

Current knowledge on nanomaterial toxicity: Implications for assessing product safety at the end of the life-cycle

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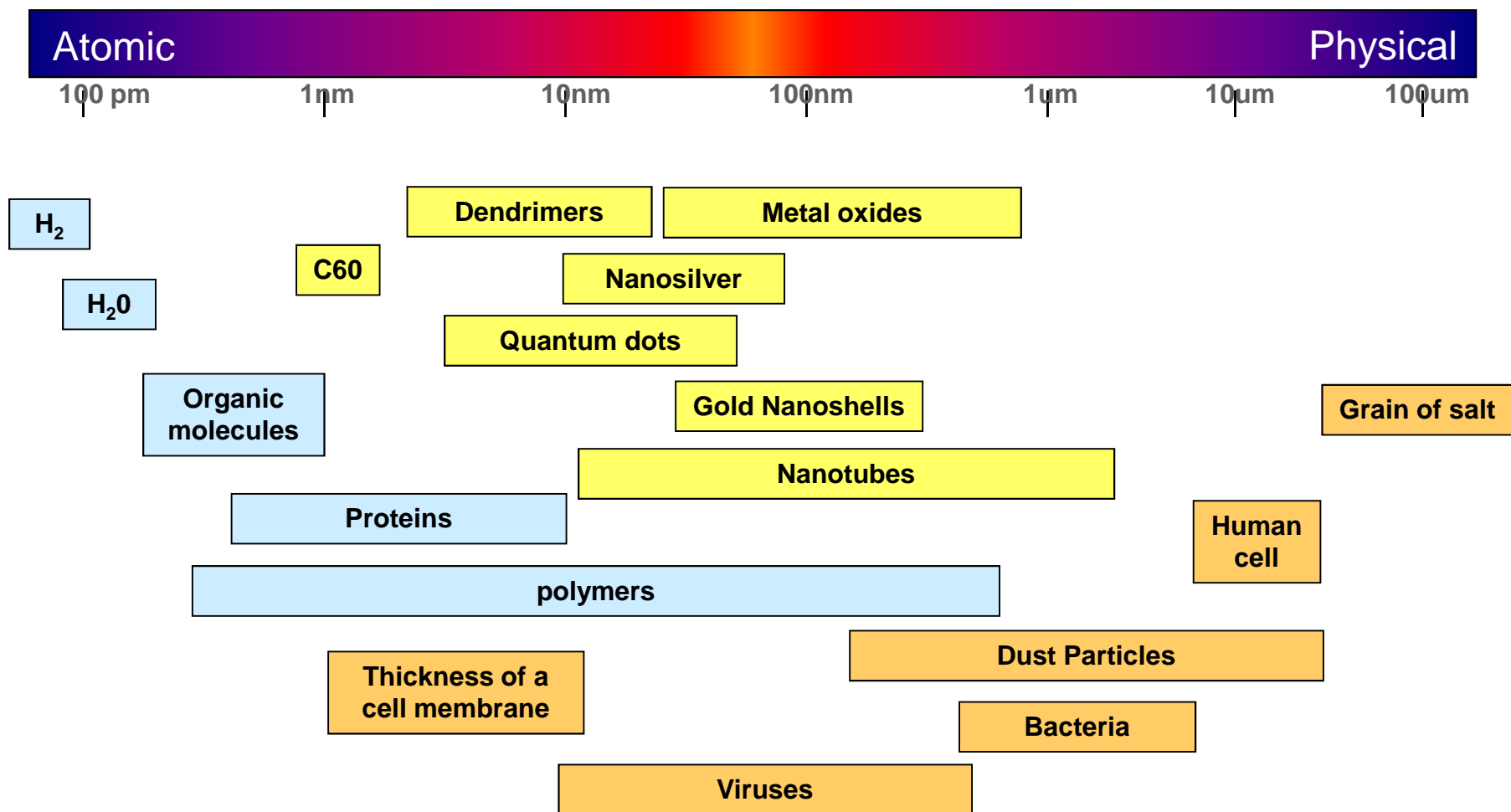
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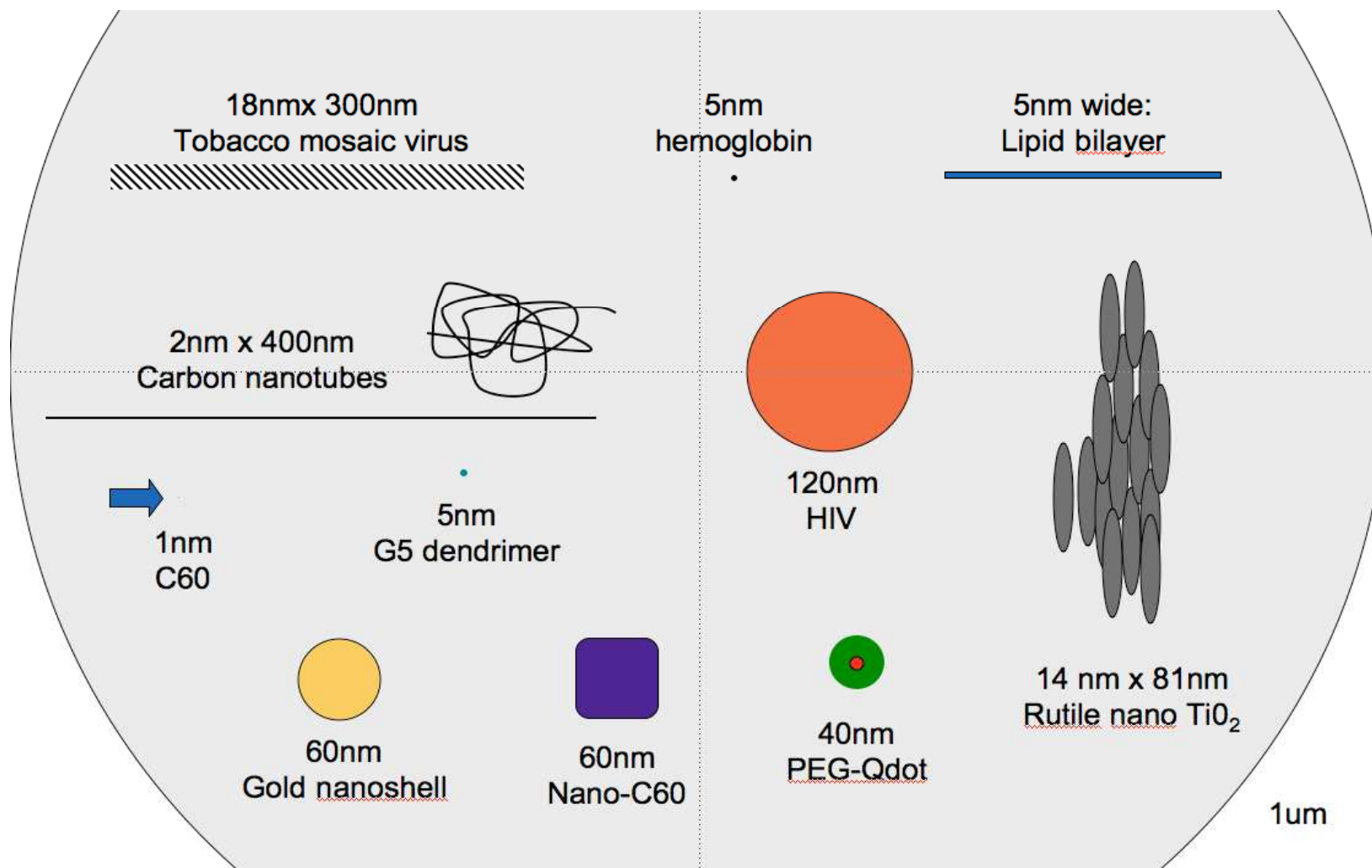
Some key issues for nanomaterial toxicology

- All nanomaterials are not the same!
- Pharmacokinetics differ as nano properties change!
- Mass based “dose” may be inadequate to assess relative risk!
- Small size can create new properties and new modes of action!
- Characterization of nanomaterials requires new skill sets!

“Nano-sized” is already part of our knowledge base

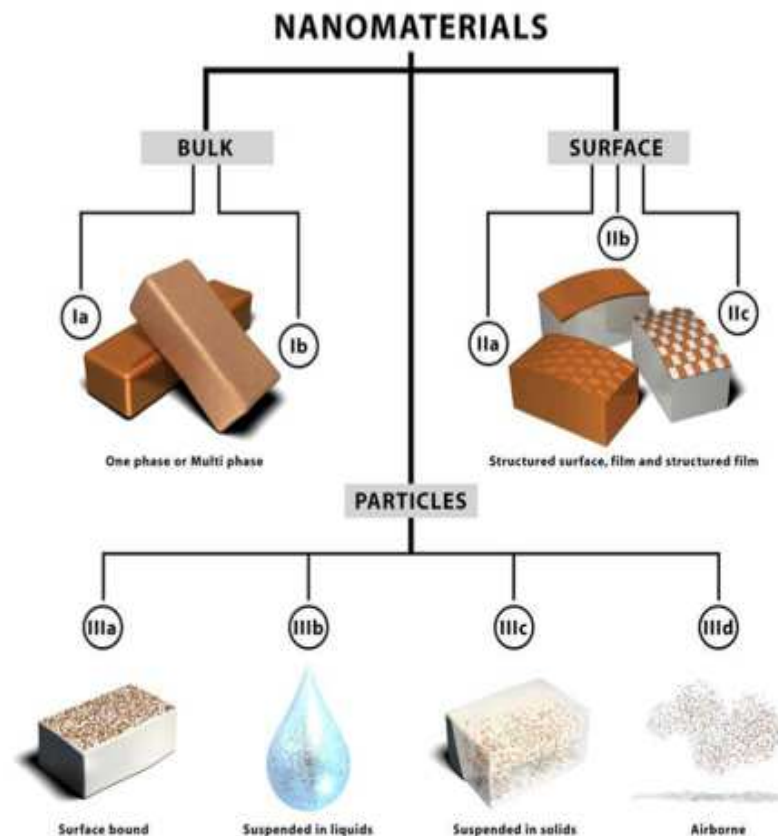


Diversity of size and shape of “nanomaterials”



Contexts for use and exposure to nanoscale materials

- Class I- Bulk
 - A-One phase in bulk
 - B-Multiphase
- Class II- Surface
 - A-Structured surface
 - B-Film
 - C-Structured films
- Class III-Particles
 - A-Surface bound
 - B-Suspended in liquids
 - C-Suspended in solids
 - D- Airborne



Increased uptake of nanoscale vs microscale particles

- Jani et al 1990.
- Uptake of polystyrene microspheres
 - 50, 100, 300, 500, 1000 and 3000 nm
 - Oral administration to female SD rats
- Size dependent increase in uptake
- As particle size changes so does the bioavailability

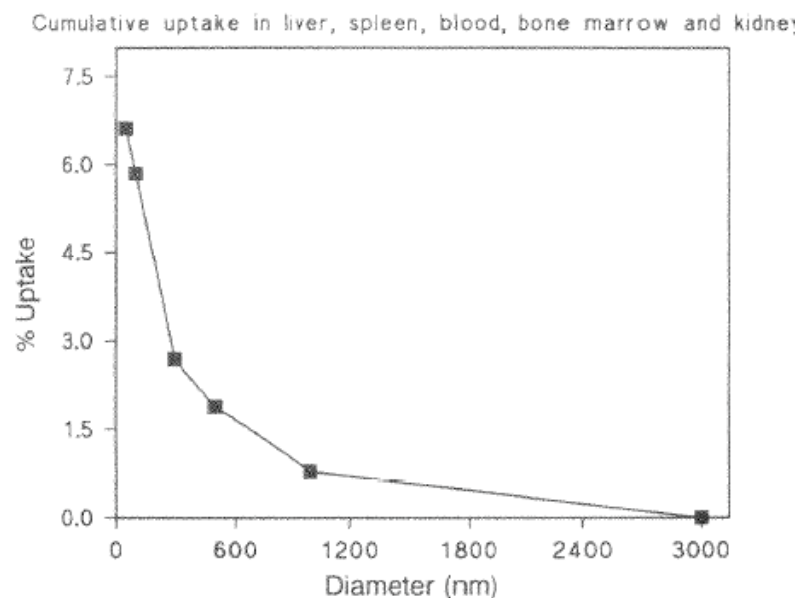
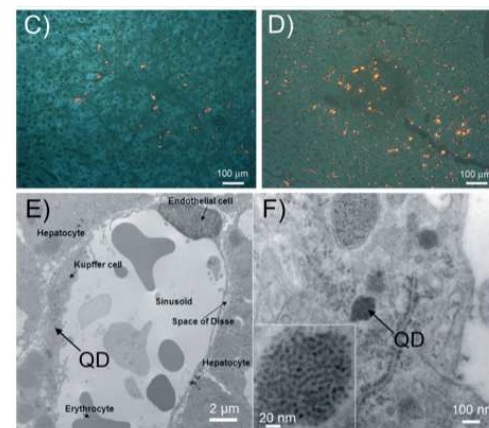
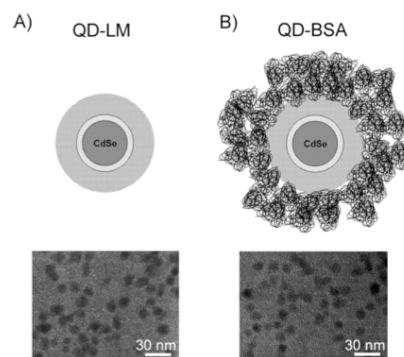
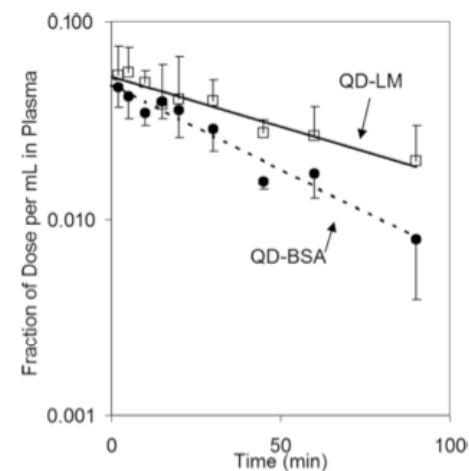


FIG. 7. The cumulative uptake of polystyrene, orally administered to female Sprague Dawley rats for 10 days at a dose of 1.25 mg kg^{-1} , as a function of particle diameter in the liver, spleen, blood, bone marrow and kidney. In the case of particles of 500 nm and $1 \mu\text{m}$ these data refer only to liver and spleen as no microspheres were detected in blood, bone marrow and kidney. For the 300 nm latex the data refer to liver, spleen and blood.

Surface changes modifies kinetics

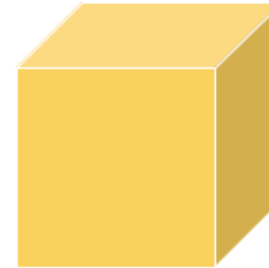
- Quantum dot pharmacokinetics
 - Fischer et al 2006
 - Male SD rats; i.p injection.
 - BSA vs lysine/mercaptoundecanoic acid coated
- Longer half life for uncoated Qdot



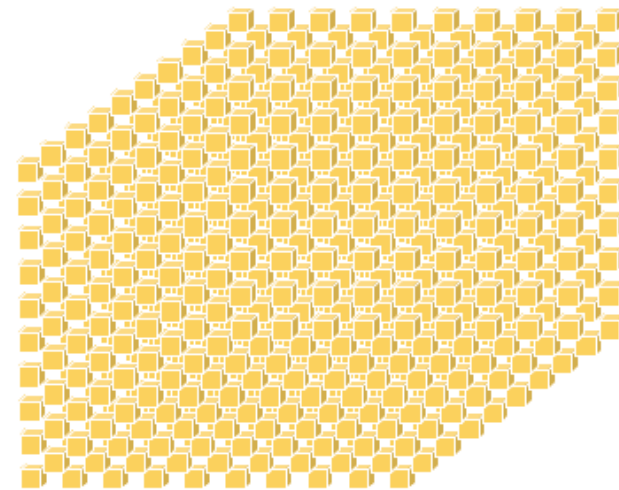
Effects may be related to surface area based “dose”

- 1 μ m cube
 - e.g. respirable particle
 - Surface area of = 6 μ m²
- 100nm cube
 - 1000 cubes is equivalent volume
 - Surface area = 60 μ m²
- 10x more surface area for the same mass

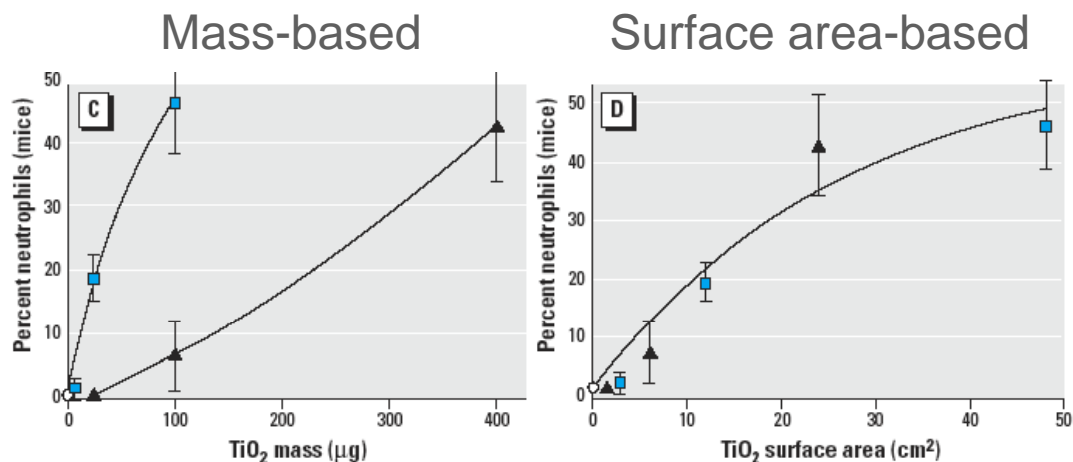
1 μ m cube



1000 x “100nm” cubes



Surface area metrics: A key consideration



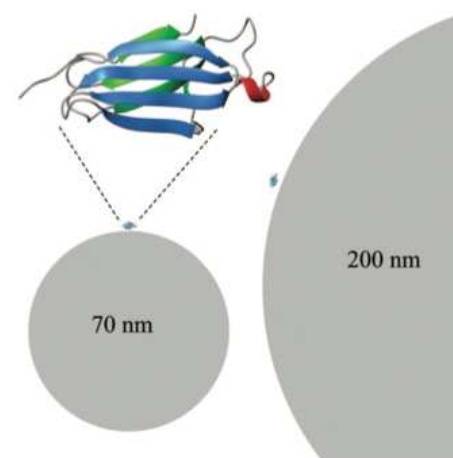
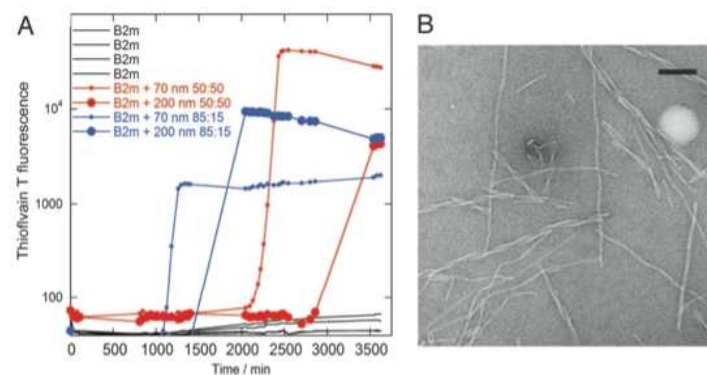
- Particle number-based and surface area-based metrics increase with decreasing particle size
- Mass-based potency may differ, but surface area-based potency may not
- Requires studying particles of similar composition but varying particle size, coatings, shape or other physicochemical parameter

Nanomaterial characterization requires new skills sets

- Chemical:
 - Unequivocal Identity
 - Spectroscopic techniques
 - Physical Constants
 - Purity Determination
 - Chromatographic Analyses – (Organics)
 - Inductively Coupled Plasma/AES or MS, XRD - (Inorganics)
 - Water Determination
 - Elemental Analysis
 - Constituents identified when at < 1 %, (primary and byproducts)
 - Byproducts when between 0.1 and 1 %,
- Nanomaterial:
 - Size, shape and size distribution
 - Electron microscopy
 - Atomic force microscopy
 - Dynamic light scattering
 - XRD-Crystalline state
 - Surface area
 - BET analysis
 - Charge
 - Zeta potential
 - Surface chemistry
 - Stoichiometry of targeting molecules on surface

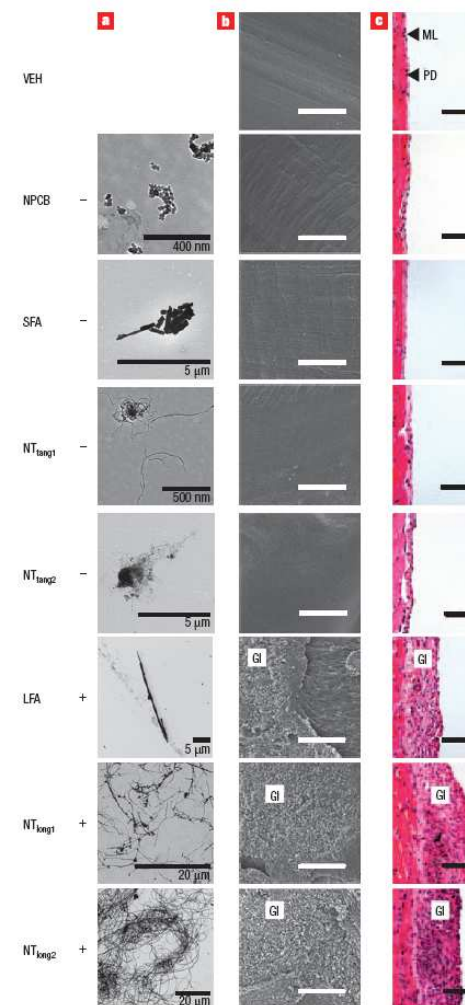
Protein fibrillation in vitro induced by nanoparticles

- Linse et al 2007, PNAS 104,8691
- Induction of b2-microglubulin protein fibril formation in vitro
 - Surface assisted nucleation
- Observed with multiple NPs
 - 70, 200 nm NIPAM/BAM NPs
 - 16nm Cerium oxide NPs
 - 16nm quantum dots
 - 6nm dia MWCNTs
- Fibril formation is implicated in development of human disease
 - Alzheimer's
 - Creutzfeldt-Jakob disease
 - Dialysis related amyloidosis



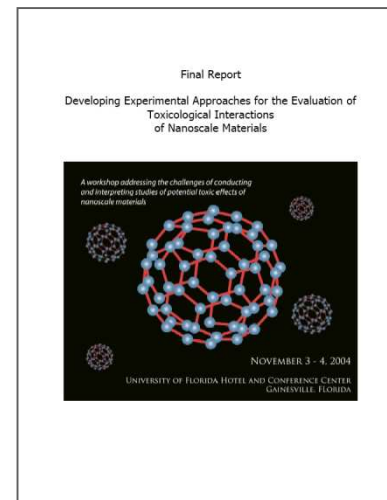
“Asbestos like” activity of long MWCNT

- Poland et al 2008
 - Nature Nanotech 3:423
- Injection to C57Bl6 mice
 - 50ug or vehicle into peritoneal cavity
 - Evaluation at 7 days
- Pathology
 - Inflammation
 - Foreign body Giant Cells
 - Granulomas
- Long MWCNTs and long fibre amosite (LFA) gave similar responses
- Tangled MWCNT gave different responses



We have experimental strategies to detect hazards

- In vivo toxicity testing models can detect manifestations of novel mechanisms of action if there are any.
 - Based on apical endpoints
- Several workshops/reports with common issues/recommendations
 - NTP workshop on Experimental strategies
 - University of Florida-Nov 2004
 - <http://ntp.niehs.nih.gov/go/100>
 - ILSI-RSI report
 - Oberdorster et al 2005, Particle Fibre Toxicol 2:8
- Use of both in vivo and in vitro approaches
- Need comprehensive physical/chemical characterizations



Key issues for the field of “nanotoxicology”

- “Are nanomaterials safe?” = “Are chemicals safe?”
 - There is no single type of nanomaterial
- Effects can scale with surface area
 - Paradigm shift in how we estimate “dose” for assessing risks relative to other agents.
- Lack of adequate characterization of what a given “test article” is
 - Major obstacle to developing structure-activity relationships
- Nanoscale phenomena occurs at the interface between chemical space and physical space.
- Very limited information on exposures