Responsible development of nanotechnology

What about safety? Is there a risk?

Wim de Jong
Consumer products with nanoclip

There will be an increase in exposure
October 2007, 650 products in inventory (16 September 2008, 871)
Nanoparticle characteristics

All: 1 x 1 cm

<table>
<thead>
<tr>
<th>size</th>
<th>number</th>
<th>Total Surface area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 cm</td>
<td>1</td>
<td>6 cm²</td>
</tr>
<tr>
<td>1 mm</td>
<td>1,000</td>
<td>60 cm²</td>
</tr>
<tr>
<td>1 μm</td>
<td>$1 \times 10^{12}$</td>
<td>6,000cm²</td>
</tr>
<tr>
<td>1 nm</td>
<td>$1 \times 10^{21}$</td>
<td>60.000.000 cm² (600km²)</td>
</tr>
</tbody>
</table>

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
  - $5.7 \times 10^{12}$
  - $4.5 \times 10^{10}$
  - $5.6 \times 10^{9}$
  - $3.6 \times 10^{8}$

- Surface area
  - $1.6 \times 10^{15}$
  - $3.2 \times 10^{14}$
  - $1.7 \times 10^{14}$
  - $6.9 \times 10^{13}$

- Mass injected
  - 85 µg
  - 106 µg
  - 98 µg
  - 120 µg

De Jong et al., Biomaterials 29, 1912, 2008
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 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

De Jong et al., Biomaterials 29, 1912, 2008
Nanoparticles do not exist as single particle entity, they adsorbe 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)?

Oberdörster et al., Environ Health Perspect 113, 823, 2005
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

Poland et al., Nature Nanotechnology 3, 423, 2008
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
• Sofar 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 for technology.

- **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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