Human health risk assessment of nanosilver

Overview of available data

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Risk Assessment of nanoparticles

Characteristics nanoparticles

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Hazard identification

Dose response assessment

Internal dose

Risk characterization

Dose Response Curve

Response

Dose
Available data

● **RIVM studies on nanosilver** (data until 2009)

● **Additional literature** (reviews ≥ 2009)
  - EPA Nanomaterial case study (2010): Nanosilver in disinfectant spray
  - Friends of the Earth reports:
    - Nano and biocidal silver, extreme germ killers present a growing threat to human health (2009)
    - Nano-silver, policy failure puts public health at risk (2011)
Consumer exposure

Increase in consumer products with nano claim

The Project on Emerging Nanotechnologies (Woodrow Wilson database)

Time period 2005-2010: 54 - 1317 products

http://www.nanotechproject.org/inventories/consumer/
Consumer exposure

Consumer products with nano-Ag

http://www.nanotechproject.org/inventories/consumer
Detection of nanomaterials in consumer products

- 21 different products, selected on basis of nano claim or on expectation on the presence of nanomaterial (Ag, Zn, Ti, Si)

- microscopic techniques were used to analyse the products, investigate whether these techniques are appropriate
  - SEM, TEM: size distribution
  - EDX: determination of chemical nature
  - XPS: mass concentration

Consumer exposure

Analysed products claimed to contain nano-Ag

Food container
Cuddly toy
Indoor wall paint
Socks
T-shirt
Wound dressing
Tooth brush
Deodorant

- Verify presence of NP in more detail (TEM)
- Size distribution of NP, XPS on isolated fibers
- Optical microscopy, number of Ag coated fibers
- Individual NP or layer, if NP: size distribution
- Presence of coating, Microscopy if it is a layer
- Focus on finding of Ag NP
### Results of analysed products with nano-Ag

<table>
<thead>
<tr>
<th>Product</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food container</td>
<td>no Ag detected (&lt;0.8 g/kg)</td>
</tr>
<tr>
<td>Cuddly toy</td>
<td>no Ag in fibrils at the outside (&lt;0.8 g/kg)</td>
</tr>
<tr>
<td>Indoor wall paint</td>
<td>no Ag detected (&lt;0.8 g/kg)</td>
</tr>
<tr>
<td>Socks</td>
<td>Ag present on 1-5/100 fibers on bottom part of sock (continuous layer)</td>
</tr>
<tr>
<td>T-shirt</td>
<td>no Ag detected (&lt;0.8 g/kg)</td>
</tr>
<tr>
<td>Wound dressing</td>
<td>fibrous materials coated with 300-500nm Ag (continuous layer)</td>
</tr>
<tr>
<td>Tooth brush</td>
<td>no Ag detected in hair or back part of toothbrush</td>
</tr>
<tr>
<td>Deodorant</td>
<td>no Ag detected (&lt;0.8 g/kg)</td>
</tr>
</tbody>
</table>

It is impossible to be **conclusive about the absence** of nanomaterial:
- only a small area of the product can be analysed
- techniques are not validated for consumer products
## Consumer exposure

### Exposure assessment – important characteristics

<table>
<thead>
<tr>
<th>Nanoparticle characteristics determining the possible exposure</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nanomaterial in consumer product</strong></td>
<td></td>
</tr>
<tr>
<td>Chemical entity of the nanomaterial</td>
<td>Actual composition of material</td>
</tr>
<tr>
<td>Shape of nanomaterial (in product)</td>
<td>Composite, solid particle, hollow particle, other particle, aggregate, agglomerate</td>
</tr>
<tr>
<td>Product form</td>
<td>Spray, powder, liquid, suspension, solid/ coating</td>
</tr>
<tr>
<td>Free/ fixed nanoparticles</td>
<td>Free particles, fixed inside matrix</td>
</tr>
<tr>
<td>Concentration</td>
<td>Mostly unknown (based on mass?)</td>
</tr>
<tr>
<td><strong>Application</strong></td>
<td>Direct/ indirect exposure</td>
</tr>
<tr>
<td>Direct/ indirect exposure</td>
<td>Direct exposure to nanomaterials in the product or indirect via release of particles out of the product</td>
</tr>
<tr>
<td>Indoor/ outdoor use</td>
<td>Inside or outside a small space</td>
</tr>
<tr>
<td>Event duration</td>
<td>&lt; 5 min, 5 min- 1 hr, 1 hr- 1 day</td>
</tr>
<tr>
<td>Frequency of events</td>
<td>&gt; 1x/day, 1x/day-1x/week, 1x/week-1x/month, 1x/month- 1x/year</td>
</tr>
<tr>
<td>Number of users in population</td>
<td>&lt;10%, 10-50%, 50-90%, &gt;90%</td>
</tr>
<tr>
<td><strong>Exposure route</strong></td>
<td>External exposure</td>
</tr>
<tr>
<td></td>
<td>Inhalation, dermal, oral, combination</td>
</tr>
</tbody>
</table>

Consumer exposure

Indications for high possible consumer exposure

Expert consultation:
- **Nanomaterial in consumer product**
  - Product form: spray
  - Free (single) particles
  - Concentration: mostly unknown

- **Application**
  - Direct exposure
  - Indoor use

- **Exposure route**
  - Inhalation
  - Oral route
Very limited data on exposure to nano-Ag
Not reviewed in previous RIVM studies

- Pilot scale ‘nanostructured particle’ gas phase facility (*Demou et al, 2008*): (representative for nano-silver manufacturing)
  - Average concentration during production was **59100 particles/cm³** for sub-micron particles

- Manual handling of nano-alumina and nano-silver in fume hoods in a laboratory scale facility (*Tsai et al, 2009*)
  - 15 g silver in beaker → peak count of **7000 particles/cm³**

- Analysis of exposure characteristics during liquid phase process in commercial production facility (*Park et al, 2009*)
  - Increase of particle number was higher than during handling of dry powder → impact of liquid phase should be studied further.
Plausible exposure routes of nanomaterials

Exposure man via environment

Man via environment????

RS/RAEng 2004
Relevance of exposure data for risk assessment

Product with nanoclaim: presence / release of nanomaterial

If no absorption = then no internal dose = no risk!!
Toxicokinetics

Toxicokinetics of nano-Ag

- Absorption of silver
  - Dermal route (wound dressings, textiles, creams, tissues)
    - Absorption shown for 15 nm particles on burned skin (wound dressings), human
    - Absorption shown on healthy skin of guinea pigs (acute and sub chronic) after exposure to colloidal silver suspension
  - Oral route (food supplements, toothpaste, lip balm)
    - Ingestion (shown for colloidal silver suspension) human
    - Systemic availability of (nano-)silver after oral exposure of nanosilver particles (60 nm), rat
  - Inhalation (sprays)
    - Systemic availability of (nano-)silver after inhalation exposure nm) silver present in lungs and brain, rat
Toxicokinetics data on nano-Ag relevant for RA

- Single and repeated dose
  - Single and 5 days iv. exposure of 20, 80 and 110 nm particles in rat
  - Silver nanoparticles disappeared rapidly from the blood and distributed to all organs evaluated
  - 20 nm mainly to liver, followed by kidneys and spleen; larger particles mainly to spleen followed by liver and lung
  - Difference in distribution can lead to difference in toxicity
  - Unlikely that silver nanoparticles dissolve all immediately to ions

*Lankveld et al, 2010, Biomaterials*
Toxicity

Toxicity data on nano-Ag relevant for RA

- Acute toxicity

  - Oral, 2.5 mg directly in stomach, *not relevant*
  - Inhalation, no studies
  - Dermal,
    - wound dressings in burn patients, *not relevant*
    - acute and subchronic tox in guinea pigs, *colloidal silver*
Toxicity data on nano-Ag relevant for RA

- Repeated dose toxicity
  - Oral
    - 28 days tox study in rats, 30, 300 and 1000 mg/kg/day (60nm): dose-dependent tox in liver, high dose *(Kim et al, 2008)*
    - 90 days tox study in rats, 30, 125 and 500 mg/kg/day (56 nm): dose dependent accumulation of silver in organs *(Kim et al, 2010)*
    - Pharmaceutical ingestion of colloidal silver in human: argyria (skin decolourization) in sun-exposed areas, 3.5 mg/kg/day, 3 times a day for 10 months *(Wadhera and Fung, 2005)*
  - Inhalation:
    - 28 days tox study in rats with 0.48, 3.48 and 61 µg/m³ (15 nm)(6h/day, 5 days/week), no sign health effects *(Ji et al, 2007)*
    - 90 days tox study in rats with 49, 133 and 515 µg/m³ (18-19 nm)(6h/day, 5 days/week), main targets for accumulation and tox were lungs and liver *(Sung et al, 2008, 2009)*
Risk assesment for consumer

- Nano-silver case study within the context of REACH (Pronk et al, 2009)
  - Quick and dirty risk assessment
  - Bathroom cleaner, trigger spray with 1% nano-Ag (spherical, 15 ± 5 nm)
  - Consumer exposure, both inhalation and dermal
  - ConsExpo
    - Dermal vs effect dose 28 and 90 days oral tox study:
      Margin of exposure: 2700 – 90000 (based on mass)
    - Inhalation vs effect dose 28 and 90 days inhalation study:
      Margin of exposure 1.3 – 170 and 140 – 1400 (based on mass)

Margins are not of such magnitude that they would support waiving of further testing of systemic effects
Risk assessment

Risk assessment for worker

- First attempt for derivation of Human Indicative No-Effect Levels (INELs) (Christensen et al, 2010)
- Semi-quantitative risk characterisation
- NOAEL/ LOAEL for repeated inhalation from literature
  - LOAEL inhalation
  - LOAEL → NOAEL (factor 3 and factor 10)
  - Assessment factors (interspecies, intra species, sub-chronic to chronic)
  - Lung effects and liver effects

Direct comparison of identified exposure data with toxicity data: with care!

Worker exposure data with derived INELs (in terms of particle numbers):
Same order of magnitude!
Knowledge gaps in human RA of nano-Ag

- Data on nanosilver in public literature relate to different types of nanosilver
  - Different size, distribution, agglomeration state, coating etc
  - Incomplete characterisation
  - Colloidal silver

- Data on exposure are missing
  - Little data on worker exposure: repeated inhalation in working environment
  - Consumer exposure: exposure frequency and levels
    - which products, what types of particles, what concentration, release from products, exposure route etc.
    - inhalation of spray products seems relevant
    - dermal and oral exposure, lack of data for consumer and worker, but exposures lower than for drugs and wound dressings
Knowledge gaps in human RA of nano-Ag

- Internal dose: lack of toxicokinetics data
  - To which extent is silver absorbed via the different routes available as ions, nanoparticles or both

Wijnhoven et al, 2009
Knowledge gaps in human RA of nano-Ag

- **Toxicity:**
  - Potential target organs may involve liver, lung and immune system
  - Very limited well controlled studies with multiple particle sizes
  - Uncertainties in possible direct genotoxic effect of nanoAg
Priorities for future research

1. Generation of exposure data
   - Occupational inhalation, consumer inhalation, dermal

2. Further toxicokinetic studies
   - Absorption, distribution of different types of nanoAg

3. Toxicity studies with levels and types of nanoAg as encountered on the workplace:
   - Sub chronic inhalation

4. Testing of possible direct genotoxicity of nanoAg

5. Oral and dermal toxicity studies relevant for occupational and consumer exposure

6. Studies to identify possible reproductive toxicity
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