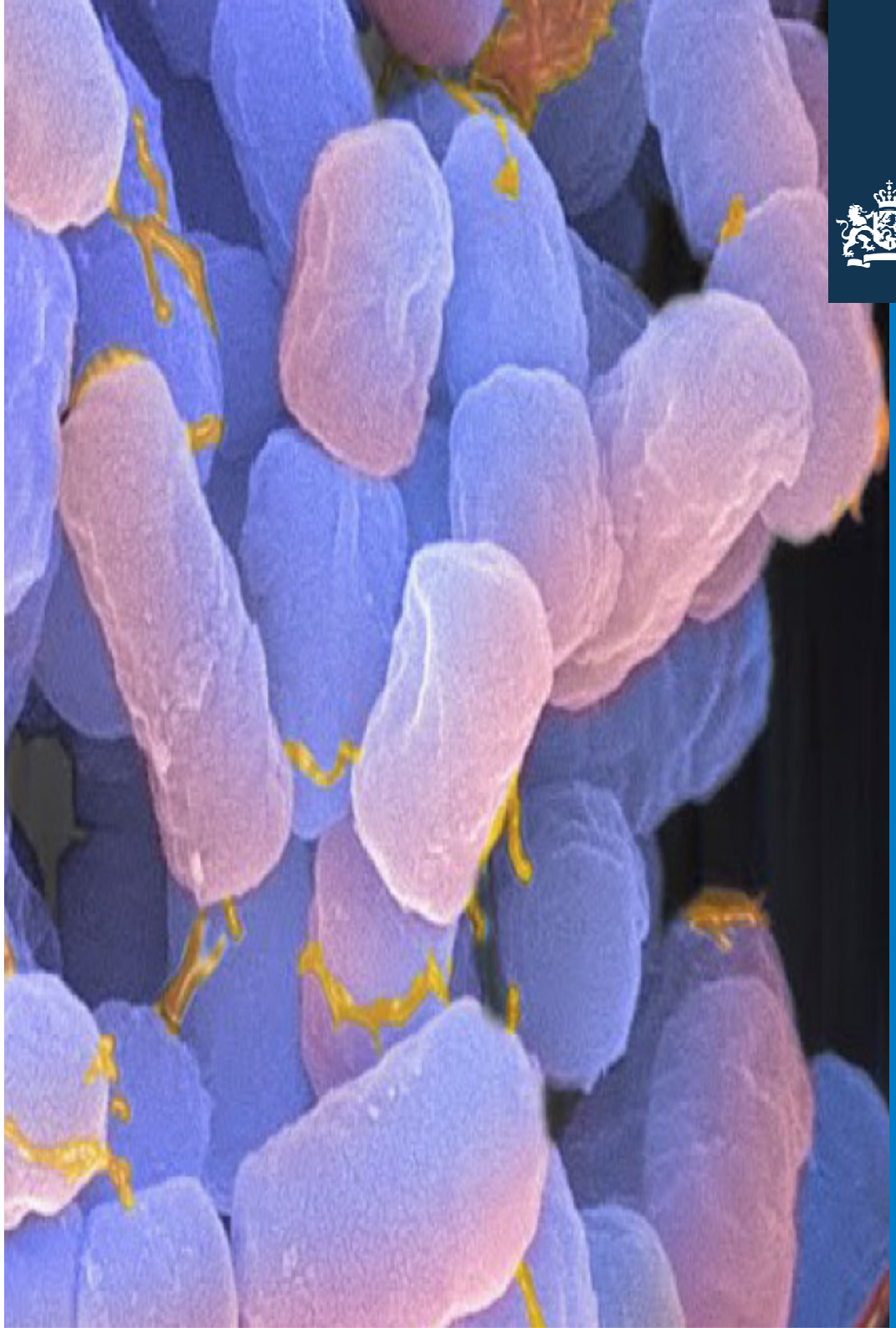


National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

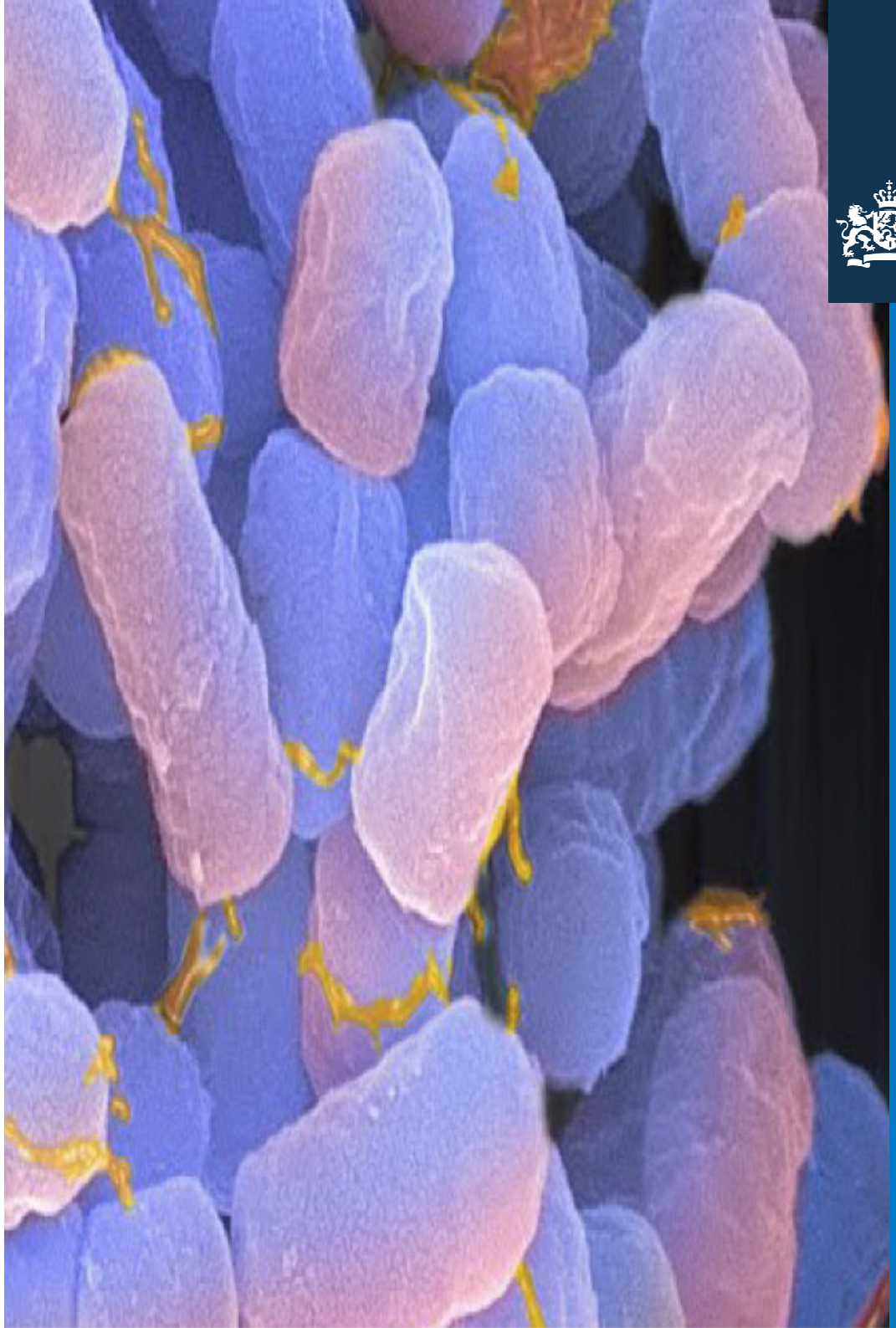
Human health risk assessment of nanosilver

Overview of available data

Susan Wijnhoven, RIVM

BfR conference on nanosilver

08 February 2012



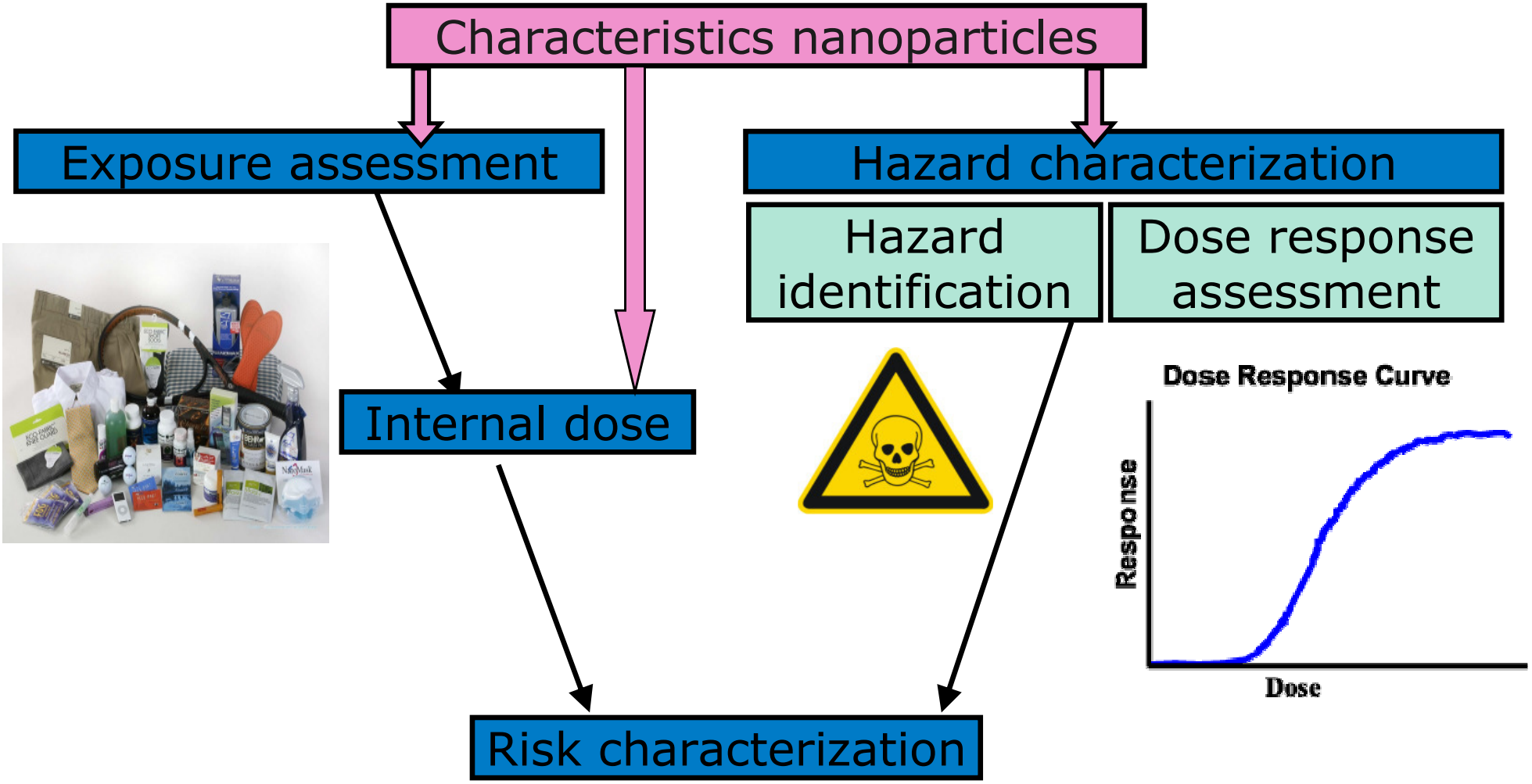
National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Content

1. Introduction risk assessment
2. RA of nanomaterials
3. Available data on nanoAg
4. Knowledge gaps and priorities for future studies

08 February 2012

Risk Assessment of nanoparticles



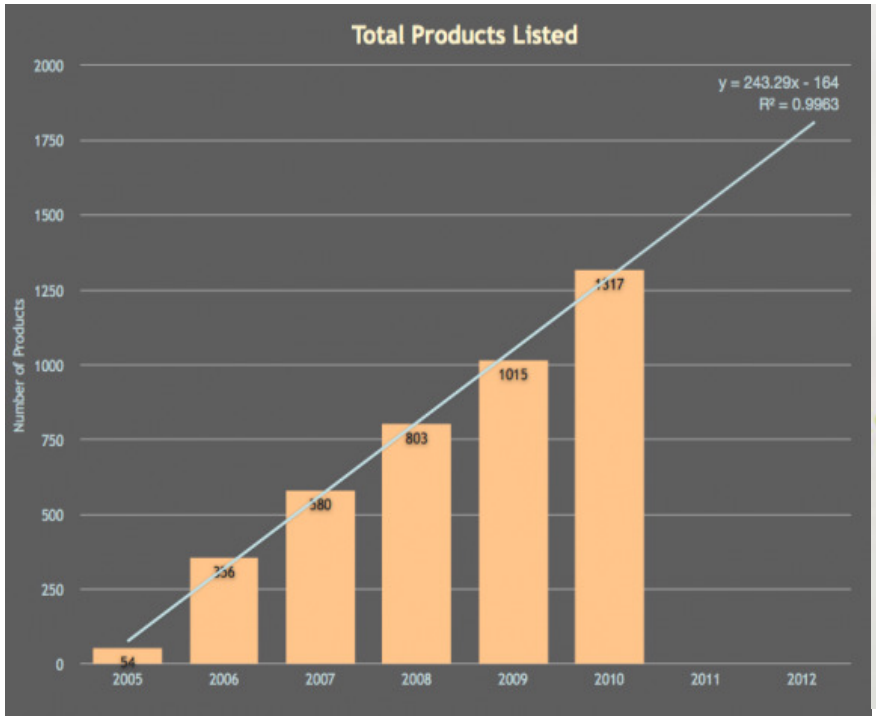
Available data

- RIVM studies on nanosilver (data until 2009)
  - Nano-silver- a review of available data and knowledge gaps in human and environmental risk assessment (2009) Wijnhoven et al., *Nanotoxicol.*
  - Nanomaterials under REACH- Nanosilver as a case study (2009) Pronk et al, *RIVM report* 60178003/2009

- Additional literature (reviews ≥ 2009)
- - Aschberger et al, (2011) Analysis of currently available data for characterising the risks to environment and human health. Four case studies. *Environment International*
- - Christensen et al, (2010) Nano-silver, feasibility and challenges for human health risk assessment based on open literature, *Nanotoxicology*
- - Johnston et al, (2010) A review of the in vivo and in vitro toxicity of silver and gold particulates *Critical reviews in Toxicology*
- - 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/

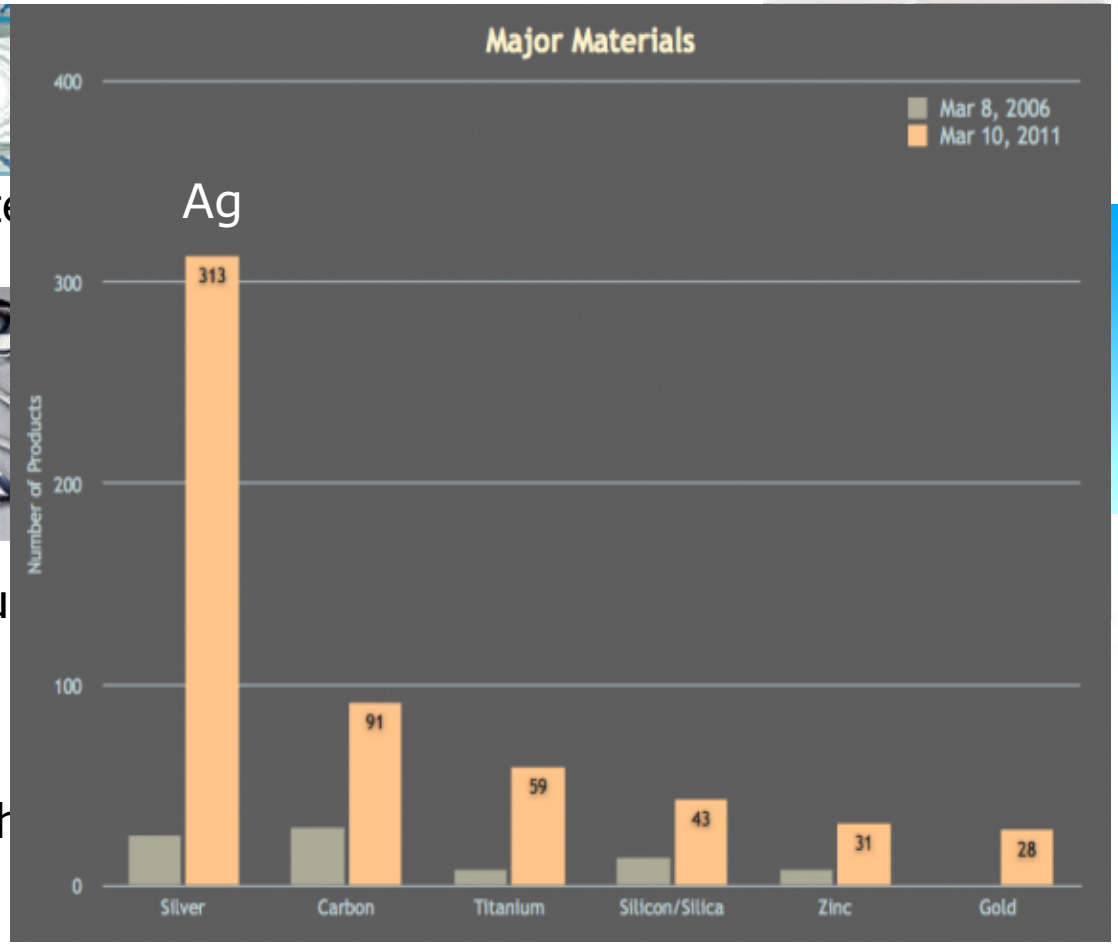
Consumer exposure

Consumer products with nano-Ag

toothpaste

cooking u

h



refrigerator

plasters

computer mouse

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)

- Miscroscopic 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

RIVM report Oomen et al, (2011) Nanomaterial in consumer products- Detection, characterisation and interpretation

Consumer exposure

Analysed products claimed to contain nano-Ag

Food container
Cuddly toy
Indoor wall paint ← Verify presence of NP in more detail (TEM)
Socks ← Size distribution of NP, XPS on isolated fibers
T-shirt Optical microscopy, number of Ag coated fibers
Wound dressing ← Individual NP or layer, if NP: size distribution
Tooth brush Presence of coating, Microscopy if it is a layer
Deodorant ← Focus on finding of Ag NP

Consumer exposure

Results of analysed products with nano-Ag

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

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

Exposure assessment – important characteristics

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

RIVM letter report Wijnhoven et al, (2009) Exposure to nanomaterials in consumer products.

Consumer exposure

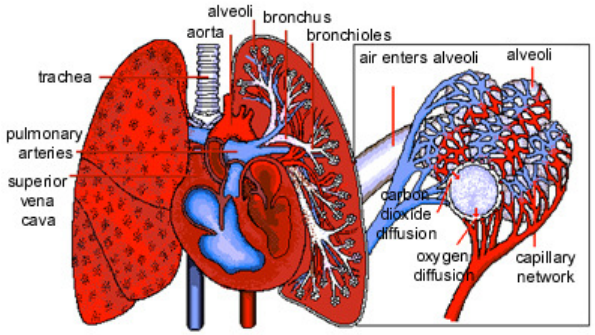
Indications for high possible consumer exposure

Expert consultation:

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

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

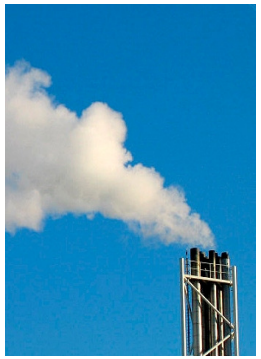
- **Exposure route**
  - Inhalation
  - Oral route



Occupational exposure

Very limited data on exposure to nano-Ag

Not reviewed in previous RIVM studies



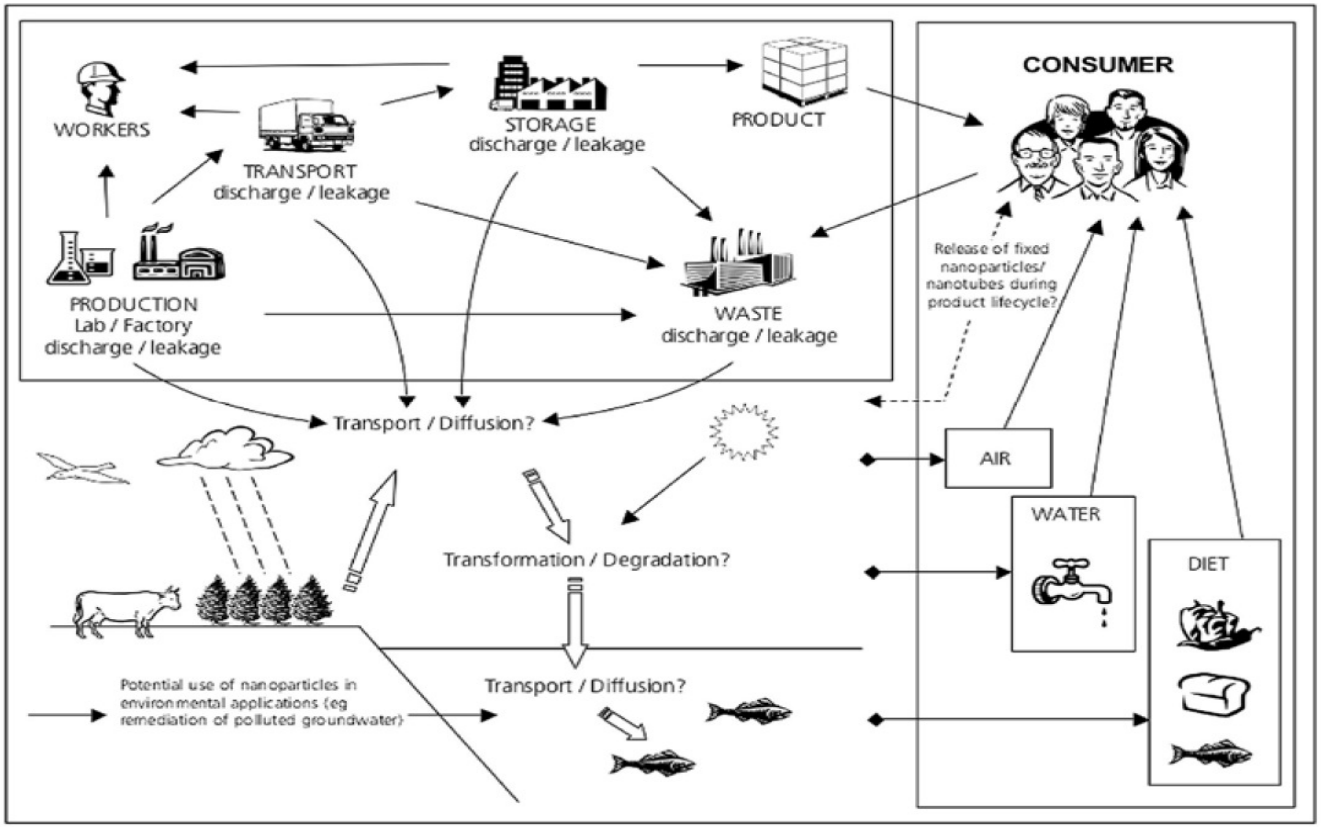
- Pilot scale 'nanostructured particle'gas phase facility (*Demou et al, 2008*): (representative for nano-silver manufacturing)
  - Average concentration during production was 59100 particles/ cm^3 for sub-micron particles

- 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/ cm^3

- 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.

Exposure man via environment

Plausible exposure routes of nanomaterials

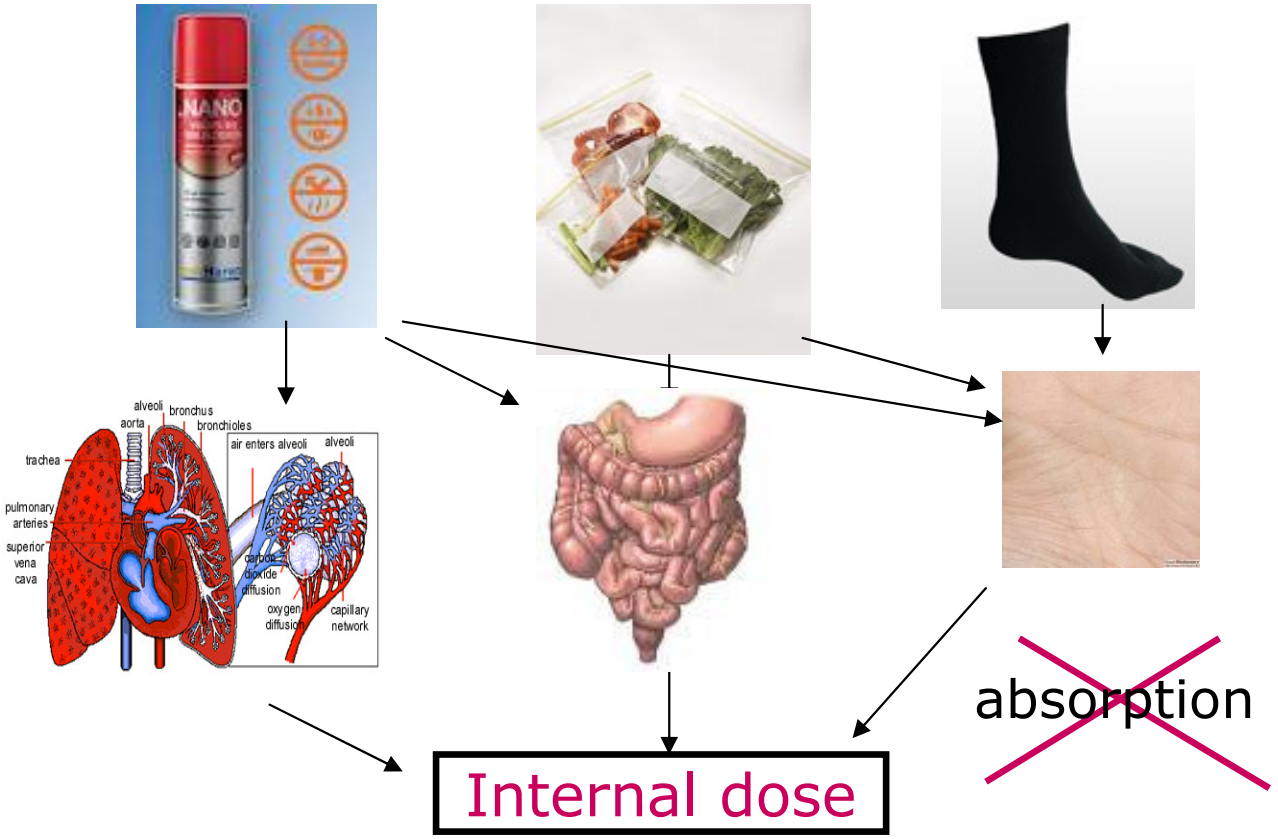


Man via environment????

RS/RAEng 2004

Relevance of exposure data for risk assessment

Product with nanoclaim: presence / release of nanomaterial



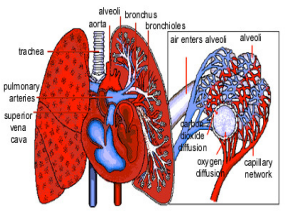
If no absorption = then no internal dose = no risk!!

Toxicokinetics 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



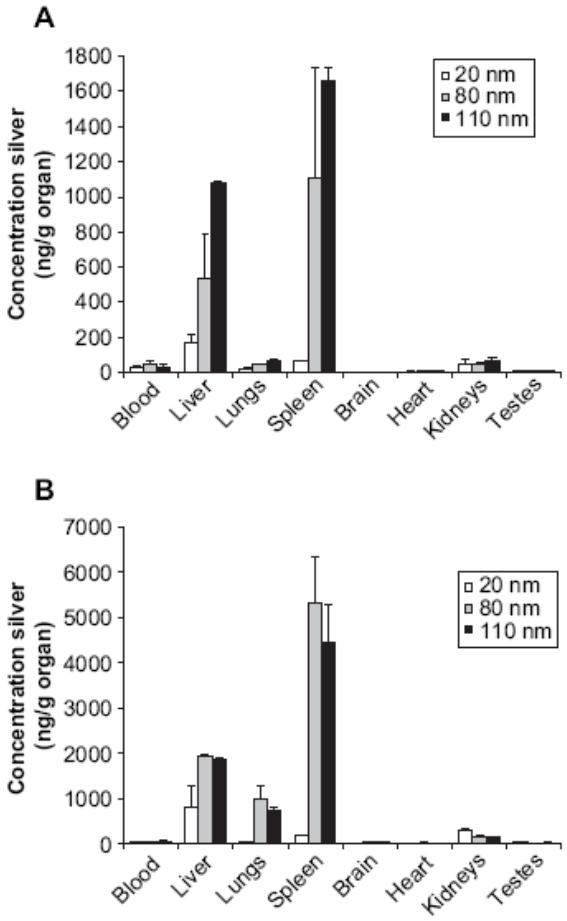
Toxicokinetics data on nano-Ag relevant for RA

- 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 dsitribution can lead to difference in toxicity
  - Unlikely that silver nanoparticles disolve all immediately to ions

Lankveld et al, 2010, Biomaterials

single



repeated

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/m^3 (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/m^3 (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 assesment 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!

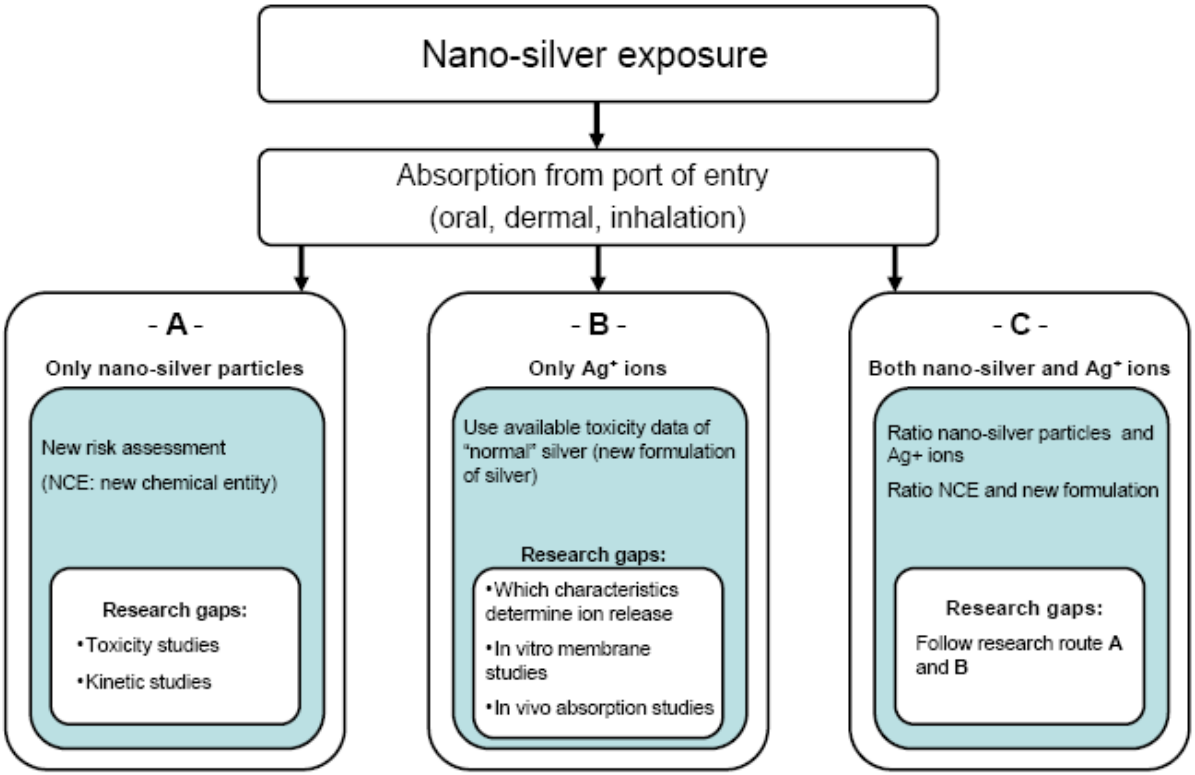
Knowledge gaps in human RA of nano-Ag

- 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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