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National Institute
for Public Health
and the Environment

Responsible development of nanotechnology

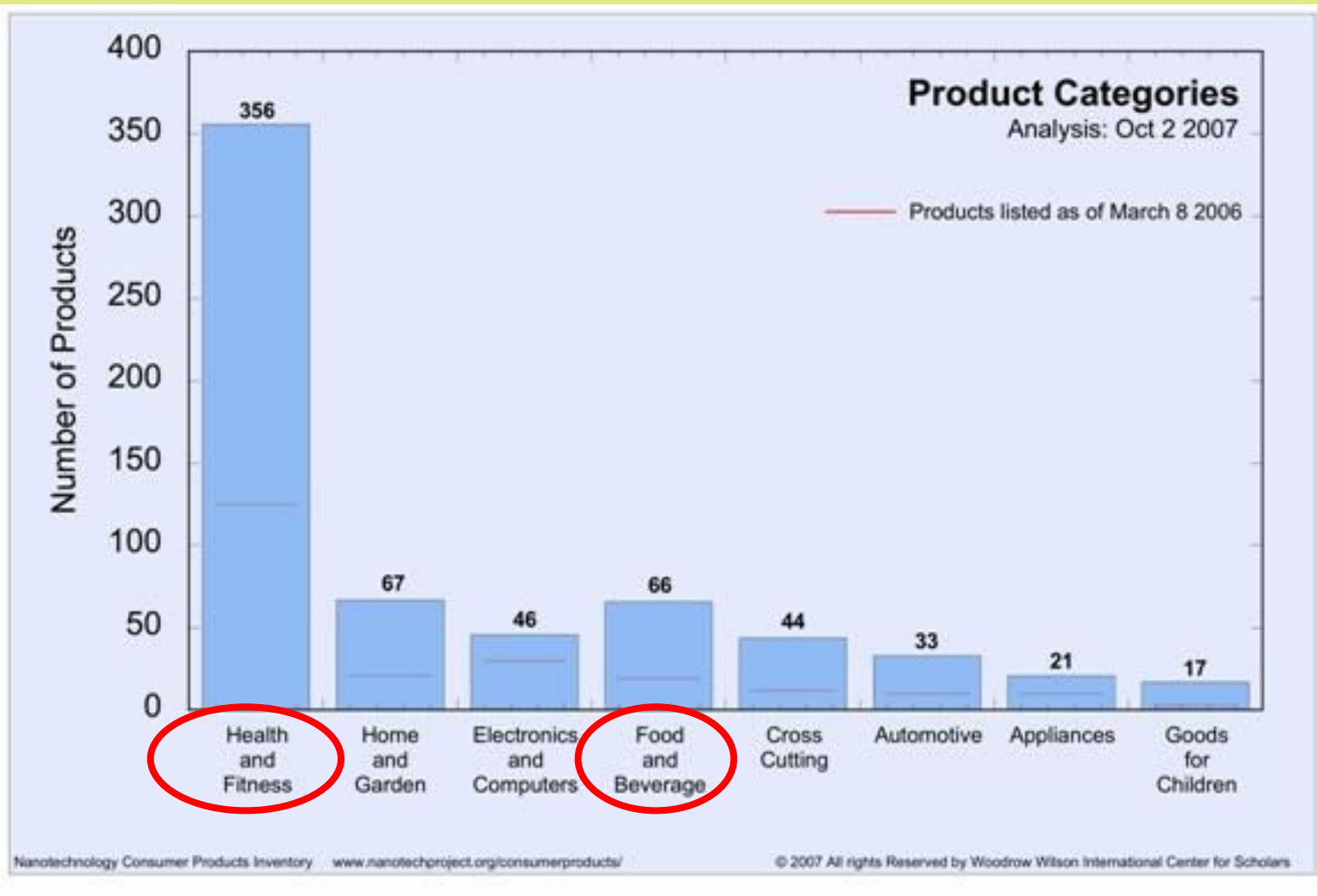
What about safety? Is there a risk?

Wim de Jong

Consumer products with nanoclaim



There will be an increase in exposure



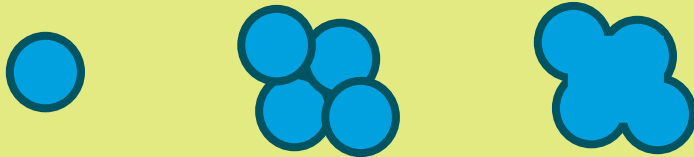
October 2007, 650 products in inventory (16 september 2008, 871)

Nanoparticle characteristics

All: 1 x 1 cm

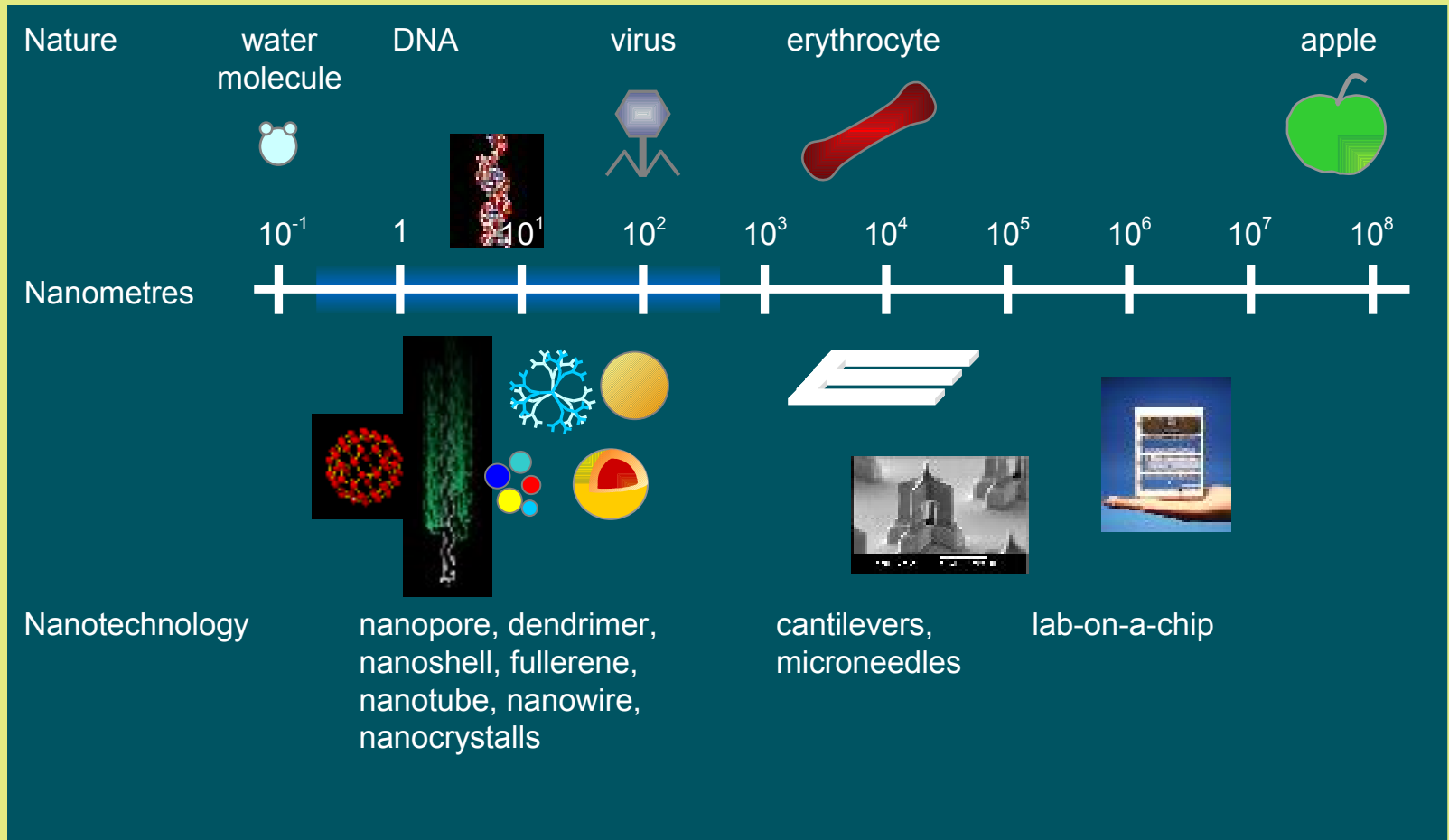


size	number	Total Surface area
1 cm	1	6 cm ²
1 mm	1,000	60 cm ²
1 μm	1 x 10 ¹²	6,000cm ²
1 nm	1 x 10 ²¹	60.000.000 cm ² (600km ²)



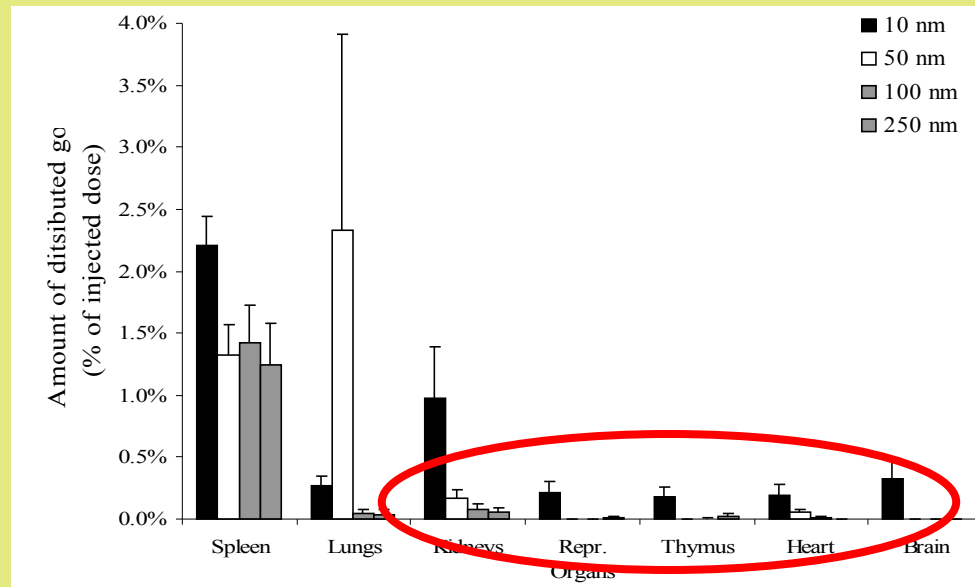
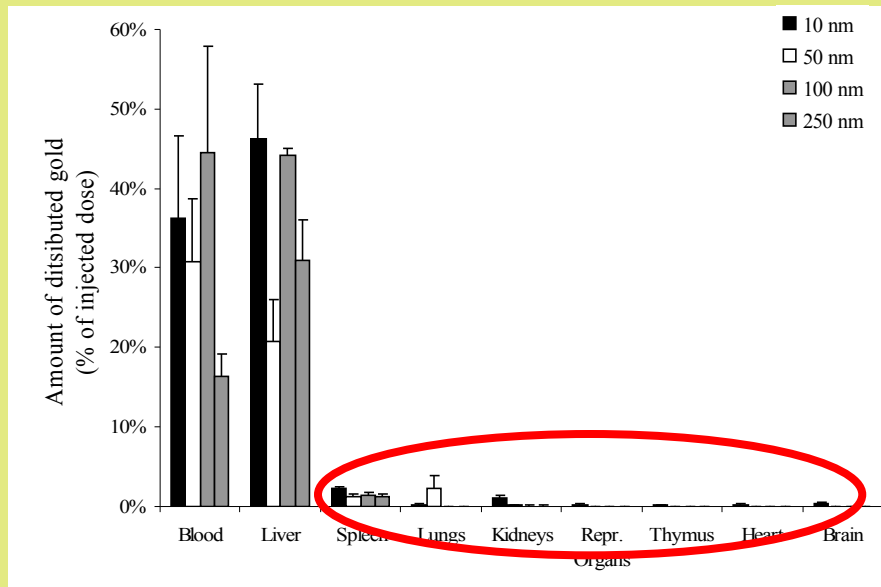
Decrease in size results in (enormous) increase in surface area

Why are we concerned?



Nanomaterials (nanoparticles) can have sizes similar to structures at subcellular level.

Nanoparticles can reach every organ depending on their size



Gold distribution at 24 h after iv injection in rats as percentage of injected dose (100 µg per animal)

Particle size	10 nm	50 nm	100 nm	250 nm
Number concentration	5.7×10^{12}	4.5×10^{10}	5.6×10^9	3.6×10^8
Surface area	1.6×10^{15}	3.2×10^{14}	1.7×10^{14}	6.9×10^{13}
Mass injected	85 µg	106 µg	98 µg	120 µg

What about safety?

- Safety evaluation is done by performing a risk assessment (RA)
 - Identification of substance
 - Hazard characterization
 - Hazard identification
 - Dose response effect (no effect level)
 - Exposure assessment



Risk characterization

- What is risk?
 - Risk, combination of likelihood of occurrence of harm to health and the severity of that harm
 - Margin of safety (no effect level/exposure level)
 - No exposure >>>> No risk

- Risk is a possibility, not an absolute value !!!

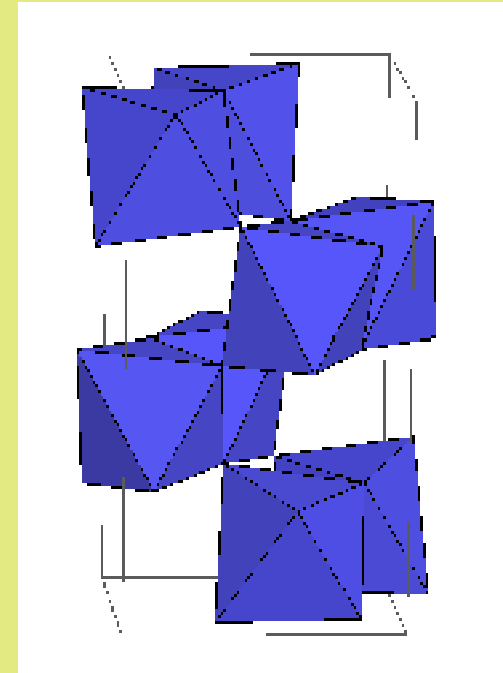
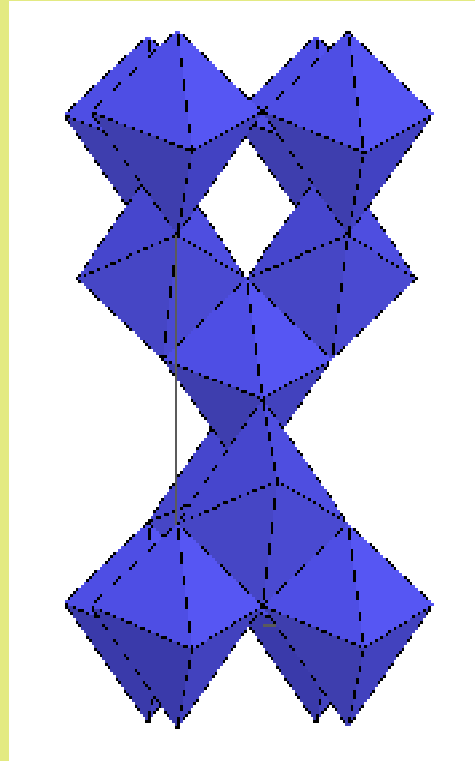
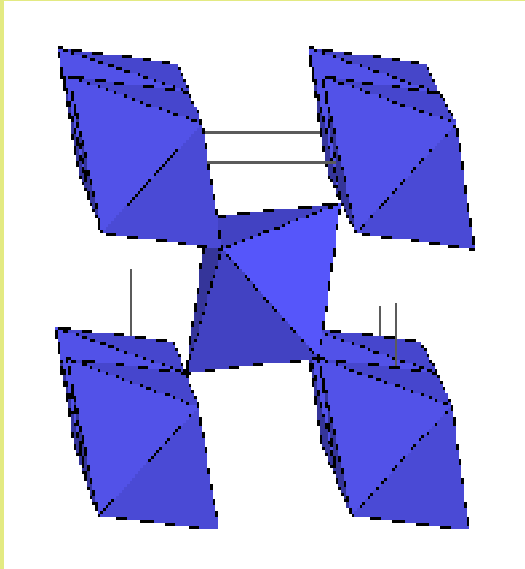
How do you determine risk?

- Hazard, a potential source for harm to health
- *In vitro* studies
 - Indicate possibility for cell damage
 - Mainly used for to screening and mechanistic studies
 - Relevance for risk assessment is limited
- *In vivo* studies
 - Overall “black box”
 - Indications for possible organ specific toxic effects and no effect levels
 - Extrapolation problems (inter- and intraspecies variation)
 - Uncertainty factors
 - More relevant for risk assessment than *in vitro*

What are the problems
in safety evaluation of
nanomaterials/nanoparticles

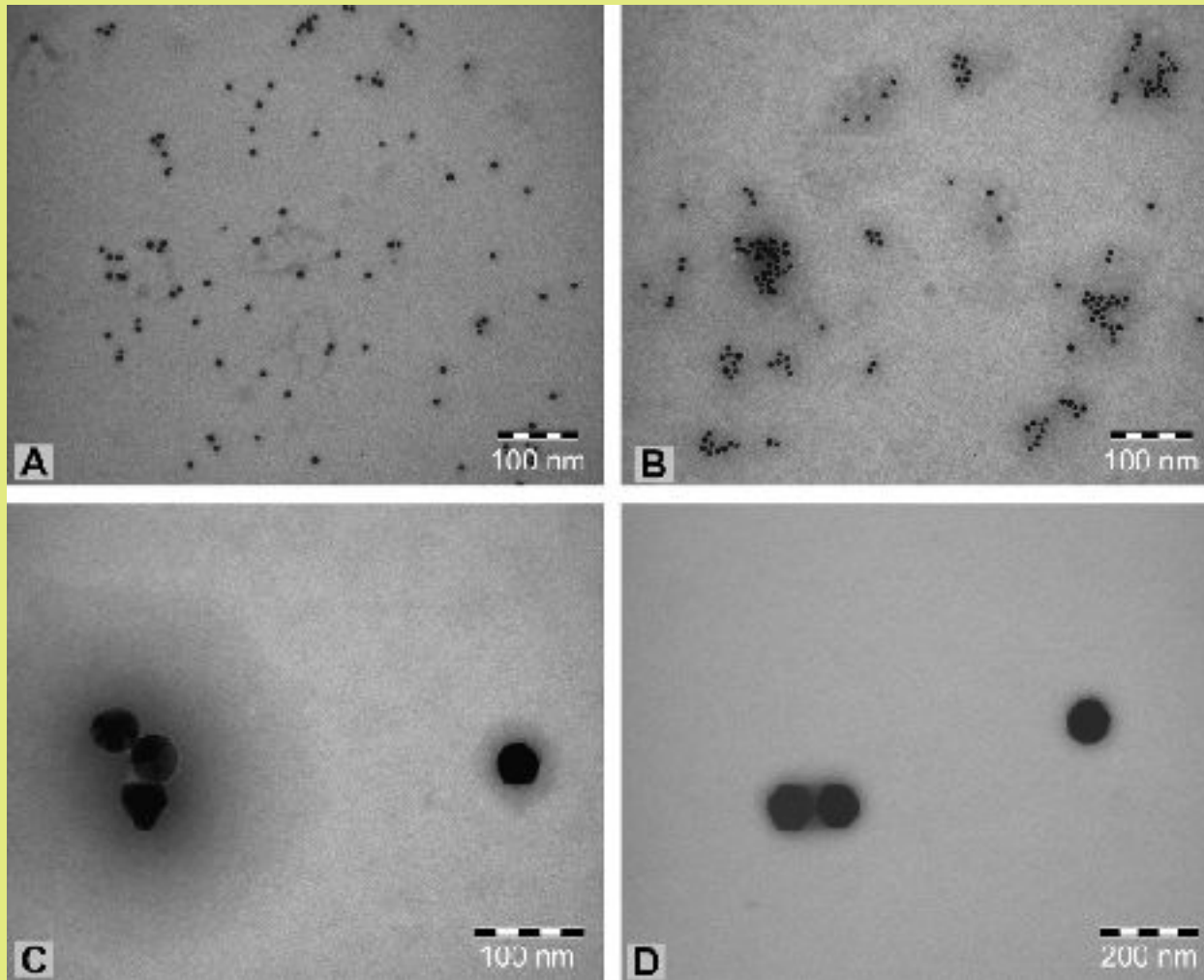
?

Nanomaterials may differ even with same chemical composition



TiO₂ group is composed of rutile, anatase, and brookite

Problems with dispersion



Gold nanoparticles in PBS, A and B 10 nm, C 50 nm, and D 100 nm diameter)

Nanoparticles do not exist as single particle entity, they adsorb things.

What do we know

- Protein corona is important for biological interactions
- Corona is not static, proteins get on and off

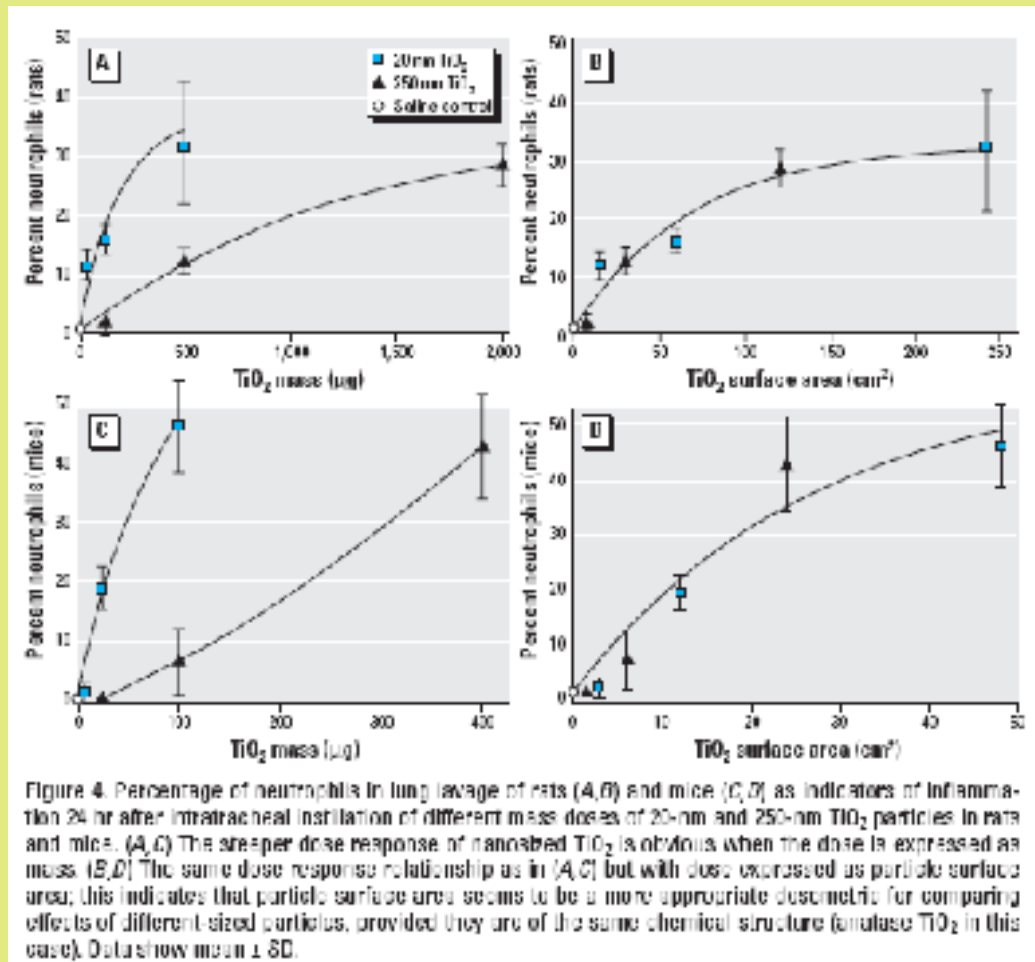


What do we not know

- Dependence on nanomaterial?
- Dependence on size?

EU FP6 project NanoInteract,
courtesy of Prof Kenneth Dawson, UCD, Dublin, Ireland

What is the dose metric for particle toxicity?



This was demonstrated for local effects in the lung after inhalation exposure.

What about other routes of exposure (oral, dermal, intravenous)?

Nanofibres, the MWCNT issue

“when a fibre has characteristics of brown/blue asbestos
(rigid, non degradable, length >20 µm)
it behaves like brown/blue asbestos” (Poland et al., 2008)

Lesson is NOT
MWCNT behave like asbestos but....

Manufacturer....when producing MWCNT
Check for these specific characteristics
(rigidity, degradability, fibre length)



Perform proper safety evaluation to exclude this specific hazard
associated with a certain types of fibres

Safety evaluation is not only toxicology

Toxicology is detection of toxic = harmful effect and study mechanisms of toxicity.

Safety evaluation is using toxicology for determination of **no-effect levels** which can be used in **risk assessment**.

You need toxic dose to determine non toxic level

Safety evaluation

No observed adverse effect level (NOAEL)

+

Uncertainty (safety) factors
(species extrapolation, intraspecies variation)

=

“Safe” exposure level for man

Where do we stand with nanotechnology?

- Multitude of products available on the market
 - Some labeled, others not
- Various hazards (toxic effects) identified
- Exposure estimation remains a problem
- So far case by case approach advocated

Conclusions

There are uncertainties in the safety evaluation of engineered nanomaterials

- Proper characterization is necessary
 - Identification and chemical composition may differ between manufacturers
 - Size and size distribution may vary
- How to handle engineered nanoparticles (dispersions)
- NP may change depending on test conditions
 - agglomeration/aggregation
 - protein adsorption
- Dose parameter (mass, number of particles, surface area)
- Altered tissue distribution *in vivo* and possibility for accumulation in organs (new/other organs at risk?)

Nanotechnology does not exist by itself.

It is an area with a multitude of applications and possibilities

We are dealing with various
NANOTECHNOLOGIES
each with its own use and application

AND ITS OWN RISKS

Societal fear fortechnology.

- **Information Technology**

- Artificial intelligence dominating man
- Big Brother is watching you (1984, George Orwell, 1949)



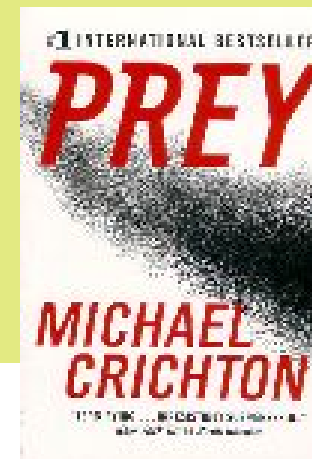
- **Biotechnology/Genetic modification**

- Manipulation of organisms/man (BBC news 1998)
- Jurassic Park (Michael Crichton, 2005)



- **Nanotechnology**

- Prey (Michael Crichton, 2002) Self assembling nanostructures become alive and thinking
- Privacy, personal tracking by electronic nanodevices



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