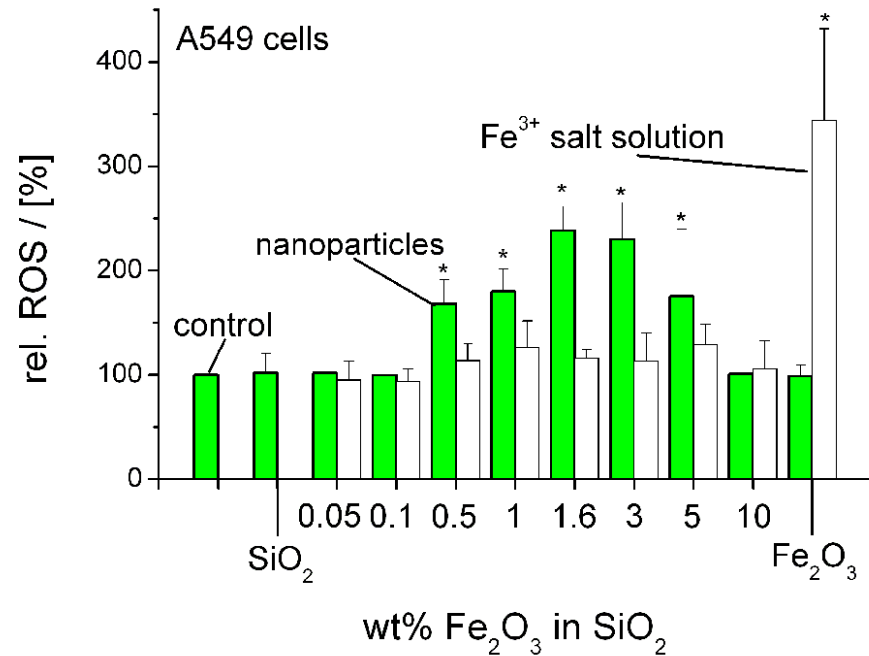
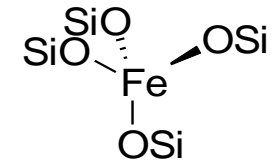
# trojan horse-type enhanced heavy metal uptake



# heterogeneous Catalysis inside living cells



# heterogeneous catalysis inside living cells



## Classical toxin

- Bio-distribution
- Action
- Clearance
- Dose/Effect relations

## Nanoparticles

- Agglomeration, diffusion and sedimentation change distribution kinetics
- Action; Solubility alters release
- Clearance
- Dose/effect
- Catalytic effects: Non-mass constant toxic action

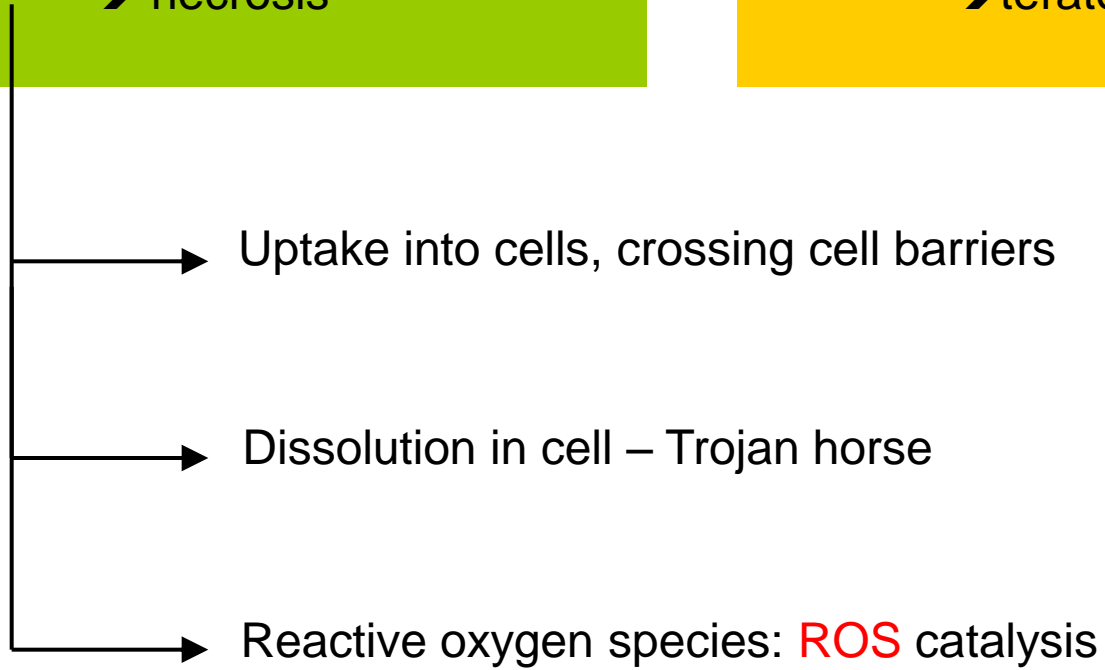
# Nanoparticle associated risk

**acute effects**

- apoptosis
- necrosis

**long term effects**

- mutagenicity
- teratogenicity



# Nano is not new

Global commodities:

- Silica np. (food additive)
  - Titania np. (white paint, toothpaste, sunscreen)
  - Carbon black np. (car tires, printing inks)
- Safely used today in consumer goods

Fullerenes, carbon nanotubes (asbestos)

known for toxicity



# Risk of nano products

risk := damage potential \* occurrence probability

## linking to measurable values

### Material properties

- solubility
- degradation
- fate
- activity
- behavior

...

acute or long term effects

### occurrence probability

- mass, sources
- exposure concentration
- frequency
- transport
- target tissue

...

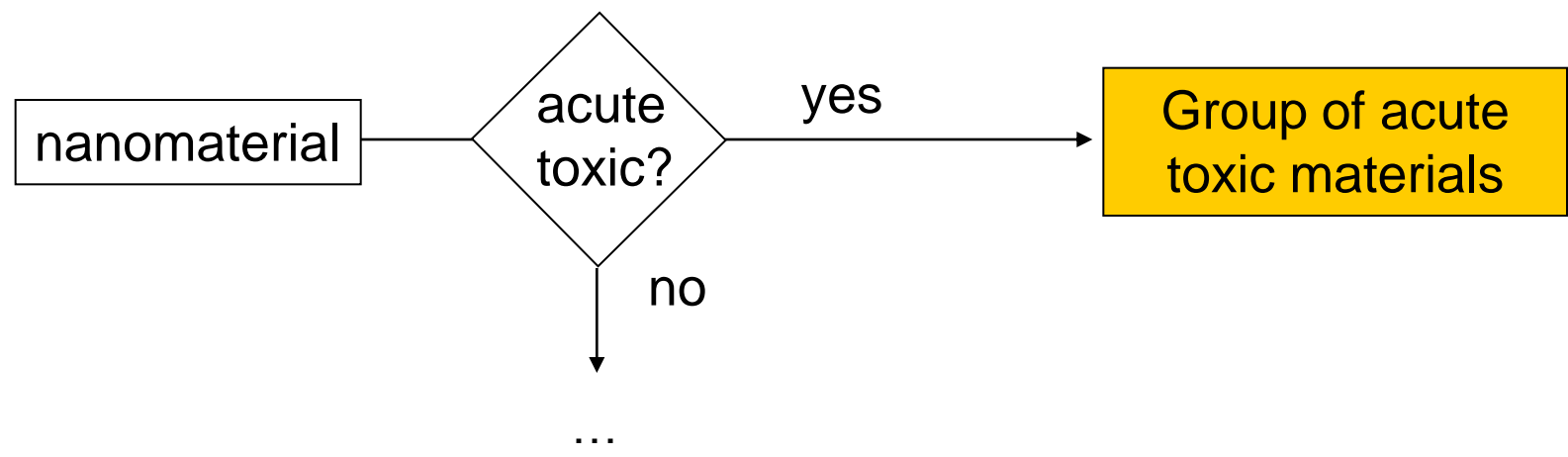
exposure and uptake



risk := damage potential \* occurrence probability

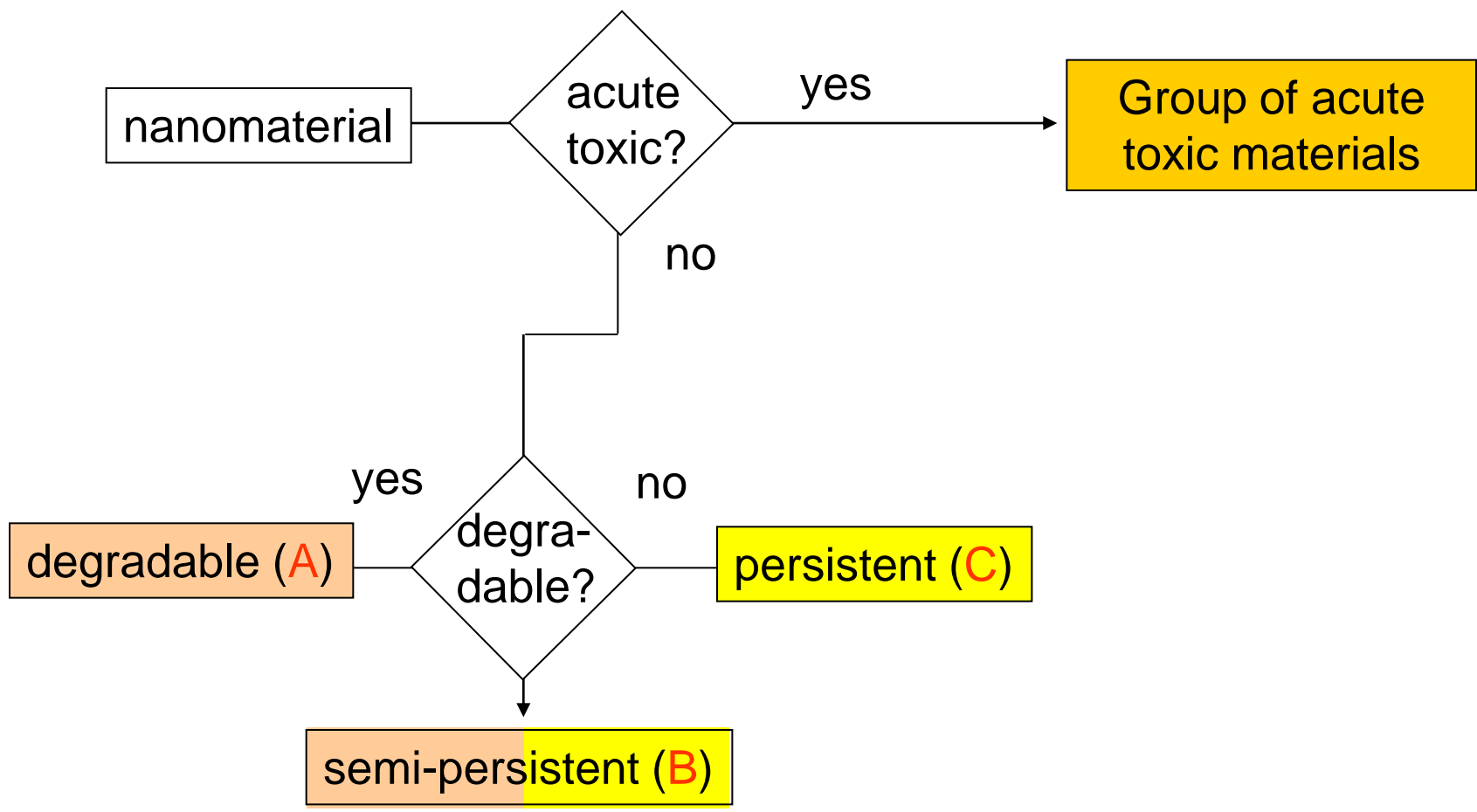
# 1<sup>st</sup> criterion -

# is it acute toxic?



## 2<sup>nd</sup> criterion -

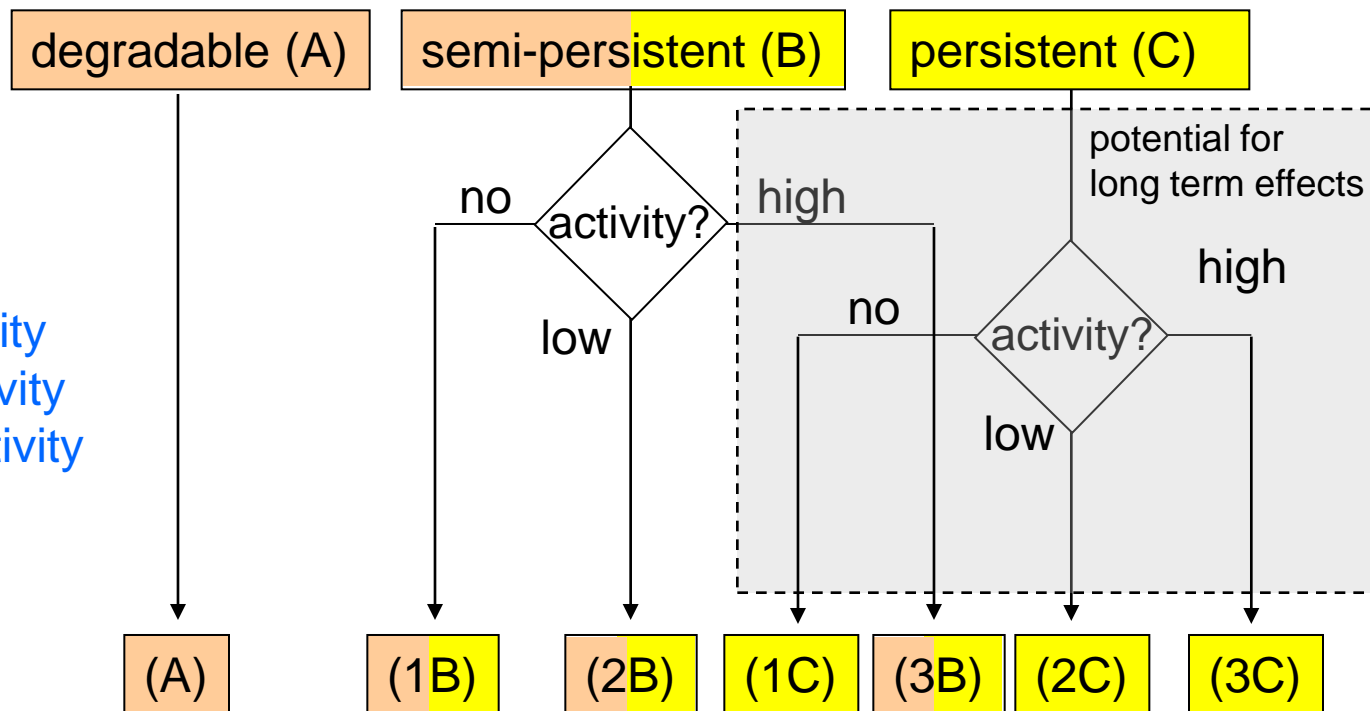
# is it degradable?



### 3<sup>rd</sup> criterion -

# chemical activity

- 1 - no chemical activity
- 2 - low chemical activity
- 3 - high chemical activity




Biological damage



# Damage potential

 ZnO      high      ⇒ acute toxic

 Ca<sub>3</sub>PO<sub>4</sub>      low      ⇒ low damage potential

 CNT      high      ⇒ potential long term effects

OVERALL RISK depends on the use (occurrence probability)

# Occurrence probability

risk := damage potential \* occurrence probability

Who is exposed?

With what ?

- an aerosol
- a liquid dispersion
- a dry powder
- a solid nanocomposite (e.g. np in polymer)

Exposure time, route of entrance

## Think about

- Nanoparticles as food additive
- Nanoparticles in cosmetics
- Nanoparticles in aerosol spray can
- Nanoparticles embedded into battery material
- Nanoparticles in technical catalyst
- Nanoparticles as cancer treatment



## In the laboratory routine

- Nanoparticles dispersed in **liquids**
  - **Treat as toxic** liquid chemicals
  - Wear gloves and safety glasses at all times
  - Wash up spills wearing gloves
- Nanoparticles don't translocate through healthy skin
- Use standard chemical/biochemical laboratory practice
- Don't wear gloves all the time
  - Doors, drawers, computers, labbook, pens only without gloves



# In the laboratory routine

- **Dry** nanopowders (agglomerated)
  - Treat in well ventilated areas (i.e. **hoods**) **only**
    - Weighing, grinding, pouring etc.
  - Nanoparticles don't deagglomerate
    - Once stuck together as a powder, they stay together
    - Unless energy is introduced
  - Metals (even coated) are potentially pyrophoric
- Nanoparticle **aerosols**
  - Nanoparticle aerosols are taken up via the lung
  - In closed environments (**glove box** or similar) **only!**

# Nanoparticle disposal

- Collect separately (including all solutions contacting nps)
- In dispersed (liquid) form
- Separated by
  - Aqueous
  - Non-aqueous
- Dispose as special waste via local authorities

# Planning science with nanotoxicology

Before starting.....

- Think about product exposure
  - Manufacturing
  - Use of product/material
  - End of life
- A fast *in vitro* cell-test won't save you
  - Throwing nps on cells and measuring dead/alive is not scientific
    - Exposure scenario with correct cell lines, exposure pathway, biological endpoint, degree of aggregation and adapted concentrations **only**

**Don't be afraid...**

**.... be cautious!**

**Don't generalize**

**.... differentiate**

Further Reading: Stark WJ, Nanoparticles in Biological systems,  
*Angew. Chem. Int. Ed.* 2011, **50**, 1242-58.