NanoSafety Cluster

WG2 Hazard Identification

WG2 Hazard Identification

Chairs:
Flemming Cassee
Teresa Fernandes

120 members -> small percentage active participation

NanoMILE

Focus groups and tasks

- Information exchange of methods available within the Cluster
- Harmonised methods/requirements for biokinetic investigation
- Create summaries of key results for further use by the dissemination group
- Immunosafety focus group
- Marine Ecotox focus group

  } eco-immunosafety
- Reprotoxicology focus group
- Genotoxicity Focus group

Inactive: biomembrane interactions:

Protocol Database

NanoSafety Cluster

EU NanoSafety Cluster

Home | Cluster Projects | EU NanoSafety Working Groups | International Cooperation | Shared Resources | News and Events | Intranet | Contact

You are here: Home » EU NanoSafety Working Groups » 2. Hazard WG » **Protocols**

- 1. Materials WG
- 2. Hazard WG
  - WG2 Hazard meetings and events
  - Information exchange
  - Harmonised methods
  - Summaries of key results
  - Upcoming meetings
  - Immunosafety Focus group
  - Marine Ecotox Focus group
  - Biomembrane Focus group
  - Genotoxicity Focus group
  - Protocol Database

Protocols

Define groupings and calculations

Category:	Other Category:	1. Name(s) of scientific protocol:	2. Scope and Domain:	3. Principle of the scientific proto
(All)	(All)	(All)	(All)	(All)
Biokinetics	0	1	2	
Eco-nanotoxicology				
Eco-nanotoxicology				

WIKI

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Page | Discussion | Read | View source | View history | Go | Search

Navigation

- Main page
- Community portal
- Current events
- Recent changes
- Random page
- Help

Toolbox

- What links here
- Related changes
- Special pages
- Printable version
- Permanent link

NSC WG2-Hazard Wiki

This WIKI to facilitate sharing knowledge on the hazard assessment obtained in primarily FP7 projects. This includes outcomes that contribute to answer specific questions on the hazard of nanomaterials and also do's and don't's during experiments, sharing protocols. To add your information you should register (as WG2 Hazard[1] member) via [2] or contact Flemming Cassee or Teresa Fernandez at [wg2chair@nanosafetycluster.eu]. Go to the nanosafety cluster website [3] for more information on this working group.

Key messages from FP7 NanoSafety project: what have we learned?

Methods/requirements for kinetic investigation

Methods/requirements for appropriate toxicological endpoints

Methods/requirements for appropriate in vitro tests (e.g. cell lines)

Comparison in-vitro versus in-vivo results

Validation of appropriate testing methods including identification of limitations

Requirements for screening tests

Key metrics (metrology) for assessing the relationship between dose and hazard

Doesn't work, no input

Protocols

- **Marine nantoxicology field progressing very well**
  - Two workshops organised
  - Two journal special issues summarising developments in the field

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- **Immuntoxicology**
  - Int Congress of Immunology (Milano, Italy, August 22-27, 2013):, workshop
  - Boraschi, D. & A. Duschl (authors/editors). 2014. Nanoparticles and the immune system: safety and effects

- **Genotoxicology**
  - OECD nanotoxicology workshop Genotoxicity in Ottawa, November 2013

- **Reprotoxicology**
  - Workshop & review reprotoxicology & (inhaled) nanosized particles and fibres

- **Review** effects on central nerve system of nanosized particles

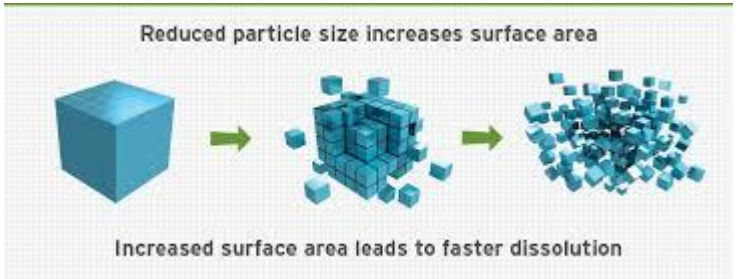
- **NanoSafety Forum** for Young Scientists Syracuse okt 2014

Development of Check list

- Sample preparation→ OECD or ISO
- In vitro human
  - Dosimetry ref to Teeugarden et al
  - Metrology: depends on hypotheses
  - Dose: suggest not to go higher than 100 ug/cm2 and provide dose-response information
  - EC50 useful for RA
  - Characterization in media that is used
    - DLS may not be appropriate for bimodal or multi model distribution
  - What do you know about the purity and contamination including endotoxins including in the suspensions used for test systems.
  - Justify the route of exposure
  - Inclusion of positive and negative controls is to be preferred
    - e.g use silver ions when studying silver particles
  - Consider benchmark or reference material to allow comparison with other studies

FP-7 self review

- Significant **better understanding** of
  - the importance of description of the dispersion state of NPs in fluids;
  - the methods used to generate this dispersion;
  - the impact on hazard in both human and environmental toxicity tests.
- At the start of FP7, there was evidence that **size and surface** area could influence particle toxicity.
  - The research of FP7 has expanded this considerably to demonstrate the importance of solubility, charge, composition, coating, functionalization, agglomeration, and importantly the protocol used to assess the hazard.



Nanoparticle
Size, shape and surface area
Surface charge, energy, roughness and porosity
Valence and conductance states
Functional groups
Ligands
Crystallinity and defects
Hydrophobicity and hydrophilicity
Suspending media
Water molecules
Acids and bases
Salts and multivalent ions
Natural organic matter (humics, proteins, lipids)
Surfactants
Polymers
Polyelectrolytes
Solid–liquid interface
Surface hydration and dehydration
Surface reconstruction and release of free surface energy
Ion adsorption and charge neutralization
Electrical double-layer formation, zeta potential, isoelectric point
Sorption of steric molecules and toxins
Electrostatic, steric and electrosteric interactions
Aggregation, dispersion and dissolution
Hydrophilic and hydrophobic interactions
Nano–bio interface

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FP-7 self review

- Considerable evidence to support the original hypotheses of **oxidative stress and inflammation** and their role in the mode of action of different types of nanomaterials,
  - allowing standardised methodologies to be considered.

- The role of the **corona** in determining NM behaviour that could influence fate and behaviour, including uptake and toxicity.

FP-7 self review

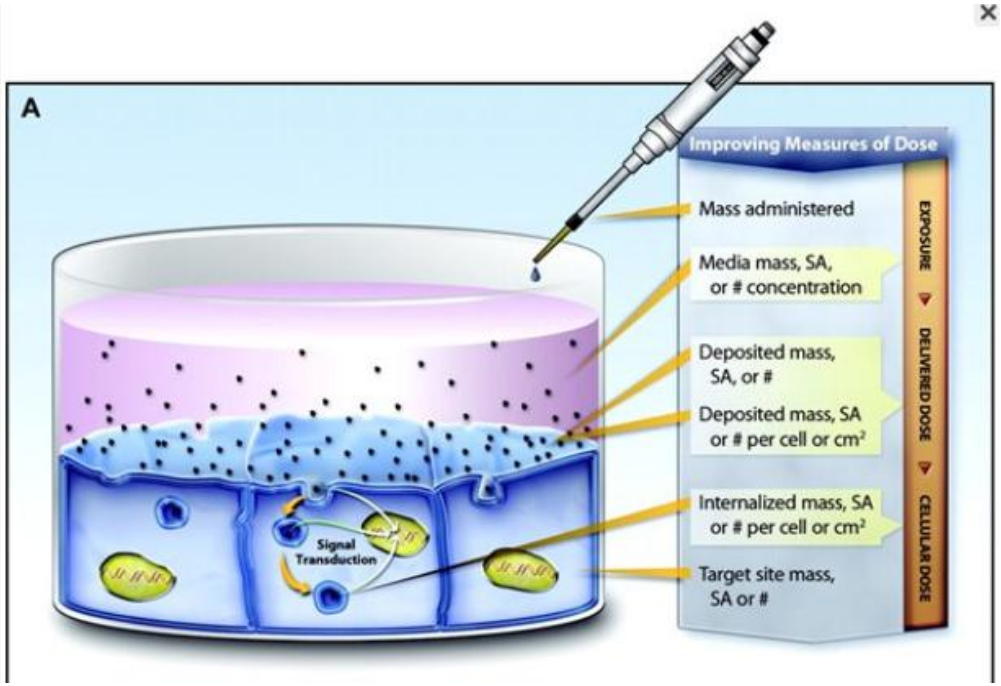
WG2 Hazard Identification

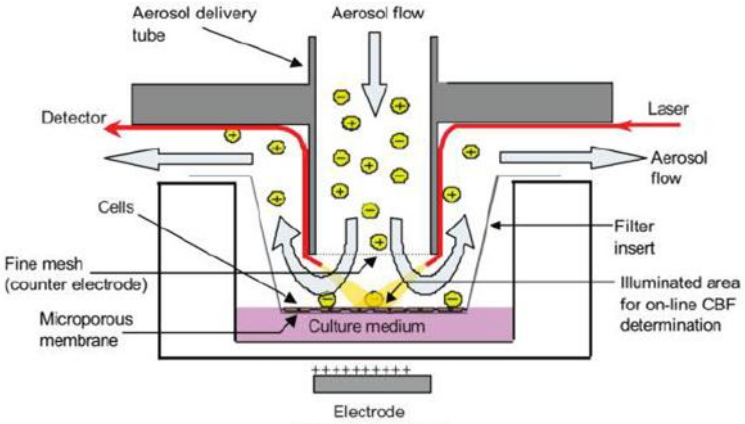
- Considerable progress has been made in the understanding that
  - **exposures** in toxicological test systems need to be **characterized**, and
  - one cannot rely on the physical-chemical data provided by the supplier.

- There is now a broader understanding of how nanomaterials can **interfere** in a wide variety of assay types
  - Improved control measures to identify and overcome such issues.
  - More work is required to make such controls more uniform across the research (and consultancy) field.
  - Protocols have been made available from other users

FP-7 self review

- Improved understanding on dosimetry and flux





FP-7 self review

- Nanomaterials have a high likelihood to pass biological barriers such as the lung-blood or gut-blood

nature nanotechnology | VOL 3 | JULY 2008 | 423 LETTERS

Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study

CRAIG A. POLAND[1], RODGER DUFFIN[1], IAN KINLOCH[2], ANDREW MAYNARD[3], WILLIAM A. H. WALLACE[1], ANTHONY SEATON[4], VICKI STONE[5], SIMON BROWN[1], WILLIAM MacNEE[1] AND KEN DONALDSON[1]*

The Journal of Toxicological Sciences (J. Toxicol. Sci.)
Vol.33, No.1, 105-116, 2008

Original Article

Induction of mesothelioma in p53+/– mouse by intraperitoneal application of multi-wall carbon nanotube

Atsuya Takagi[1], Akihiko Hirose[2], Tetsuji Nishimura[3], Nobutaka Fukumori[4], Akio Ogata[4], Norio Ohashi[4], Satoshi Kitajima[1] and Jun Kanno[1]

TOXICOLOGICAL SCIENCES 110(2), 442–448 (2009)
doi:10.1093/toxsci/kfp100
Advance Access publication May 8, 2009

Sakamoto Y, Nakae D, Fukumori N, Tayama K, Maekawa A, Imai K, Hirose A, Nishimura T, Ohashi N, Ogata A.

Induction of mesothelioma by a single intrascrotal administration of multi-wall carbon nanotube in intact male Fisher 344 rats.

The Journal of Toxicological Sciences, 34, 65-76, 2009

Absence of Carcinogenic Response to Multiwall Carbon Nanotubes in a 2-Year Bioassay in the Peritoneal Cavity of the Rat

Julie Muller,* Monique Delos,† Nadtha Panin,* Virginie Rabolli,* François Huaux,* and Dominique Lison*,[1]

Fibre Paradigm

Thin

Small aerodynamic diameter enables deposition beyond the ciliated airways

Bio-persistent

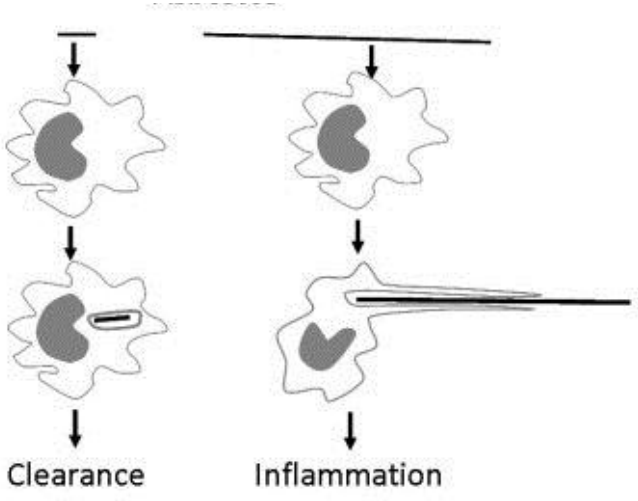
Retains its long term shape over long-term residence in the lungs

Long

Cannot be completely enclosed by a macrophages producing frustrated phagocytosis

Longer than 15-20µm

- Metal wires
- CNTs
- asbestos



- Fibrous shape represents an attribute conveying enhanced toxicity to a particle due to the physical hindrance of normal clearance from the thoracic region and interaction with cells

FP-7 self review

WG2 Hazard Identification

- **No unexpected mechanisms** of acute toxicity have been identified compared to what is already known for larger non-nanosized particles.
  - This is therefore a significant step forward. The most important insight of the past research is that concepts of modes of actions of particles that were established in particle toxicology are still valid.

- The **relevance** of the current **dispersion and exposure protocols** for hazard studies need to be investigated in order to optimize them to better represent real life exposure scenarios

Achievements (environmental field)

- Outcomes of FP7 funded projects
  - The **standard RA tools** can be used for nanomaterials with some minor modification
  - Accounting for **ionic toxicity** of the metal nanomaterials involved on a simple mass basis would cover (most of) the hazard presented by metal NMs
  - NM hazard on a mass basis is unlikely to exceed that of ionic metals,
  - uptake and short term accumulation might be higher for ENM derived metals, and that the real risk differences lie on the Fate and Exposure pathways.

WG2 Hazard Indentification

- Thank you and all the contributors to the summary/synopsis/self-review

http://tinyurl.com/wg2hazard