Biological Evaluation of Nanomaterials

14.10 **Managing the biological evaluation of nanomaterials and assessing the current regulatory environment**

- Relevance of nanotechnologies and nanomaterials for medicine, and medical devices in particular
- Biological evaluation of nanomaterials and scientific and regulatory developments
- What your Notified Body needs to know: Co-education in risk management
- Overcoming the challenge associated with a lack of guidance for nanomaterials and timelines for when guidance will be available

Paul Borm, *CSO,* **Nano4Imaging** *and Co-Founder of Open-Access Journal,* **Particle & Fibre Toxicology,** Germany

14.45 Networking and afternoon tea

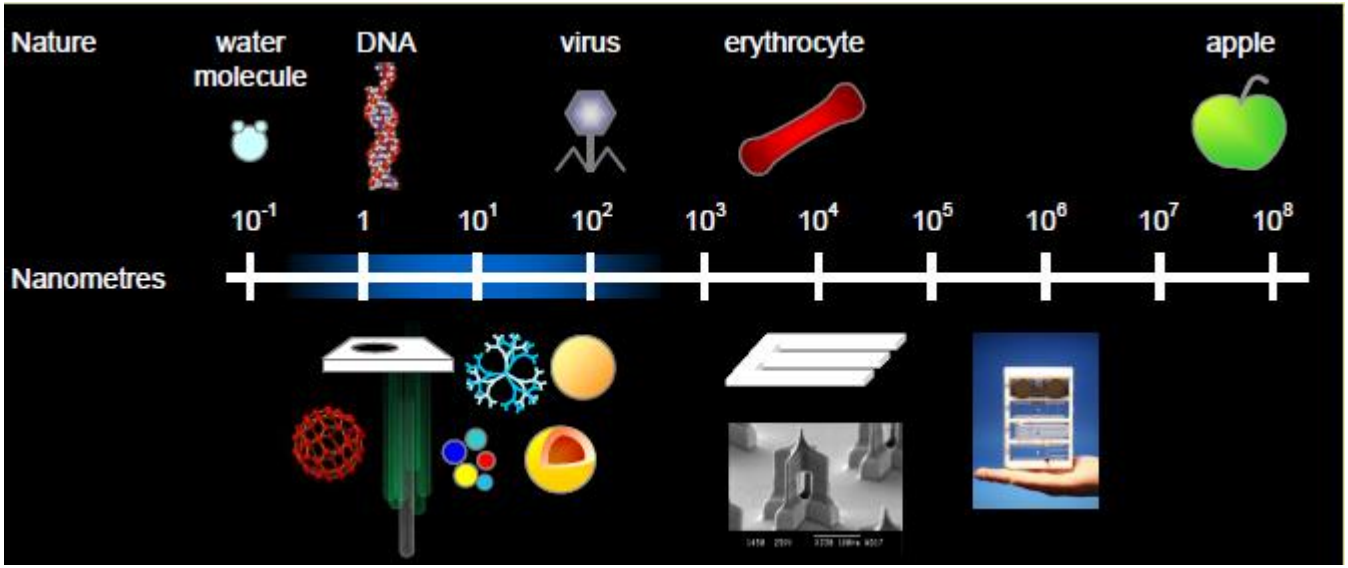
2-3 December 2014
Radisson Blu Hotel Berlin | Berlin
Germany

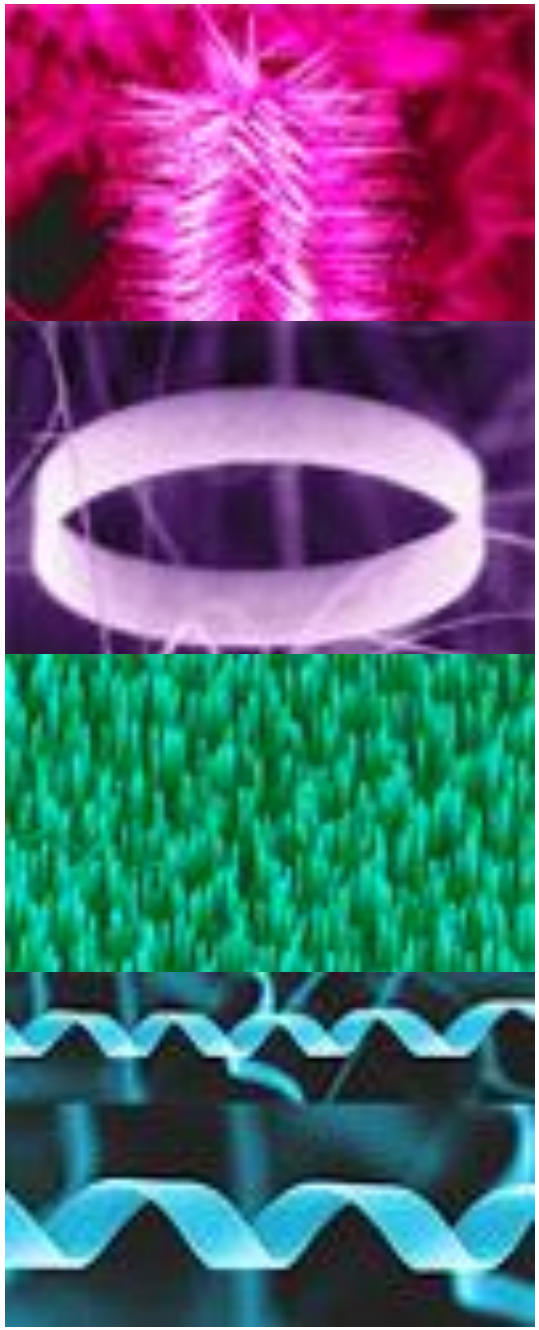
Why me?

- Toxicologist, specialist on particles.
- Former member of WHO, SCENIHR, MAK, DECOS
- Author of CEFIC White paper nanomaterials, risk assessment (2007), Particle & Fibre Toxicology
- Founder and Editor of PFT (impact 7.0)
- Several handbooks and chapter on the issue.
- Entrepreneur using and producing nanomaterials since 2004.
- Hands-on experience in succesful CE certification of medical device with nano-inside. FDA ongoing
- Still part of tox networks where nano is being studied

What are nanomaterials?

- Materials with at least one dimension (< 100 nm).
- A building block and constituent of more and more products
- A buzz word.
- A source of debate with regard to opportunities & risks.
- Still unknown to a large part of the public and companies





Nanotechnology and regulation. Think about this challenge

All materials are
nanoforms of Zinc oxide

Same chemistry (ZnO)

- Different shapes,
- Different properties
- Different applications
- Different regulation?
- Different testing?

Where are nanomaterials being used?

- **Life Sciences** (nanomedicine, contrast agents, drug delivery)
- Polymer- composites (nanoparticles influence melting, permeability, porosity)
- Computer industry (chips, screens, biosensors)
- **Cosmetics** (sunscreens)
- **Coatings** (anti-bacterial coatings, self-cleaning glass)
- Endless list of consumer products (estimated > 5000 products in the USA 2011 with nanoclaim, majority nanosilver)

What is special about their biological properties?

- Same materials change properties at different sizes
- One material more passports
- Small particles may cross membranes like chemicals do (eg placenta, blood brain barrier)
- Biological properties are related more to surface then to mass
- Standards are based on mass concentration
- Special interest in inflammatory, cardiovascular and carcinogenic properties.
- Size matters, but few rules of thumbe

Concern over the Potential Impact of Nanotechnology

ETC Group 2003

VDI (Germany) 2004

SwissRe 2004

Environmental Health Perspectives 2004

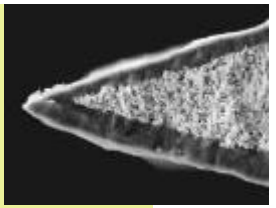
Royal Society 2004

Nanomaterials, medicine and medical technology

- Surgery and minimal invasive interventions
- Therapy (especially cancer)
  - Drug (gene) delivery
- Diagnostics
  - Contrast agents for in-vivo and molecular imaging
  - In vitro rapid diagnostics, Point-of-Care systems
- Biosensors/biodetection
- Implantable materials/devices
- Textiles and wound care products

Surgery and minimal invasive interventions

Conventional surgical tools

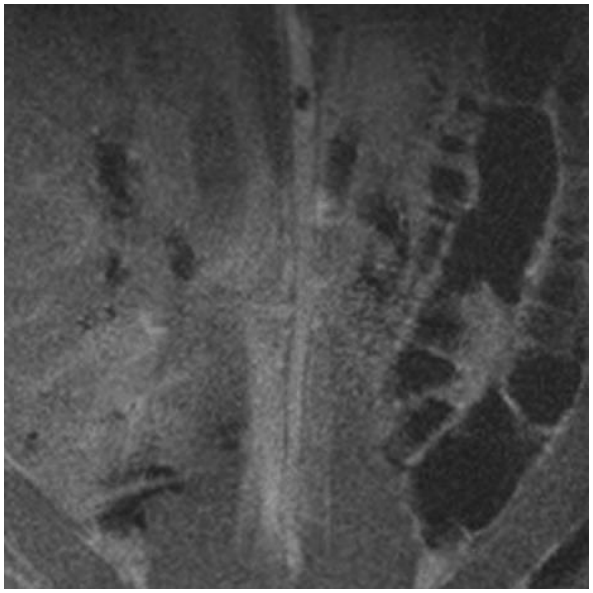


- Suture needle with stainless steel nanocrystals (1-10 nm) – *on the market*
  Sandvik Bioline 1RK91™ needles (AB Sandvik, Sweden)
- Diamond-coated surgical blade (surface roughness 20-40 nm) – *on the market*
  Diamaze PSD (GFD Gesellschaft für Diamantprodukte mbH, Germany)

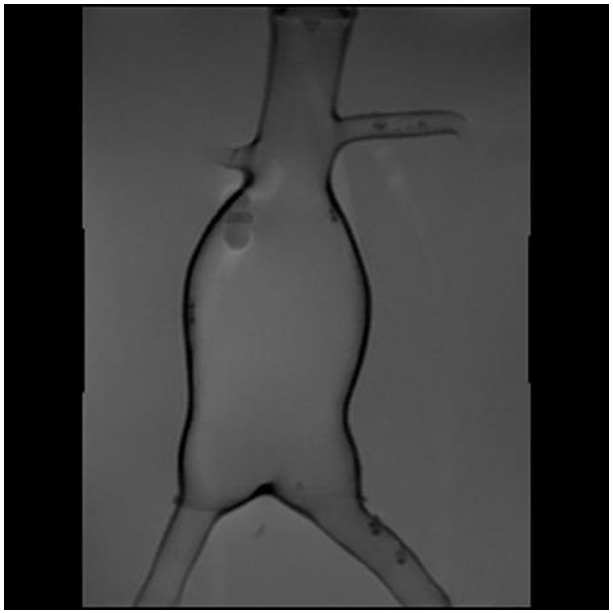
Cardiovascular interventions in MRI/Fluoroscopy

- **Contrast agents such as SPIOS** (iron oxide nanoparticles, 20 nm for injection- e.g. ResoVist (on the market)
- **Guidewire with SPIOS inside-** CE certifed (tip visible in MRI)
  Nano4Imaging GmbH, Germany)

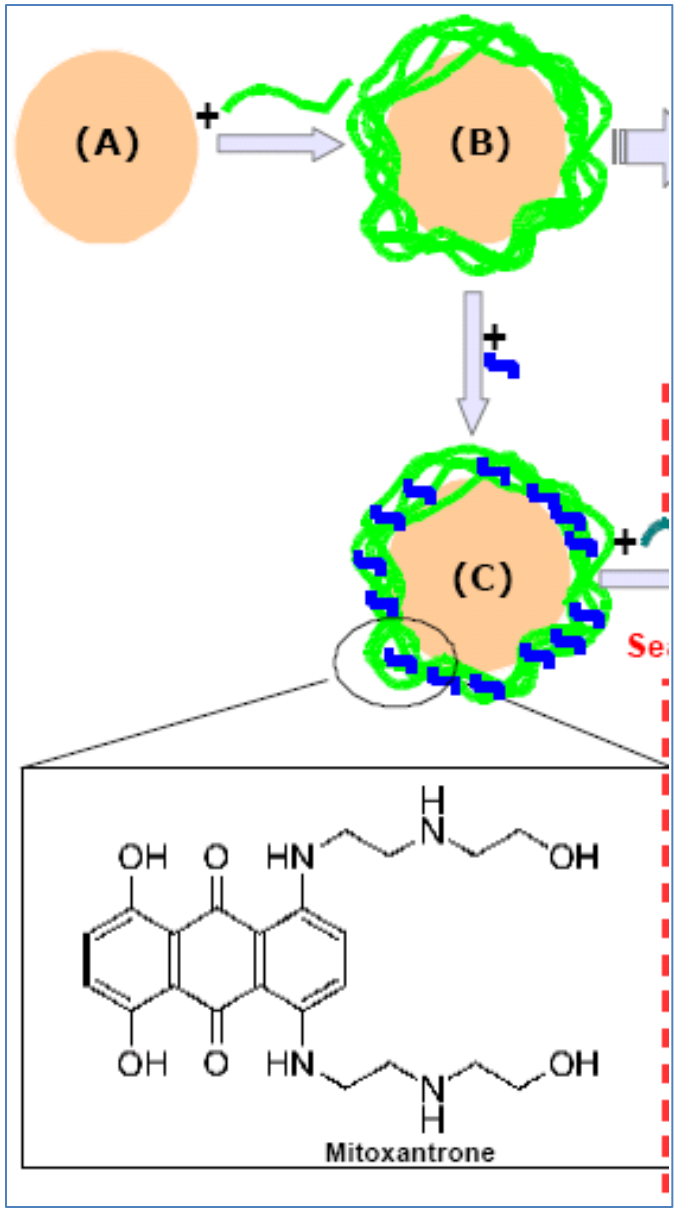
Right renal artery stenting



Moving in phantom



In both cases rings of SPIONS on the guidewire cause an image artifact Int the magnetic field.

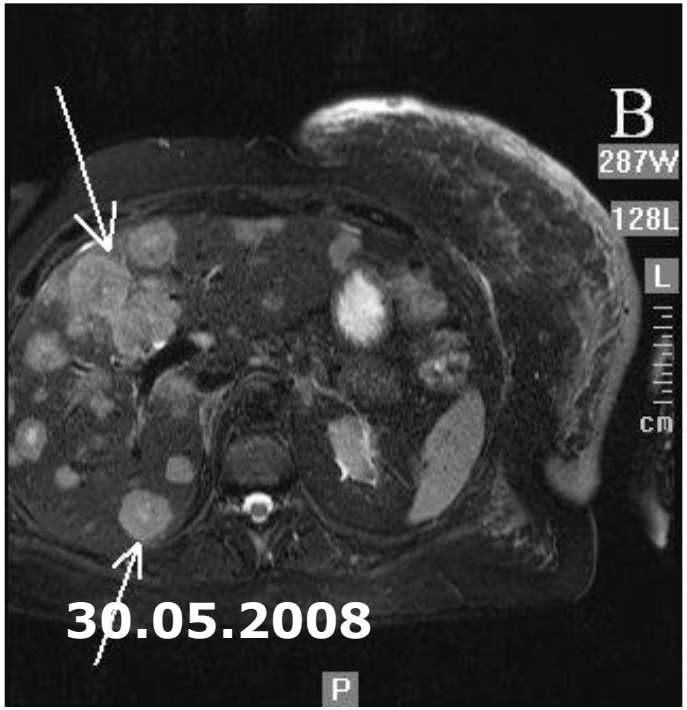


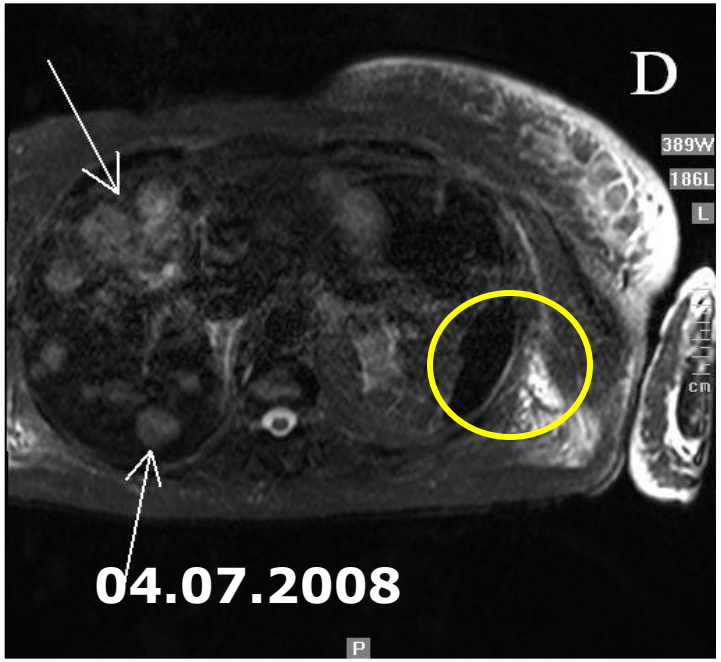
Mitoxantrone loaded on dextrane-coated Iron nanopartciles

Particle size: 256 nm
Particle concentration: 20 mg/ml
Drug payload: 0.6 mg/ml
Total iron: 6.3 mg/ml
Stability: > 3 months
Sterile: bioburden (-), LPS < 2 EU/ml
Application: by infusion

Dose MT: 25- 100 mg/m^2,

Patient study: mitoxantrone-FF (100 mg/m^2) liver metastasis reduced from 14.9 to 8.0 cm^3 in 4 weeks





Biological evaluation of nanomaterials?

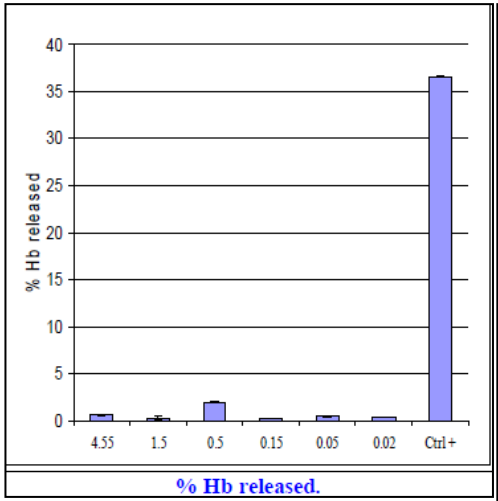
- Not different from normal chemicals
- REACH and nanomaterials (1: 2008; 2: 2012, and recently public consultation completed, june 2014), see e.g.

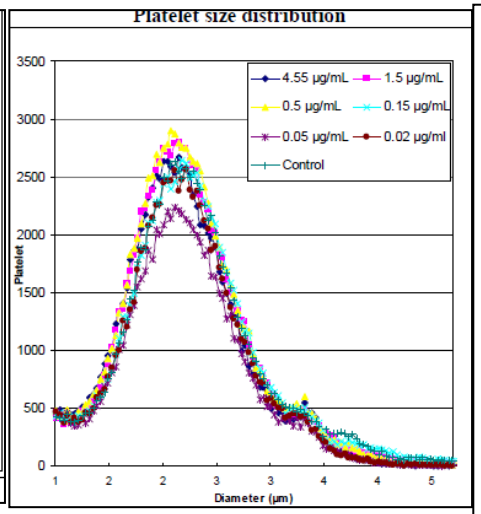
http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012SC0288&from=EN

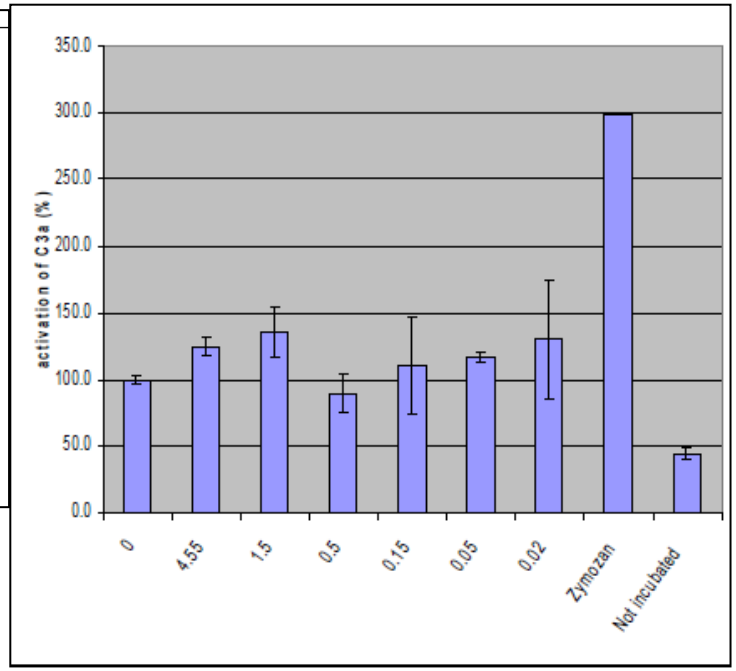
- SCENIHR advice on testing of medical devices with nanomaterials (june 2014).

Worst-case testing at start

- Imagine all particles are released at one time
- Study relevant acute effects in compartment of release (blood)







No effect of Hb-release, platelet aggregation
Or complement activation (C3a)

Testing of a medical device with nano inside?

Table A.1 — Evaluation tests for consideration

Medical device categorization by			Biological effect							
nature of body contact (see 5.2)		contact duration (see 5.3) A – limited (≤ 24 h) B – prolonged (> 24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Category	Contact									
Surface device		A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

[a] The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

ISO 10993-1

Biological evaluation of medical devices —

Part 1:
Evaluation and testing within a risk management process

New regulation coming up?

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

July 17th 2014, comments possible untill november 1st 2014

New regulation coming?

The use of nanomaterials in medical devices poses a challenge for the safety evaluation and risk assessment of these medical devices as the specific character of the nanomaterial used should be taken into consideration. The various aspects of safety evaluation and risk assessment of medical devices containing nanomaterials are addressed in this Guidance. The use of nanomaterials in medical devices can vary considerably. Examples are the use of free nanomaterials being a medical device and administered to the patient as such (e.g. iron oxide or gold nanomaterials for heat therapy against cancer), free nanomaterials in a paste-like formulation (e.g dental filling composites), free nanomaterials added to a medical device (e.g nanosilver as antibacterial agent in wound dressings), fixed nanomaterials forming a coating on implants to increase biocompatibility (e.g. nano-hydroxyapatite) or to prevent infection (e.g. nano-silver), or embedded nanomaterials to strengthen biomaterials (e.g. carbon nanotubes in a catheter wall). In all these cases, the potential exposure to the nanomaterials should be considered. It is additionally recognised that wear and tear of medical devices may result in the generation of nano-sized particles even when the medical device itself does not contain nanomaterials.

This Guidance is aimed at providing information to help with safety evaluation and risk assessment on the use of nanomaterials in medical devices that should be considered in conjunction with the ISO 10993-1:2009 standard. The Guidance highlights the need for special considerations in relation to the safety evaluation of nanomaterials, in view of the possible distinct properties, interactions, and/or effects that may differ from conventional forms of the same materials.

For the risk evaluation of the use of nanomaterials in medical devices, a phased approach is recommended based on potential release and characteristics of the nanomaterials.

Major messages

- No best test (vivo or vitro) available
- Safety by design materials and products
- Test your materials before use and modify where possible
- Consider added value of nanomaterial in different steps for product use (insertion, manipulation, operation)
- Prevent release and/our contact is preventing risk. This can be done by embedding in polymers, coatings or confined compartiments.
- Keep reminding everyone why nano is inside:

  necessary, nice to have, USP, competition, costs

Nanomaterials: 3 Challenges for testing medical devices

- **Biocompatibility:**
  Rethink the Big Three (Cytotoxicity, Sensitization & Irritation Testing).
- **Risk-benefit analysis** : Putting iron oxide nanoparticles in a disposible product reduces radiation exposure (life time cancer risk, iv contrast agent effects (kidney).
- **Environmental and ecotox effect** to be included for disposables and drugs. Materials considered harmless (ZnO) can have specific ecotox.

Communication?

- Express unique properties for product
- Indicate your steps to come to selection and inclusion in product.
- Communicate what you have done to mimimize risks and how the risk related to nanomaterials affect your product.
- Communication needed to customer and in value chain
- Educate legislator and auditos, joint product responsbibility.

More information and support?

- scientific perspectives on hazard assessment, from NanoMILE
  scientific perspectives on fate assessment (NanoFATE)
  scientific and pre-regulatory perspectives for safety-by-design, (NanoREG II)
  regulatory perspectives (ECHA or NanoMILE)
- Workshops and best-practice development in relation to sustainable use of nanomaterials (SUN, GUIDE, NanoSUSTAIN)
- Education on nano-opportunities en risks (NanoEIS)
- Private initiatives (NanoHouse; NanoBCA; IoN;
- National working groups (Dechema,