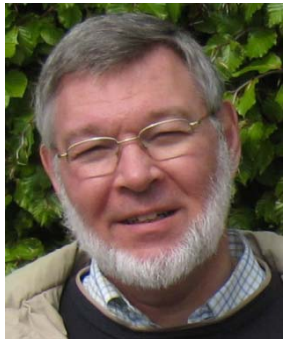
SCENIHR Opinion on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices



Speaker:
Wim De Jong, DVM, PHD

Moderator: Kevin Trout,
MDCPSS Grad Student Representative

- Webinar will begin at 11:00AM EST
- Attendee audio lines will be on mute
- Questions submitted via "Q&A" will be addressed at the end of the presentation. The "Q&A" text function of WebEx is located on the side panel.
- Webinar recording and slides will be available on the MDCPSS website

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

The SCENIHR Opinion Guidance on the Determination of Potential Health Effects of Nanomaterials used in Medical Devices

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Vice chair SCENIHR 2004 - 2013

Content of presentation

- Role and work of EU Scientific Committees
- Use of nanomaterial in medical devices
  - Expectations on future use in medical devices
  - Potential benefits of use of nanomaterials
- Potential risks of nanomaterials
- Risk assessment of products of nanotechnologies
- What make risk assessment of nanomaterials problematic?
- Risk assessment of nanomaterials in medical devices

The European Commission's non-food Scientific Committees

DG SANTE - Health Information and Scientific Committee Unit

Health and Food Safety

European Commission

3 SCIENTIFIC COMMITTEES

SCCS – SCHER – SCENIHR

The three independent non-food Scientific Committees ensure systematic assessment of risks, based on best practice for EU policy needs on health, consumers and environment.

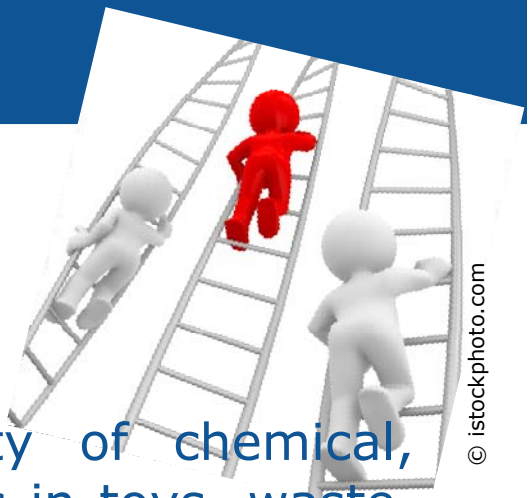
Other EU risk assessment bodies are European Food Safety Authority (**EFSA**); the European Medicines Agency (**EMA**); the European Centre for Disease Prevention and Control (**ECDC**); and the European Chemicals Agency (**ECHA**)

Composition of the Scientific Committees

- Scientists from academia, research or other scientific bodies, appointed by the EC in their personal capacity, following an open call. Scientists have to provide a **declaration of commitment, a declaration of interests and a declaration of confidentiality**
- Selection criteria: competence and independence. As far as possible, geographical and gender balance
- External experts may be invited to WG when special expertise is needed

European Commission

Mandates



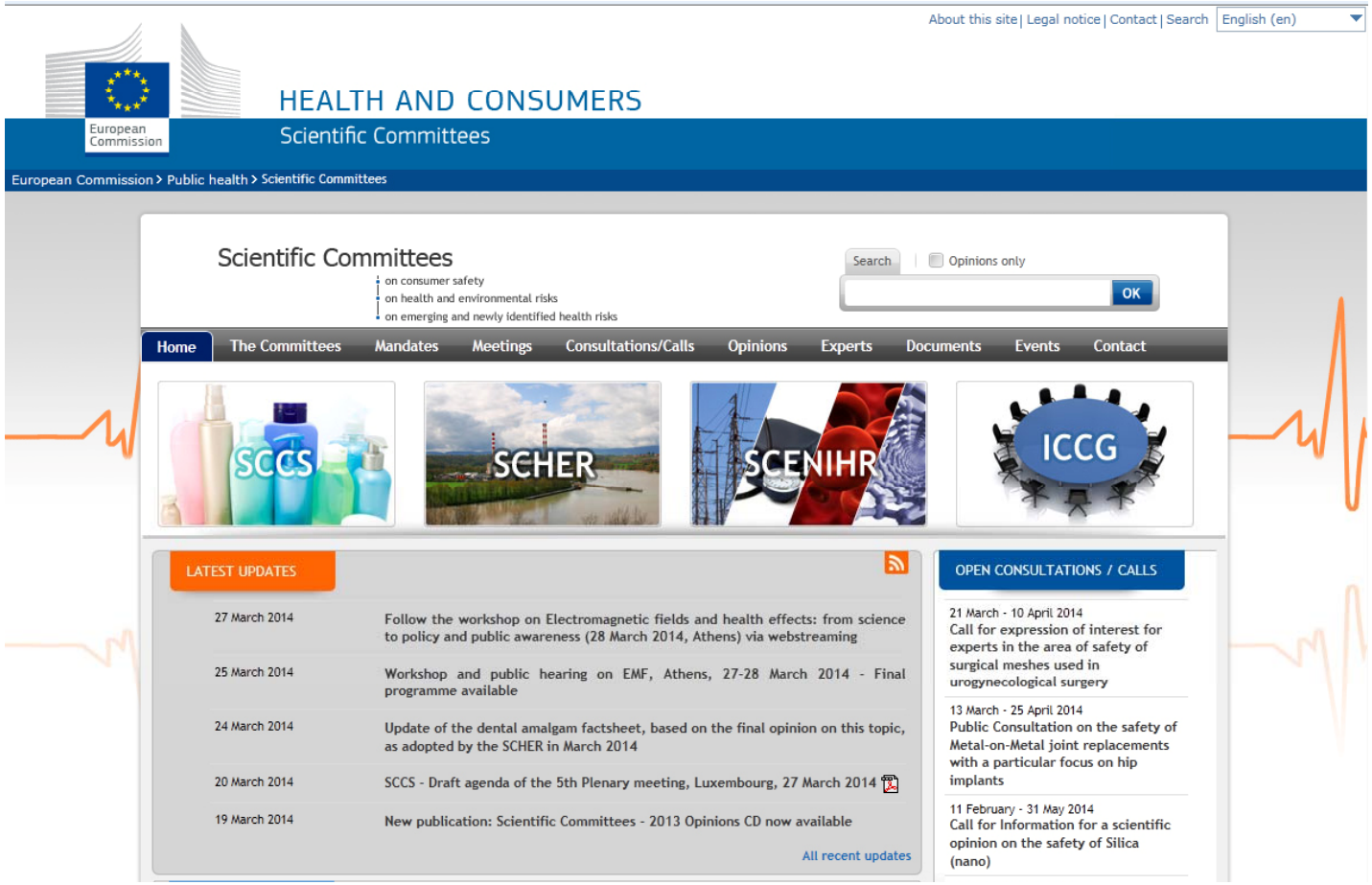
- **SCHER:** advice on toxicity and eco-toxicity of chemical, biochemical and biological products, chemicals in toys, waste, environmental contaminants, drinking water quality, indoor and ambient air quality, endocrine disrupters

- **SCENIHR:** advice on emerging risks, newly identified risks, complex or multidisciplinary issues requiring comprehensive assessment, issues not covered by other bodies

- **SCCS:** advice on risks related to consumer products (non-food) mostly on cosmetics but also on toys, textiles, clothing, household products, non-chemical risks (mechanical, physical, biological), consumer services (for example, tattooing, tanning devices)

Communicating science

- Scientific Committees' **website**



Communicating science

- Dedicated **newsletter**: 2 editions per year

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European Commission

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European Commission > DG Health & Consumers > Public health > Newsletter > 120

NEWSLETTER : SPECIAL EDITION - SCIENTIFIC COMMITTEES

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Health-EU newsletter 120 - Focus

SCENIHR: Protecting citizens against new health risks

Prof. Philippe Hartemann, Chair of the Scientific Committee on Emerging or Newly Identified Health Risks

In April 2013, new members of the Scientific Committee on Emerging or Newly Identified Health Risks (SCENIHR) were nominated for the 2013-2016 term in Luxembourg.

The Committee members were selected by the European Commission as independent experts based on their outstanding scientific expertise via a public call for expression of interest. They have also to guarantee the absence of a conflict of interest which is an excluding criterion. Besides the written declaration of any conflict of interest presented at the time of their appointment, members and external experts working for SCENIHR have to provide written annual declarations confirming this and declare orally during each session, and for each examined issue, any possible conflict of interest. Their declarations are assessed by the Secretariat, the Chair and other members in order to exclude any conflict of interest with the items on the agenda. CVs and declarations are publicly available on the Scientific Committees website.

Due to the complexity of the requested opinions, an ad hoc working group is organized for each topic, recruiting some members of the committee and some external experts selected on the basis of their excellence, such as internationally recognized expertise and peer reviewed publications linked to the subject, and their independence.

The mandate of SCENIHR is to give advice to the European Commission on Emerging risks, Newly Identified Risks, broad, complex or multidisciplinary issues requiring comprehensive assessment and issues not covered by other bodies. This includes for example

Email version

Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

Preliminary Opinion

Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices

Scientific Committees
on consumer safety
on emerging and newly identified health risks
on health and environmental risks

SCENIHR adopted this preliminary opinion by written procedure on 17 July 2014

Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

Opinion on the

Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices

Scientific Committees
on consumer safety
on emerging and newly identified health risks
on health and environmental risks

SCENIHR adopted this opinion by written procedure on 6 January 2015

ACKNOWLEDGMENTS

The members of the working group are acknowledged for their valuable contribution to this Opinion. They are:

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 Disclaimer: this presentation/webinar does not necessarily represent the views of the European Commission and/or RIVM

Nanotechnologies in Medical Devices

- Wide range, very diverse products and technologies
- Therapy, diagnosis, monitoring, prevention of disease
- Non-invasive or invasive – any kind of tissue contact
- Using nanomaterials or other types of nanotechnologies
- All medical disciplines potentially benefit
- No overview available of nanomedical devices in literature
- Request from Dutch Ministry of Health: Provide overview
  - Availability, Benefits, Risks
- Methods: Literature, Databases
  - FDA, Health Canada, Clinical Trials, Patents
  - Categorised by medical specialism

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

Nanotechnologies in medical devices

RIVM Report 2015-0149
R.E. Geertsma et al.

Colophon

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This investigation has been performed by order and for the account of the Health Care Inspectorate and the Ministry of Health, Welfare and Sport

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Summary Trends & Benefits (1)

- **Nanotechnology in medical devices is a growing area**
  - Increasing number of patents, clinical trials, products on market
- **Dentistry by far largest number of products**
- **Nanocoatings / surface modification one of the most important types of nanotech applied**
  - Cardiology, dentistry, neurology, orthopaedics
  - Benefits: increased biocompatibility, thus better integration in tissue
  - Other benefits: coatings with antimicrobial properties

Nanomedical devices

Summary Trends & Benefits (2)

- **Nanomaterials increasingly used to mimic naturally occurring structures**
  - Dentistry, orthopaedics
  - Optimal biological, physical, mechanical aesthetic characteristics compared with human tissues

- **Electrical & magnetic properties of nanomaterials exploited**
  - Cardiology, neurology
  - Improved bioelectrical interface, increased battery lifetime

- **In oncology: “free” NM used for therapy & for surgical guiding**

Nanomedical devices

Summary Opportunities

- **Nanotechnology is expected to have great impact on many areas in medicine, especially:**
  - Surgery
  - Cardiology
  - Oncology
  - Neurology
  - Orthopaedics
  - Dentistry
  - Infectious diseases
  - Implant technology
  - Drug delivery
  - Tissue Engineering

- **Nanotechnology is foreseen to change health care in a fundamental way:**
  - Novel methods for disease diagnosis and therapy
  - New and effective tools for disease prevention
  - Point-of-care, fast testing → daily screening of health
  - Therapeutic selection tailored to the patient's profile (Personalised treatment)

Dentistry

CE-marked (examples)

- **FIDE (European Dental Industry) estimate 3500 dental products containing nanomaterials on EU market.**

- **The main product groups reported are:**
  - Impression materials (600)
  - Dental composites (340)
  - Denture base resins (320)
  - Veneering materials (230)
  - Accessories for verification of occlusion (200)
  - Bonding agents (200)
  - Final luting cements (180)
  - Plastic materials for bite registration (140)
  - Materials for crowns and bridges (140)
  - Cements (130)
  - Materials for temporary crowns and bridges (120)
  - Artificial teeth (110)

Orthopaedics

CE-marked (examples)

- **Bone replacement materials (bone graft materials)**
  - Hydroxyapatite (HA) and tricalcium phosphate (TCP) NPs
    - Ostim®, Heraeus Kulzer, DE
    - NanOss® Bioactive, Pioneer Surgical Technology Inc, USA
    - VITOSS®, Orthovita Inc, USA
- **Implant surface coatings**
  - Nano-structured HA for hip, knee prostheses;
    - IONTITE, Spire Biomedical Inc, USA
    - BoneMaster, BioMet, USA
    - NANANO, Promimic, SE
  - Titanium dioxide nanocoating
    - TiMesh, GfE Medixintechnik GmbH, DE
- **Cartilage scaffold – knee repair**
  - MaioRegen, Finceramica, IT
- **Tantalum metal implant material**
  - Trabecular Metal, Zimmer Inc, USA

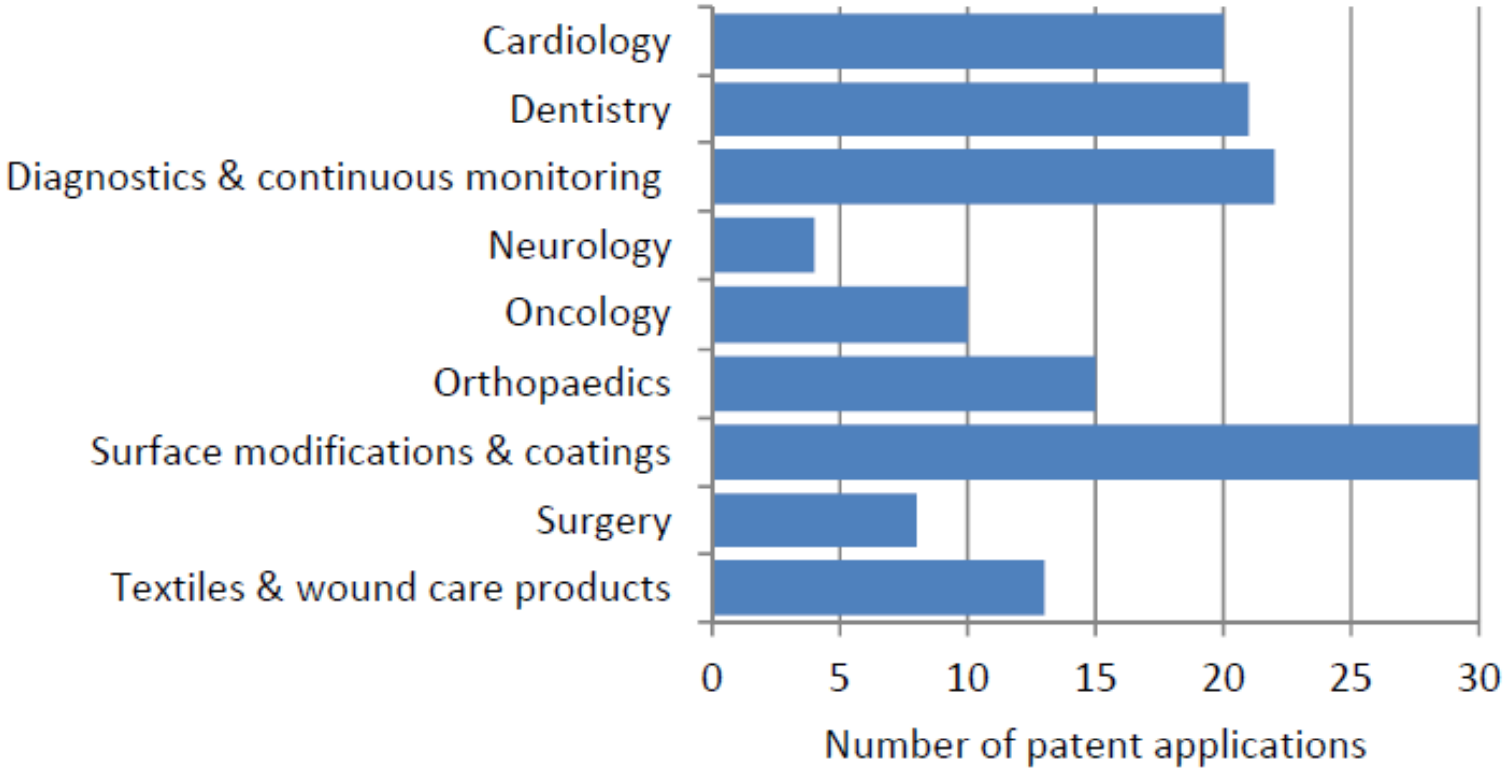
Textiles / wound care products

- **Textiles**
  - **Antimicrobial** Nanocrystalline silver particle-incorporated yarns
    - Nano-silver particle for textile, AgPURE, RAS Materials, DE
    - Nano-Magic Silver®, Hyosung Mipan, South Korea

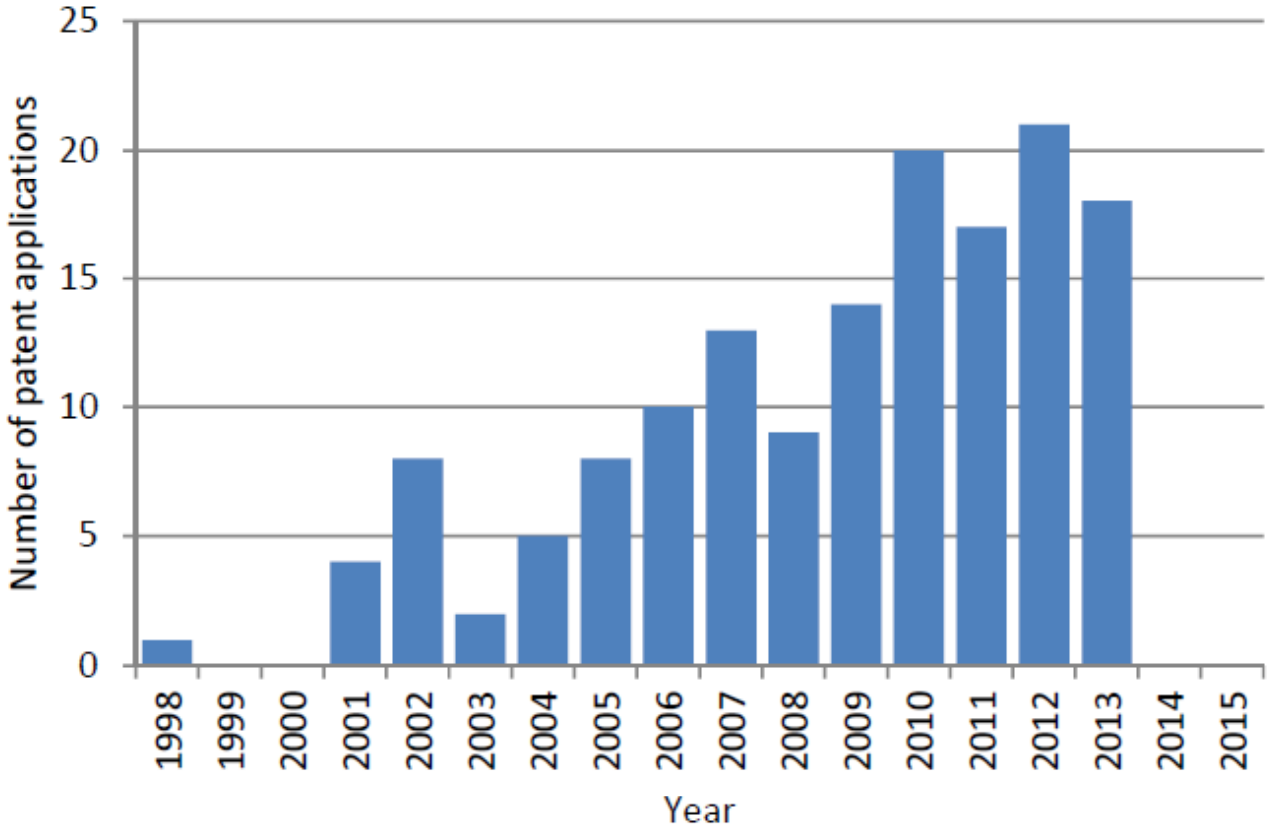
- **Wound care products**
  - Nanocrystalline silver particle-based wound dressing – *on the market*

    Acticoat* SYLCRYST™, Smith & Nephew plc, UK
  - Wound dressings made from nanofibres, often by electrospinning
    - Nanogen Aktiv, Genadyme Biotechnologies Inc, USA
    - Chitoflex, HemCon Medical Technologies, USA
  - Skin substitute from nanofiber cellulose
    - Nanoderm, Axcelon Dermacare Inc, USA

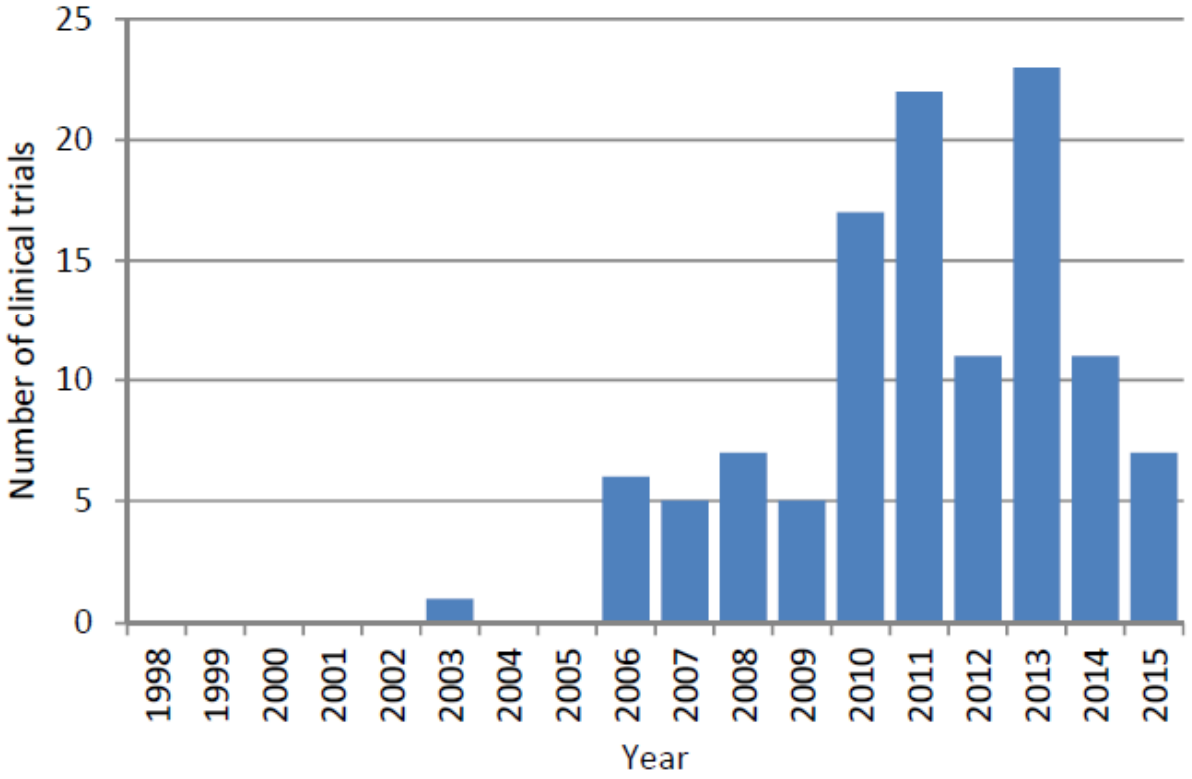
EU Patent applications nanomedical devices (Total 150)



EU Patent applications nanomedical devices (Total 150)

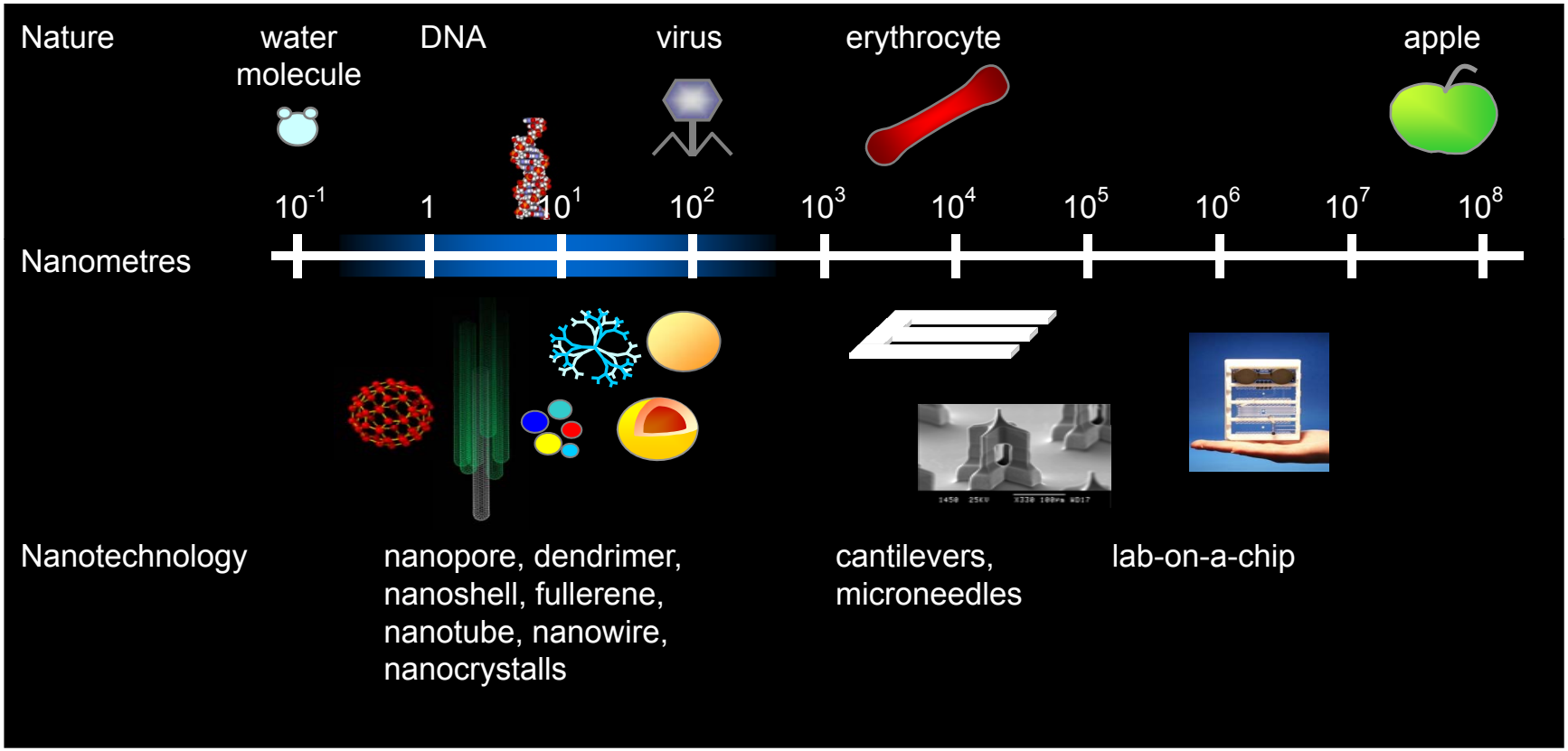


Clinical trials with nanomedical devices (Total 115)



Dentistry	34
Oncology	24
IVDs	20
Wound Care	13
Cardiology	6
Orthopaedics	5

Nanomedicine: new opportunities – also new risks?



Nanomaterials (nanoparticles) can have sizes similar to structures at subcellular level and (theoretically) can reach and interact with such structures.

Main question/concern for safety

Increase in surface area >> increase in surface activity, but also increase in possible contact with cells and tissues

Does this also result in increased toxicity?

In view of the multitude of nanomaterials expected to be developed, the question arises whether we do need to test all new (modified) nanomaterials for safety aspects or is extrapolation between nanomaterials possible?

SCENIHR 2009 Opinion

Risk Assessment of Products of Nanotechnologies

The hypothesis that smaller means more **reactive** and thus more **toxic** **cannot be substantiated by the published data**. In this respect nanomaterials are similar to normal substances in that some may be toxic and some may not”

Although this may be considered comfortable that in principle there is no difference between “normal chemicals” and nanomaterials, it also has the implication that nanomaterials should be investigated on a **case-by-case** basis as the risks cannot be estimated beforehand.

Classical approach of risk assessment is applicable

Exposure assessment / Hazard identification / Hazard characterisation / Risk characterisation

Guidance on determination of potential health effects of nanomaterials used in medical devices

- Included
  - Characterisation of NM used in medical devices
  - Use of NM in medical devices
  - Exposure to nanomaterials from medical devices
    - › Also generation of NM by wear and tear processes included
  - Toxicological evaluation
  - Safety evaluation of NM used in medical devices (ISO 10993-series)
  - Risk assessment
- Excluded
  - broader application of nanotechnology in medical devices like nano-electronics, lab-on-a- chip technologies
  - *In vitro* diagnostic medical devices in view of unlikely exposure
  - Contrast agents for imaging (in EU medicinal products)
  - Occupational and environmental risks during manufacturing/disposal

Risk assessment of nanomaterials

What is a nanomaterial?

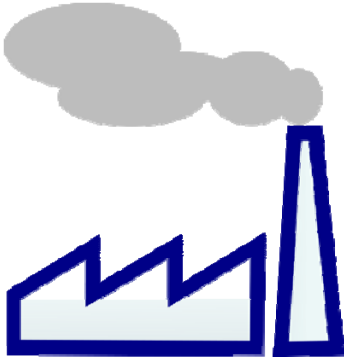
Exposure assessment

Internal dose

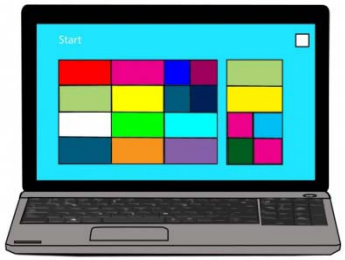
Hazard characterisation

Hazard identification

Dose response assessment



Risk characterisation



Why is safety evaluation and risk assessment of nanomaterials difficult?

- Knowledge gaps in risk assessment
  - Nanoparticle characterisation, detection, and measurement
  - Dose responses of possible effects (including, what is the dose?)
  - Fate and persistence of NP in humans and environment
  - Aspects of (eco)toxicology (interaction at sub-cellular and molecular levels)

In view of uncertainties extrapolation from convential form of "large" particles considered not possible.

Why is safety evaluation and risk assessment of nanomaterials difficult?

- Diversity of nanomaterials (inorganic, organic, composite, coated,…)
- Solubility, agglomeration/aggregation (stability, size distribution)
- Matrix (interactions, effects on size, digestion)
- Quality of available nanomaterials (polydispersity, purity, concentration)
- Test protocols (dispersion, reproducibility, comparability)
- Choice & preparation of test medium (concentration, solvents)

Many factors with varying effects !

Knowledge gaps !

Complexity of nanomaterials

- More variation in physicochemical parameters possible that can affect exposure, kinetics and hazard of a material than for 'normal chemicals'
- Physicochemical parameters that may affect exposure, kinetics and/or hazard
  - Size
  - Aggregation/agglomeration
  - Shape
  - Coating/surface functionalisation/surface chemistry
  - Surface charge
  - Dissolution rate
  - Composition
  - Reactivity
  - Photoreactivity
  - …

What we already know/use (nanodefinition)

- SCENIHR Opinion on "Scientific basis for the definition of the term 'nanomaterial' " (2010)
  - Most physicochemical characteristics not useful for definition
  - Only size is appropriate characteristic to be used in definition
- EU Recommendation for a definition of nanomaterials (2011)
  - Sets NM apart as group particulates (1 – 100 nm), >50%
- ISO/TS 80004-1:2015
  - Nanoscale 1 – 100 nm
- Auffan et al., 2009
  - Size not sufficient for definition
  - Novel size dependent properties
  - Inorganic nanoparticles (metal and metal oxide NP)
  - Properties affected/changing when size below 20 – 30 nm

What do we want to know for Risk Assessment?

We really want to know is which physicochemical characteristics drive potential adverse (toxic) effects.

Physicochemical characterisation is essential.

See Table 1 in SCENIHR Opinion 2015 for various parameters and methods for characterisation.

Biological behaviour/toxicokinetics

How is a nanoparticle/nanomaterial defined? What do we mean by size?

Particle type	Nominal	TEM*	AFM*	FCS^	NTA*	DLS'	FlFFF^
TiO_2 & FA 1mg/L	5	16.1 +/-6.4	3.7 +/-2.1	6.5 +/-2.8	164 +/-32 (30mg/L)	1230 +/-430 (30mg/L)	3.7 (100mg/L)
ZnO & FA 1mg/L	20	12.2 +/-4.5	25.7 +/-8.5	28.5 +/-10.5	130 +/-50 (100mg/L)	870 +/-680 (30mg/L)	228.3 (100mg/L)
QDs 1.92 ug/L	6-10	6.5 +/-1.9	5.9 +/-3.4	81.8 +/-4.9	213 +/-17	234 +/-35	41.5

*number average ^weight average 'z average

Domingos *et al.* 2009

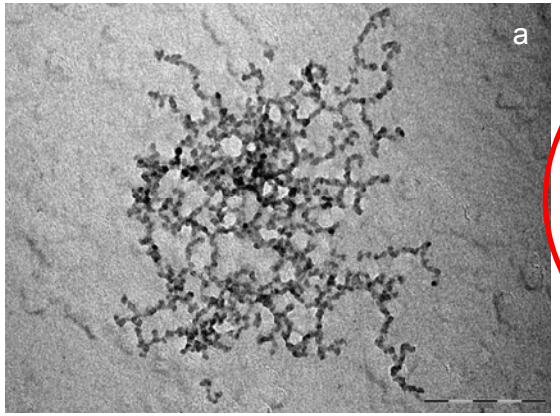
Understanding and correlation of size measurement techniques is essential

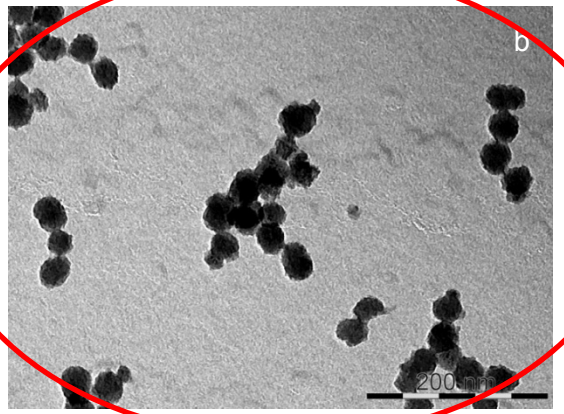
TEM, transmission electron microscopy; AFM, atomic force microscopy; DLS, dynamic light scattering; FCS, fluorescence correlation spectroscopy; NTA, nanoparticle tracking analysis; FIFFF, flow field flow fractionation

Courtesy of Karin Tiede, FERA, York, UK

Transmission Electron Micrographs of silica NPs

11 nm

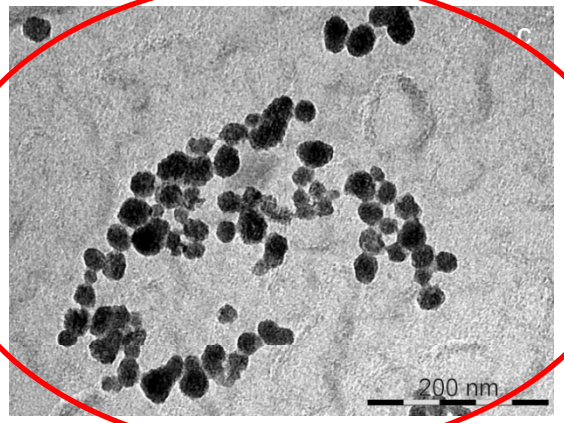


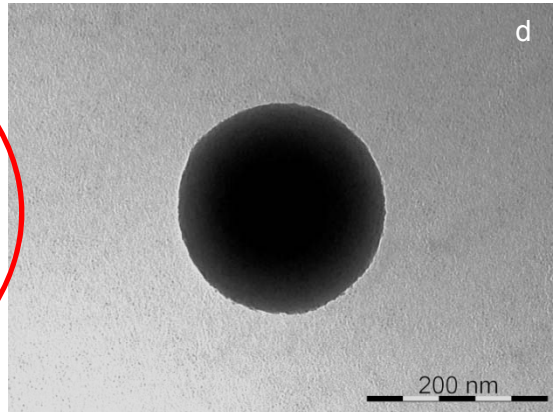


34 nm

~~80 nm~~

34 nm



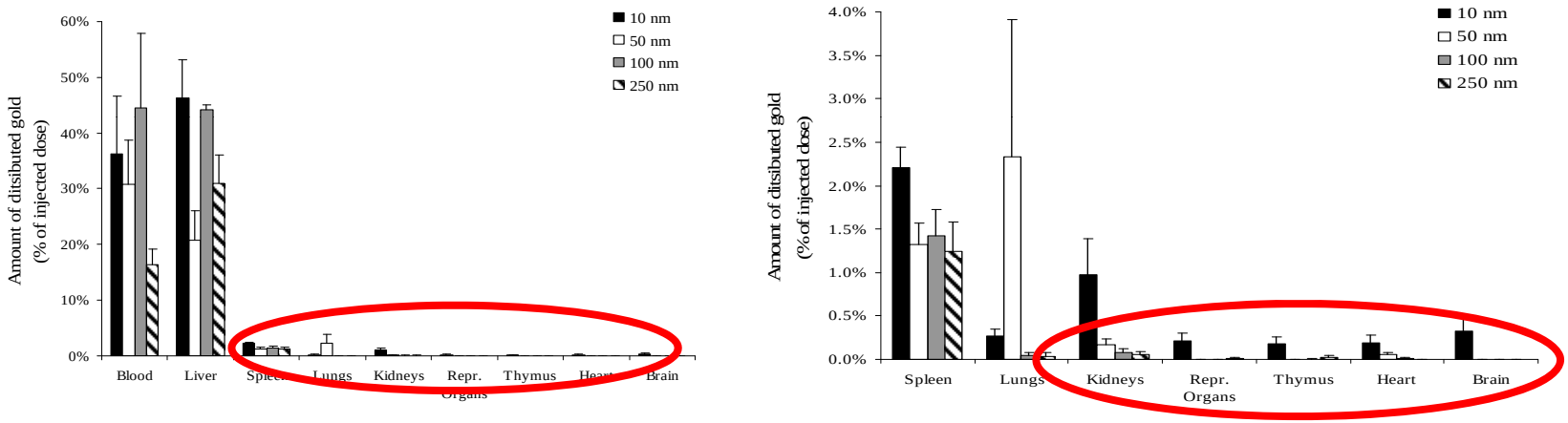


~~400 nm~~

248 nm

Park et al., Toxicol Appl Pharmacol, 2009

Pharmacological availability
Effect of nanoparticle size on tissue distribution



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

De Jong et al., Biomaterials, 2008

Pharmacological availability
Effects of size on toxicokinetics

Table 6
The average number of gold particles distributed to the various organs (estimated)

Tissue	10 nm, Number of particles (number/g organ)	50 nm, Number of particles (number/g organ)	100 nm, Number of particles (number/g organ)	250 nm, Number of particles (number/g organ)
Blood	1.9E + 12	1.2E + 10	2.2E + 09	4.6E + 07
Liver	2.4E + 12	8.2E + 09	2.3E + 09	9.5E + 07
Spleen	1.1E + 11	5.2E + 08	7.3E + 07	3.8E + 06
Lungs	1.4E + 10	9.0E + 08	2.2E + 06	1.2E + 05
Kidneys	4.9E + 10	6.5E + 07	3.8E + 06	1.6E + 05
Testis	1.1E + 10	–	–	4.2E + 04
Thymus	9.1E + 09	–	–	6.4E + 04
Heart	9.9E + 09	2.2E + 07	4.3E + 05	–
Brain	1.6E + 10	–	–	–
	$N = 7$	$N = 2$	$N = 4$	$N = 5$

Although only a few % of the administered dose
a considerable amount may be present in organs in terms of particle numbers.
What about local accumulation and chronic effects?

De Jong et al., Biomaterials, 2008

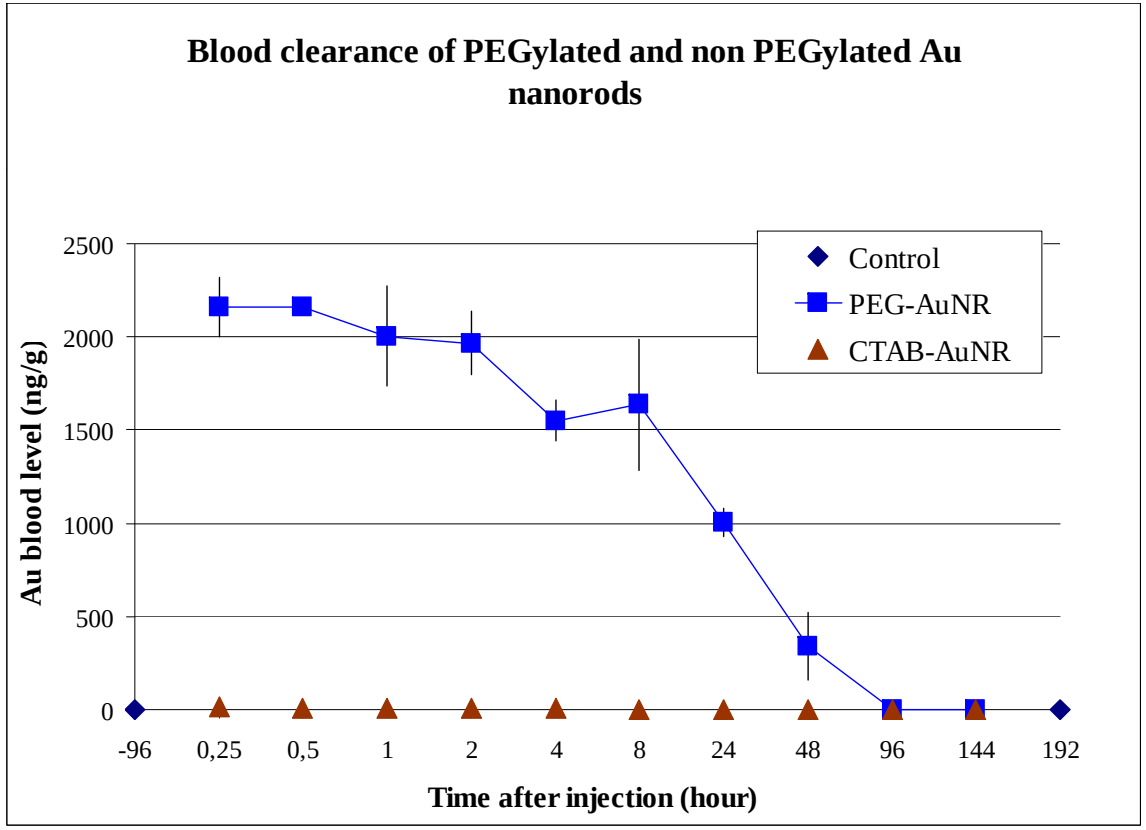
Conclusions of Au (and Ag) distribution studies

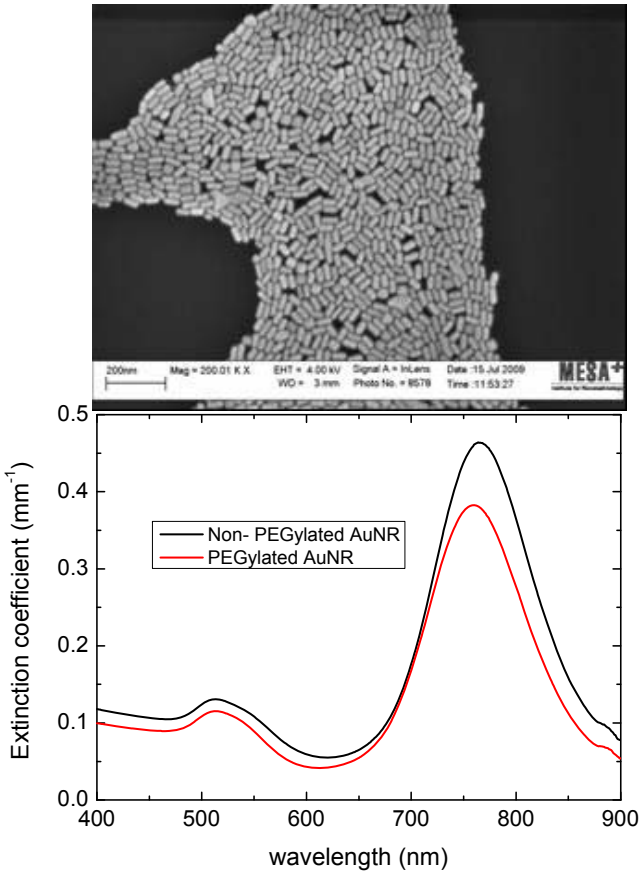
- Most nanoparticles end in liver and spleen
- Smaller nanoparticles can have more widespread organ distribution

- Liver and spleen are part of RES (reticulo endothelial system), organs with phagocytosing cells along blood vessels

- How to avoid trapping of nanoparticles/nanomedicines by RES?

Effects of surface (PEG coating) of gold nanorods on toxicokinetics





Lankveld et al., Nanomedicine, 2011

Effects of coating of gold nanorods on toxicokinetics

	DAY 1		DAY 6	
	PEG-AuNR$_{770}$	CTAB-AuNR$_{770}$	PEG-AuNR$_{770}$	CTAB-AuNR$_{770}$
Liver	320 ± 105	2339 ± 390	978 ± 145	2059 ± 299
Spleen	3477 ± 153	1643 ± 236	6644 ± 1973	1132 ± 204
Kidney	183 ± 32	13 ± 1	176 ± 29	5 ± 3
Lung	264 ± 22	239 ± 102	106 ± 17	172 ± 99
Heart	192 ± 5	3 ± 1	104 ± 13	4 ± 3
Thymus	66 ± 19	2 ± 0	66 ± 26	2 ± 0
Brain	27 ± 3	5 ± 6	2 ± 0	2 ± 1
Testes	33 ± 10	2 ± 0	23 ± 6	2 ± 0
Blood	1007 ± 76	3 ± 0	3 ± 1	3 ± 0

Data are presented as gold concentration in ng per gram tissue. Gold nanorods were administered intravenously at day 0. Number of animals (samples) n=3 for day 1 and n=6 for day 6. Tissue samples were prepared by organ digestion before ICP-MS measurement.

For toxicity local organ dose is of importance.

For PEGylated gold nanorods now SPLEEN is target organ with highest exposure dose.

What about local accumulation and chronic effects?

Lankveld et al., Biomaterials, 2010

Safety evaluation

- Problems with testing
  - Problems with identification/characterization
  - Problems with dispersion for testing *in vitro* and/or *in vivo*
  - Protein adherence, effect of protein corona
  - We know it exists, but we do not know its biological effects

Potential assay artifacts

- Interference in assay
  - Spectrophotometer, absorbance of (fluorescence) signal used in various assays
- Chemical interactions
  - Interaction with assay substrates due to chemical properties of nanomaterials
- Depletion of cell culture medium
  - Adsorbance of tissue culture components (nutrients, growth factors) due to adsorptive properties of nanomaterials
- Inability of nanomaterials to enter prokaryotic cells (e.g. Ames test)
  - Ames test generally considered not appropriate for determination of genotoxicity of nanomaterials

Papers referring to assay interferences

- Worle-Knirsch *et al*., Nano Letters 6, 1261-1268, 2006
- Kroll *et al*., Eur J Pharmaceutics Biopharmaceutics 72, 370-377, 2009
- Oostingh *et al*., Particle Fiber Toxicology 8:8, 2011
- Kroll *et al*., Particle Fiber Toxicology 8:9, 2011
- Kroll *et al*., Archives of Toxicology 86, 1123-1136, 2012
- Ong *et al*., PloS One 9, e90650, 2014
- Kucki *et al*., Innate Immunity 20, 327-336, 2014
- Guadagnini *et al*., Nanotoxicology 9, Suppl 1:13-24, 2015

Some characteristics for toxicity already known.

- Nanoparticle charge
- Nanoparticle solubility
  - Release of toxic ions
- Composition
  - Impurities, **coatings**
- Shape
  - Carbon nanotubes, rigidity

- Biological behaviour
  - **Toxicokinetics**
  - Ability to cross biological barriers (size, coating)

Donaldson and Poland 2013

Is dose metric of mass applicable?

- Dose metrics per kg body weight
  - Mass (milligram, gram)
  - Number of particles, as effects may be determined by the particle characteristics
  - surface area, as demonstrated for inhalation toxicity of TiO_2
  - .....something else?

Adverse effect.., What to do?

Specific use: Rationale for conclusions on safety of use of nanoTiO_2 as UV-filter in sunscreen formulations

Adverse effects identified:

- Positive genotoxic effects reported in open literature
  - also negative effects were reported, so it is overall inconclusive
- Inhalation toxicity observed (inhalation exposure to be avoided)
- Penetration in outer layer of *stratum corneum*
  - limitation of acceptable photo-catalytic activity

However, based on provided information and open literature it was concluded that skin exposure was found to be unlikely to lead to:

- Skin penetration and thus systemic exposure
- Acute toxicity via dermal application or oral ingestion
- Skin irritation, eye irritation or skin sensitization when applied on healthy skin
- Reproductive effects when applied on healthy skin

Risk assessment of nanomaterials used in invasive medical devices: Principles

- **Basis risk assessment nanomedical devices same as for other MD**
- **Specific characteristics of NM to be taken into account, i.e.:**
  - Detailed physicochemical characterisation and identification of NM
  - Exposure
    - ›Toxicokinetic studies in case of potential release of NM
  - Pitfalls in toxicity testing – sampling, read-out, mechanism, …
- **ISO 10993-series Biological Evaluation of Medical Devices**
  - Framework based on type of device, type of contact, contact time
  - Depending on device category, various biological/toxicological tests
  - Guidance document TR ISO 10993-22 under development
- **Nano-related risk primarily related to release of nanomaterials**

- **Also generation of NM by wear and tear processes included**

Table 3: An estimation of potential external and internal exposure as starting point for a risk evaluation for medical devices containing nanomaterials

			Type of application of nanomaterials External exposure/internal exposure				
			Free	Fixed (coating)	Fixed (coating)	Embedded	Embedded
Type of device	Type of contact	Duration of contact		Weak (physisorb)	Strong (chemisorb)	In degradable materials*	In non-degradable materials
Surface device	Intact skin	≤ 24 h	H/N	M/N	M/N	L/N	N/N
		>24 h to 30 d	H/N	M/N	M/N	M/N	N/N
		>30 d	H/N	M/N	M/N	H/N	N/N
	Intact mucosal membrane	≤ 24 h	H/L	M/L	M/N	L/L	N/N
		>24 h to 30 d	H/M	M/M	M/L	M/M	N/N
		>30 d	H/M	M/M	M/L	H/M	N/N
	Breached or compromised surface	≤ 24 h	H/H	M/M	M/L	L/M	N/N
		24 h to 30 d	H/H	M/M	M/L	M/M	N/N
		30 d	H/H	M/M	M/L	H/M	N/N

H=high, M=medium, L=low, N=negligible, na=not applicable

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			Type of application of nanomaterials External exposure/internal exposure				
			Free	Fixed (coating)	Fixed (coating)	Embedded	Embedded
Type of device	Type of contact	Duration of contact		Weak (physisorb)	Strong (chemisorb)	In degradable materials*	In non-degradable materials
External Communicating device	Blood path, indirect **	≤ 24 h	na	M/M	M/L	L/L	N/N
		>24 h to 30 d	na	M/M	M/L	M/M	N/N
		>30 d	na	M/M	M/L	H/M	N/N
	Tissue/bone/dentin	≤ 24 h	H/H	M/M	M/L	L/L	N/N
		>24 h to 30 d	H/H	M/M	M/L	M/M	N/N
		>30 d	H/H	M/M	M/L	H/H	N/N
	Circulating blood***	≤ 24 h	na	H/H	H/H	L/L	N/N
		>24 h to 30 d	na	H/H	H/H	M/M	N/N
		>30 d	na	H/H	H/H	H/H	N/N

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Table 3: An estimation of potential external and internal exposure as starting point for a risk evaluation for medical devices containing nanomaterials

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Type of device	Type of contact	Duration of contact		Weak (physisorb)	Strong (chemisorb)	In degradable materials*	In non-degradable materials
Implant device	Tissue/bone	≤ 24 h	H/H	H/H	H/L	L/L	N/N
		>24 h to 30 d	H/H	H/H	H/L	M/M	N/N
		>30 d	H/H	H/H	H/L	H/H	N/N
	Blood	≤ 24 h	H/H	H/H	H/L	L/L	N/N
		>24 h to 30 d	H/H	H/H	H/L	M/M	N/N
		>30 d	H/H	H/H	H/L	H/H	N/N

H=high, M=medium, L=low, N=negligible, na= not applicable

H/L means high potential contact and/or external exposure to the nanomaterial / low potential for internal systemic exposure of all organ systems

Device testing considerations according to ISO 10993-1:2009

- Device category
  - Surface device
  - External communicating device
  - Implant device
- Contact location
  - Skin, mucosal membrane, breached or compromised surface
  - Blood, tissue/bone/dentin
- Contact time
  - Limited ≤24 h
  - Prolonged >24 h to 30 days
  - Permanent > 30 days

Tests that need to be considered depending on category, contact location and contact time

- Cytotoxicity
- Sensitization
- Irritation or intracutaneous reactivity
- Systemic toxicity (acute toxicity)
- Subchronic toxicity (subacute toxicity)
- Genotoxicity
- Implantation
- Haemocompatibility

These are assays that need to be considered for a biological safety evaluation based on a risk analysis. No testing is needed when sufficient data are already available.

Table 4: Framework for specific nanomaterial toxicity testing based on potential release (exposure) of nanomaterials from medical devices.

Testing proposed	Non-invasive short term use	Non-invasive long term use	Invasive short term use	Invasive long term use
Low exposure	Phys: chem data	Phys: chem data	Phys: chem data	Phys: chem data
	Cytotoxicity *in vitro*	Cytotoxicity *in vitro*	Cytotoxicity *in vitro*	Cytotoxicity *in vitro*
	Irritancy *in vitro*	Irritancy *in vitro*	Irritancy *in vitro*	Irritancy *in vitro*
	Hypersensitivity	Hypersensitivity	Hypersensitivity	Hypersensitivity
		Genotoxicity *in vitro*		Genotoxicity *in vitro*
				General Immuno toxicity testing
Medium exposure Additional tests		Genotoxicity *in vivo*	Other *in vitro* plus *in silico* testing*	28/90 day *in vivo* toxicity test
		Immuno toxicity at location site	Genotoxicity *in vitro* and *in vivo*	*In vitro* and *in vivo* (repeated dose) genotoxicity testing
		Persistence /accumulation studies at location site only		ADME including persistence /accumulation studies
High exposure Additional tests	Selected *in vivo* acute toxicity tests focussed on location site(s)	Selected *in vivo* chronic toxicity tests focussed on location site(s)	*In vivo* acute toxicity tests	*In vivo* chronic toxicity tests may include reprotox depending on patient group.

Risk assessment of nanomaterials used in invasive medical devices: a phased approach

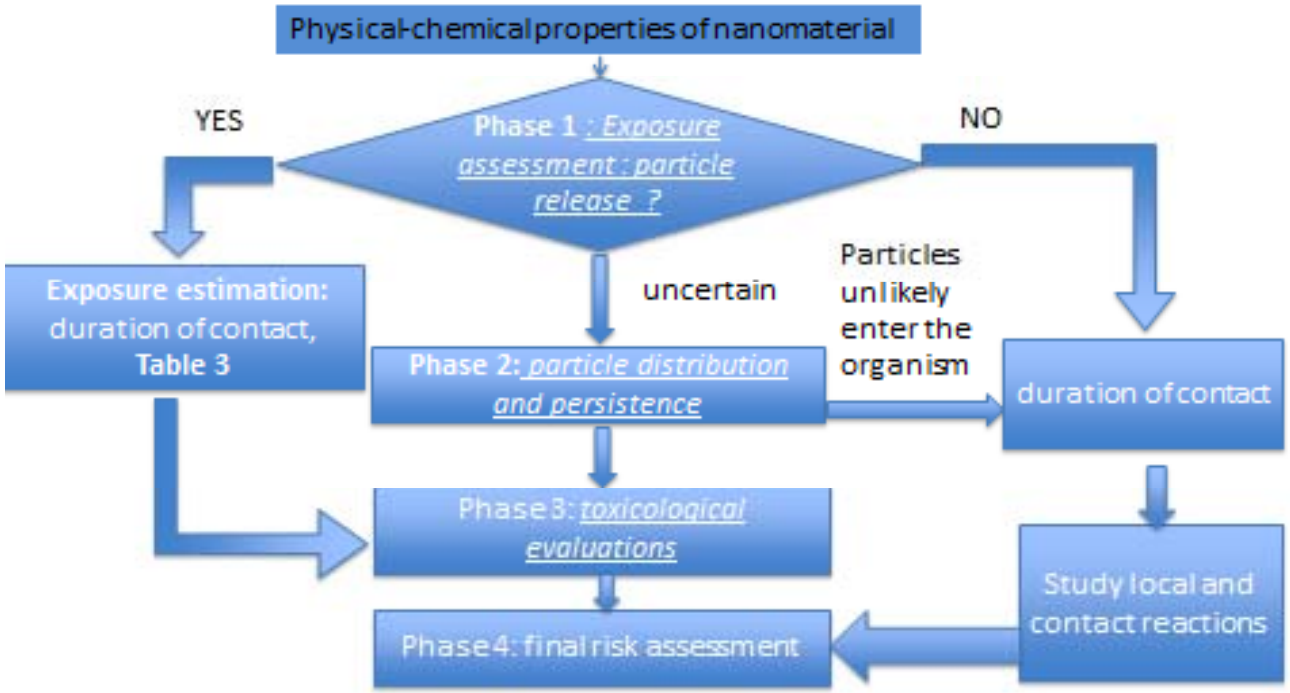


Table 5: Framework for risk assessment of nanomaterials used in medical devices

Release of nanoparticles	Non-invasive		Invasive Lung		Invasive Other	
	Short exposure	Long exposure	Short exposure	Long exposure	Short exposure	Long exposure
Low/insignificant	N/VL*	L/F**	L	F	L	F
Medium	L/F	L/F	L/F	F	L/F	F
High	L/F	L/F	F	F	F	F

*F=full assessment L=limited assessment VL =very limited or N= no further assessment *=limited assessment if it can be shown that penetration/distribution is very limited.*

*** Full assessment when absorption is indicated in toxicokinetic studies*

What is specific for “nano”?

- Identification might be an issue
  - Is the nanomaterial used in the product the same as used in the safety evaluation/toxicity studies
- The particulate character (it is not a soluble chemical)
  - Different toxicokinetics need to be considered
  - Size may be an issue
- Location of the nanomaterial
  - Embedded in matrix
  - Surface
- Exposure drives risk, so potential release and migration is important
  - This includes wear and tear
  - Also normal wear and tear may generate nanoparticles
- Free nanoparticle presents potentially the highest risk
- NPs may have specific characteristics, but no specific toxicity

What do we know about toxicological risk assessment of nanomaterials?

- The particulate nature of nanomaterials influences the toxicokinetics
  - ADME – absorption, distribution, metabolism, excretion
  - Dependent on size, shape, material, etc…
- Physicochemical and toxicological properties of nanomaterials (and surfaces) different from bulk material – parameters?
  - What value is border/turning point for toxic behaviour?
- Not all nanomaterial formulations are toxic
  - Increase in surface activity does not automatically imply toxicity
- You are dealing with many factors with a variety of effects

Risk assessment of nanomaterials in medical devices

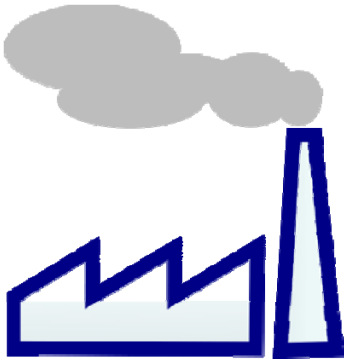
Identify the nanomaterial

Exposure assessment

Hazard characterisation

Hazard identification

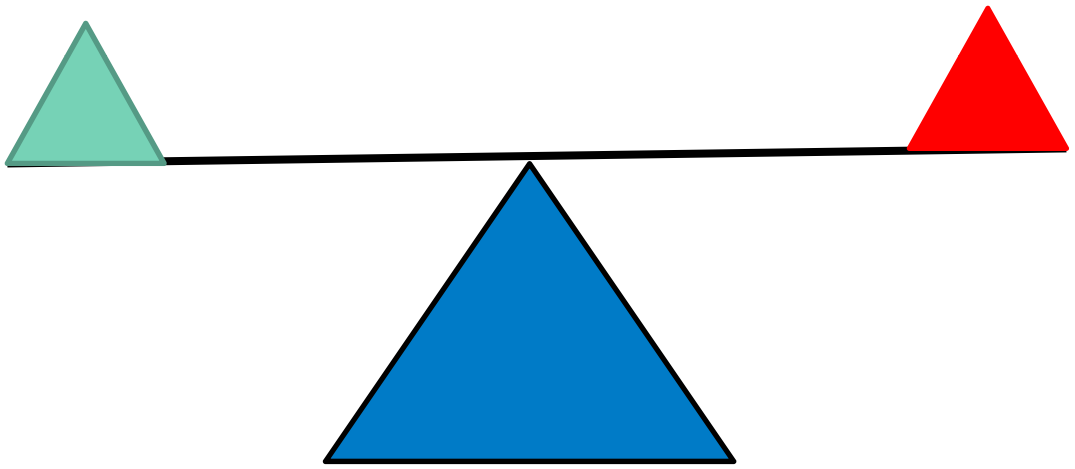
Dose response assessment



Internal dose

Risk characterisation

In the end we need to consider the benefit for the patient that will be treated with the medical device



Balance patient safety - availability of innovation