Nanoparticelle e Apparato Respiratorio

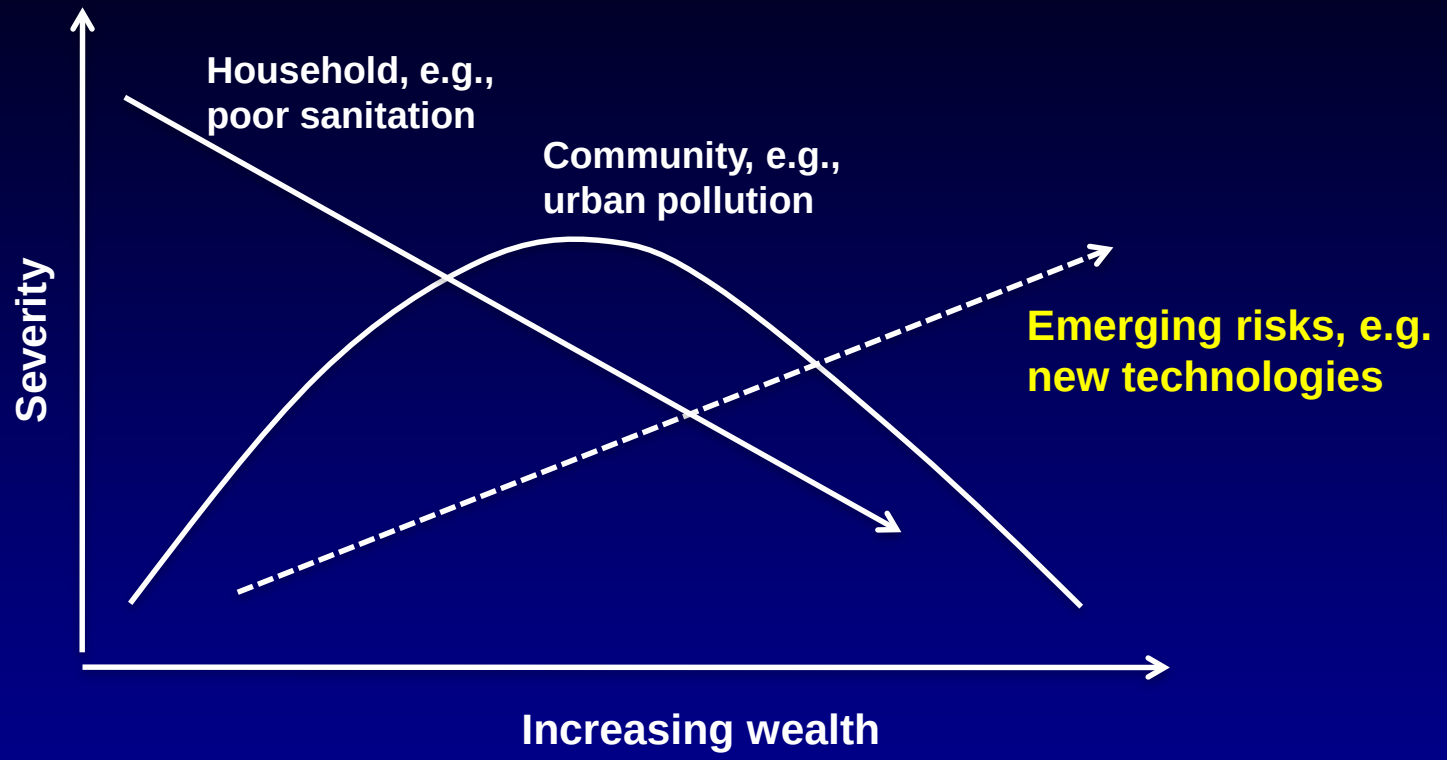
Luigi Manzo

Università degli Studi
Scuola Universitaria Superiore
Risk Centre, Pavia

luigi.manzo@unipv.it

Roma, Corso Sipro Patologie Occupazionali
Apparato Respiratorio, 2 Dicembre 2017

SHIFTING ENVIRONMENTAL BURDEN OF DISEASES



Environmental risk transition framework.

Household risks fall with development, community risks rise and then fall, and emerging risks rise throughout the development process.

INDICE

Effetti biologici e tossici delle nanoparticelle

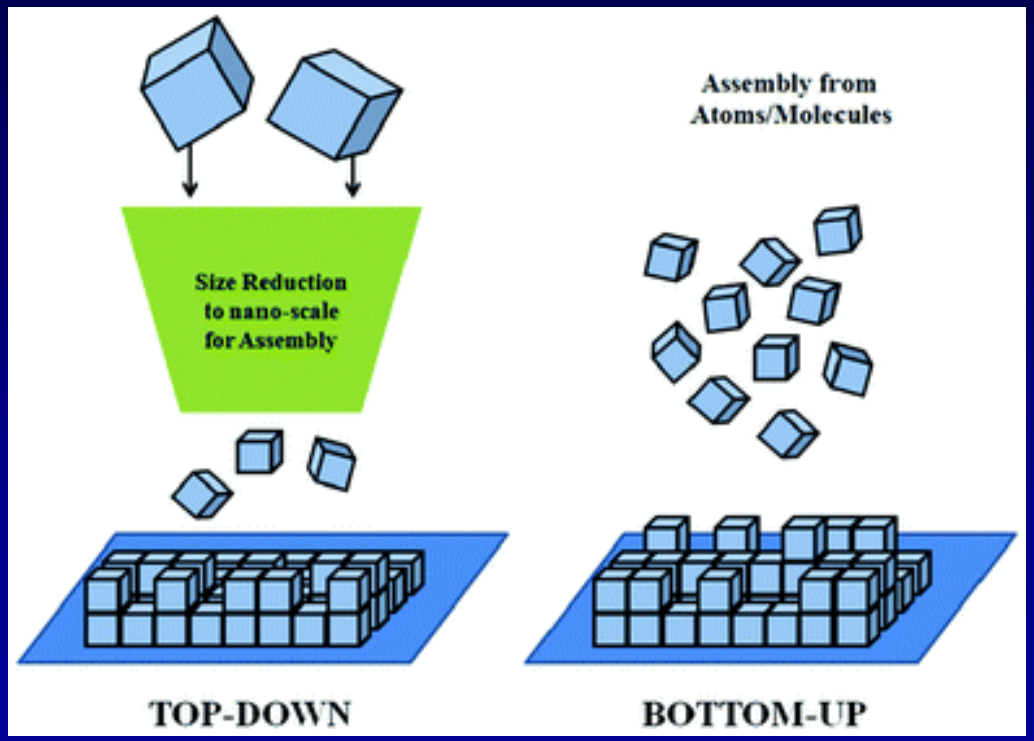
Apparato respiratorio come target di tossicità delle nanoparticelle

Analisi di rischio dell’esposizione occupazionale

Elementi di risk management

NANOTECNOLOGIE

Tecnologie che permettono di manipolare e assemblare la materia nelle dimensioni nanometriche, prossime alla scala atomica e molecolare (in genere, nell'intervallo 1÷100 nanometri).



Un nanometro (1 nm) = un miliardesimo di metro.

Molecola di H_2O: 0.27 nm

Atomo di carbonio: 0.34 nm

Elica del DNA: diametro circa 2 nm

Nanotubi di carbonio: diametro 1.3 nm

Proteine: 1-20 nm

Molecola ATP: circa 10 nm

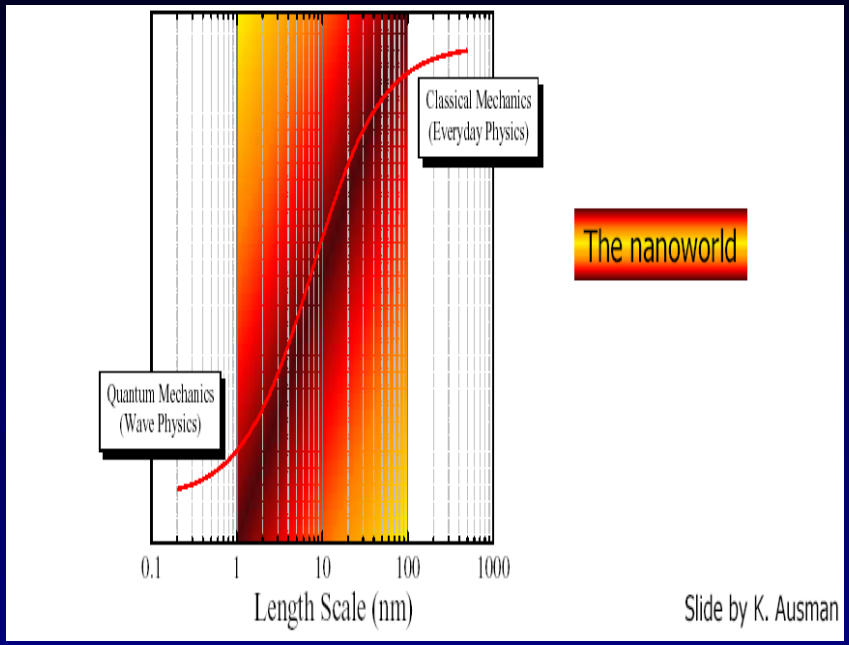
Virus: 100 nm

Batteri: 1000 nm

Globulo rosso: diametro ca. 7.000 nm

Capello umano: diametro 60.000-120.000 nm

L’assemblaggio della materia in dimensione nanometrica comporta cambiamenti delle proprietà fisico-chimiche fondamentali (effetti quantistici): colore, durezza, resistenza, elasticità, conducibiità elettrica, comportamento magnetico, reattività chimica….



.

Materiali prodotti con le nanotecnologie (nanomateriali) sono dotati di proprietà nuove e di funzionalità uniche, talora assai diverse da quelle di prodotti convenzionali aventi identica composizione chimica.

L’alluminio, elemento sostanzialmente inerte, se ridotto in particelle nanometriche, dà vita ad un materiale esplosivo usato come catalizzatore nei carburanti per missilistica.

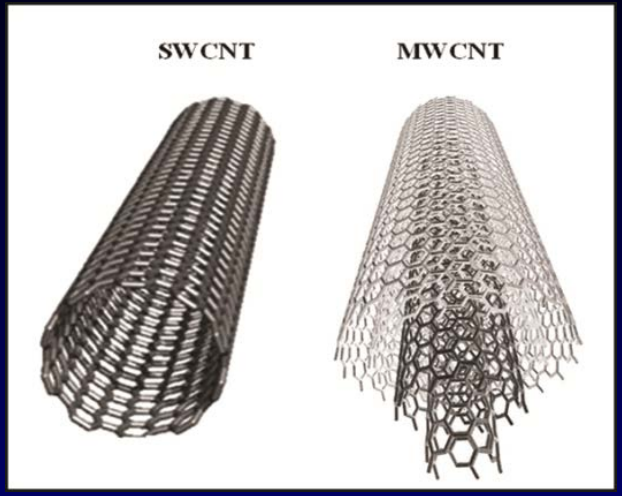
Oro (Macro): giallo

Nano-oro: rosso

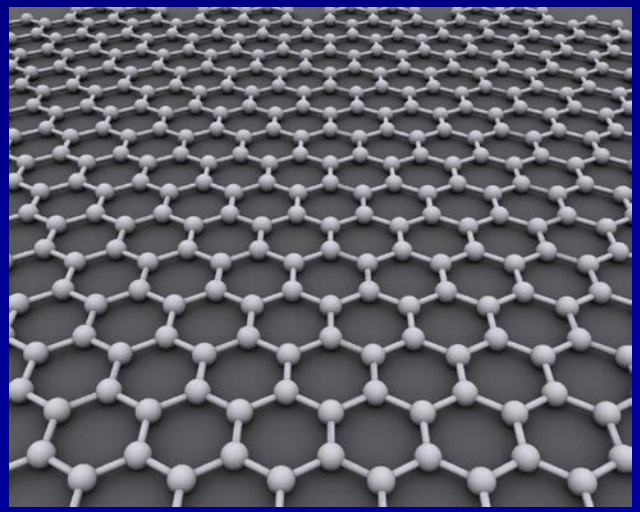
Nanofotonica: il colore varia con la dimensione delle nanoparticelle

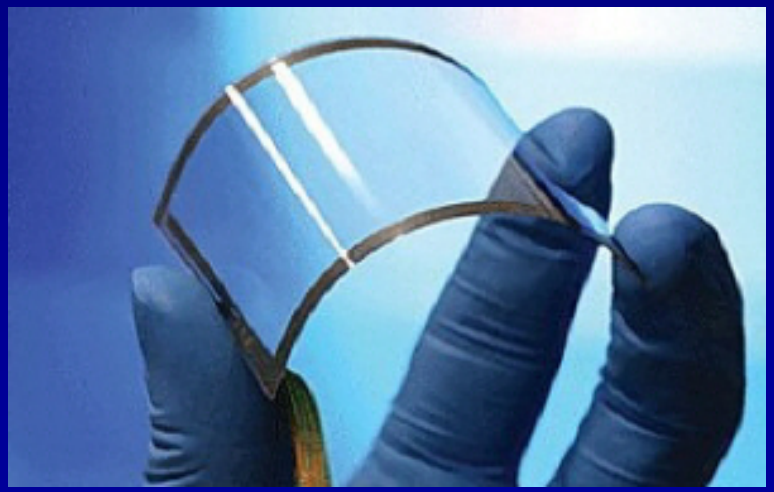
Da K. M. Kulinowski, Nanotechnology “The Big Science of the Very Small”, CBEN

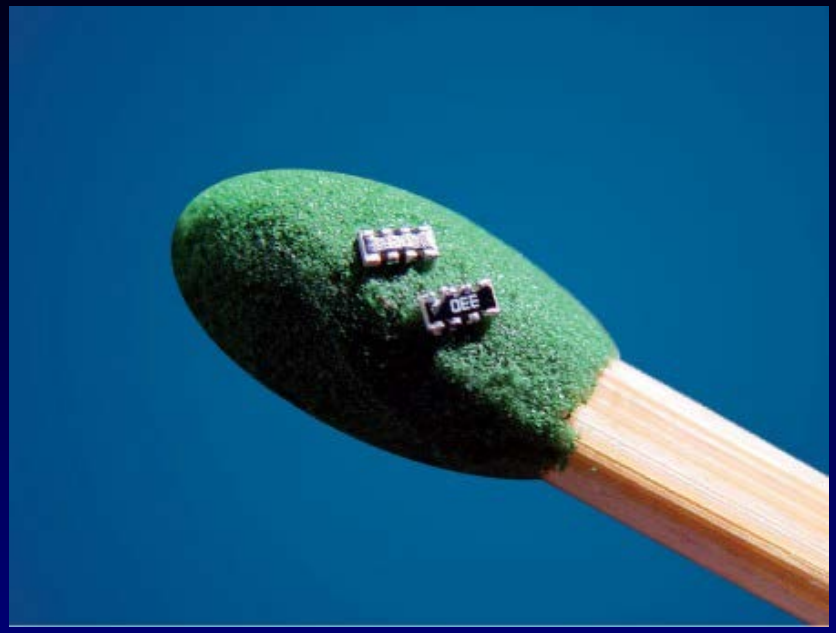
Il carbonio sotto forma di grafite (es. mina delle matite) è relativamente “tenero”; sotto forma di nanotubi di carbonio è 100 volte più resistente dell’acciaio.

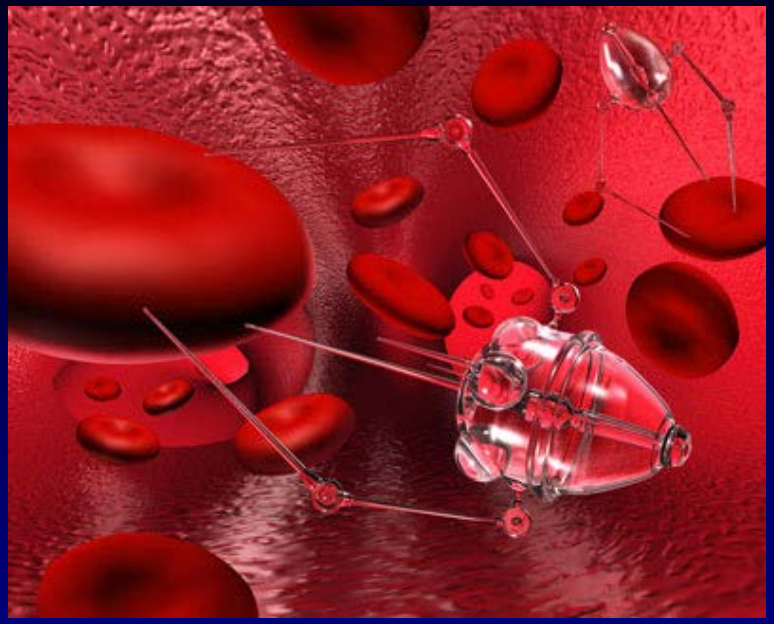


Sotto forma di grafene (materiale costituito da uno strato monoatomico di atomi di carbonio, con spessore equivalente alle dimensioni di un solo atomo), il carbonio ha la resistenza meccanica del diamante e la flessibilità della plastica.



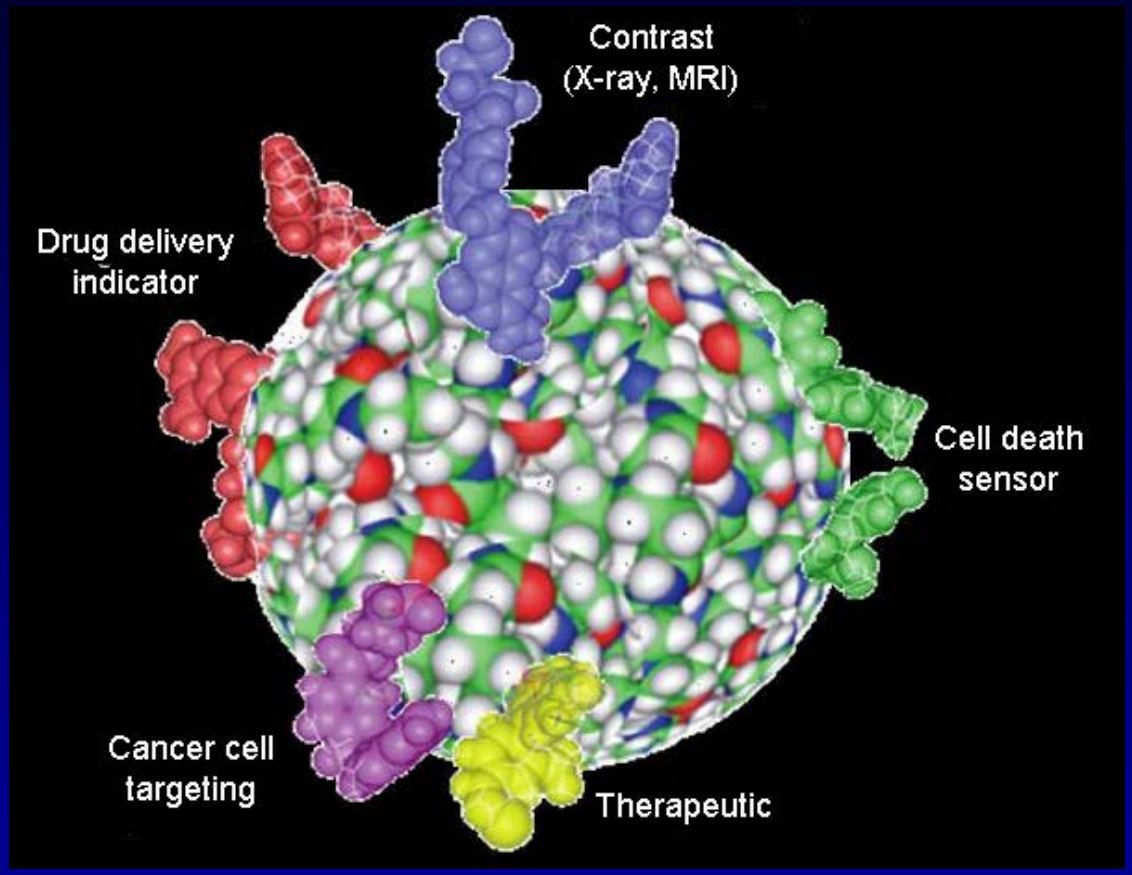






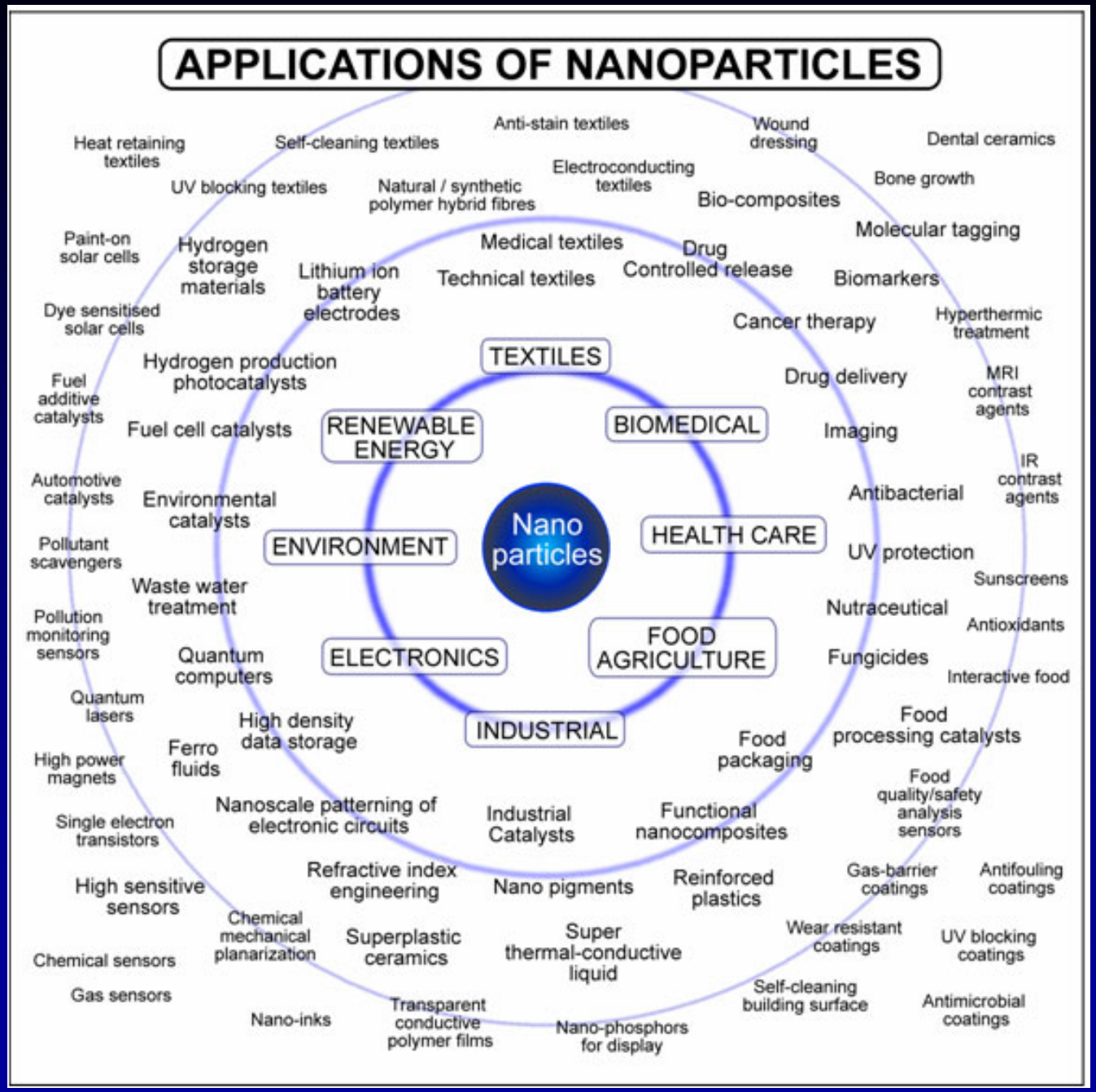
Handheld NMR Biosensor.
Science of Nanoscale Systems and their Device Applications, Harvard University. National Science Foundation 2011

Multi-Functional Nanoplatform for Cancer Diagnosis and Treatment.

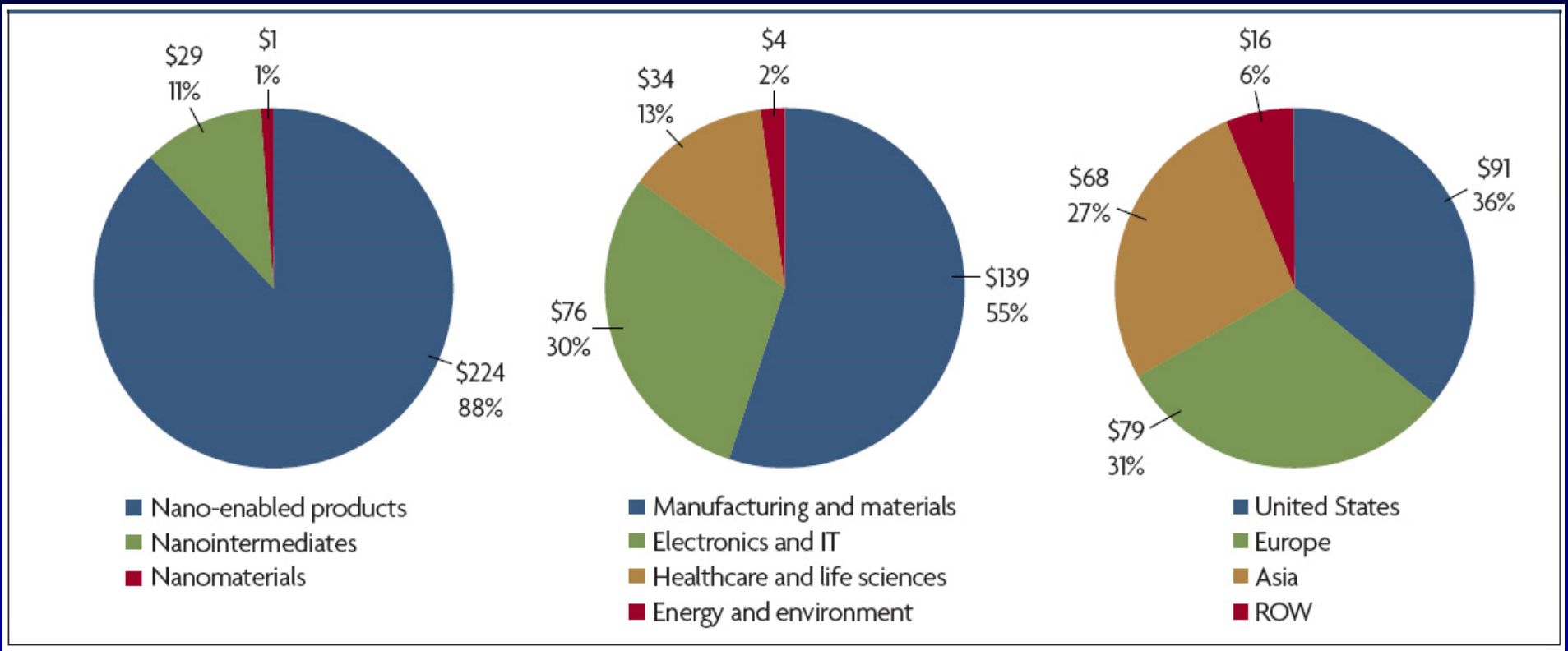


Combined modalities for targeting, imaging, stealth coating, and monitoring.

Geertsma RE et al. RIVM Report 65/07; BMT/RB/RG/cvr


APPLICATIONS OF NANOPARTICLES
Nano particles
TEXTILES
BIOMEDICAL
HEALTH CARE
FOOD AGRICULTURE
INDUSTRIAL
ELECTRONICS
ENVIRONMENT
RENEWABLE ENERGY
Anti-stain textiles
Wound dressing
Heat retaining textiles
Self-cleaning textiles
Dental ceramics
Electroconducting textiles
UV blocking textiles
Natural / synthetic polymer hybrid fibres
Bone growth
Bio-composites
Molecular tagging
Paint-on solar cells
Hydrogen storage materials
Medical textiles
Drug Controlled release
Lithium ion battery electrodes
Technical textiles
Biomarkers
Dye sensitised solar cells
Cancer therapy
Hyperthermic treatment
Hydrogen production photocatalysts
Drug delivery
MRI contrast agents
Fuel additive catalysts
Fuel cell catalysts
Imaging
IR contrast agents
Automotive catalysts
Environmental catalysts
Antibacterial
Pollutant scavengers
UV protection
Sunscreens
Waste water treatment
Nutraceutical
Antioxidants
Pollution monitoring sensors
Quantum computers
Fungicides
Interactive food
Quantum lasers
High density data storage
Food processing catalysts
Ferro fluids
Food packaging
High power magnets
Food quality/safety analysis sensors
Nanoscale patterning of electronic circuits
Industrial Catalysts
Functional nanocomposites
Single electron transistors
Refractive index engineering
Gas-barrier coatings
Antifouling coatings
High sensitive sensors
Nano pigments
Reinforced plastics
Chemical mechanical planarization
Wear resistant coatings
Superplastic ceramics
Super thermal-conductive liquid
UV blocking coatings
Chemical sensors
Self-cleaning building surface
Gas sensors
Antimicrobial coatings
Nano-inks
Transparent conductive polymer films
Nano-phosphors for display

Products touched by nanotechnology generated $254 billion worldwide in 2009.



Rocho MC et al. Science Policy Report 2011

Top 10 Countries in Nanotechnology Patents (2016)

Rank*	Country	No. Nanotech Patents in US	No. Nanotech Patents in Europe
1	**USA**	**4316**	**577**
2	**South Korea**	**914**	**105**
3	**Japan**	**819**	**188**
4	**Taiwan**	**514**	**19**
5	**China**	**416**	**59**
6	**Germany**	**301**	**289**
7	**France**	**210**	**208**
8	**Netherlands**	**136**	**71**
9	**UK**	**123**	**81**
10	**Canada**	**106**	**22**

*** Ranking according to the number of published patents in**

Source: StatNano.com, 2017.

Sectors where occupational exposure to nanomaterials may occur (*list not all-inclusive*)

Chemical industry

Textile industry

Construction

Health care

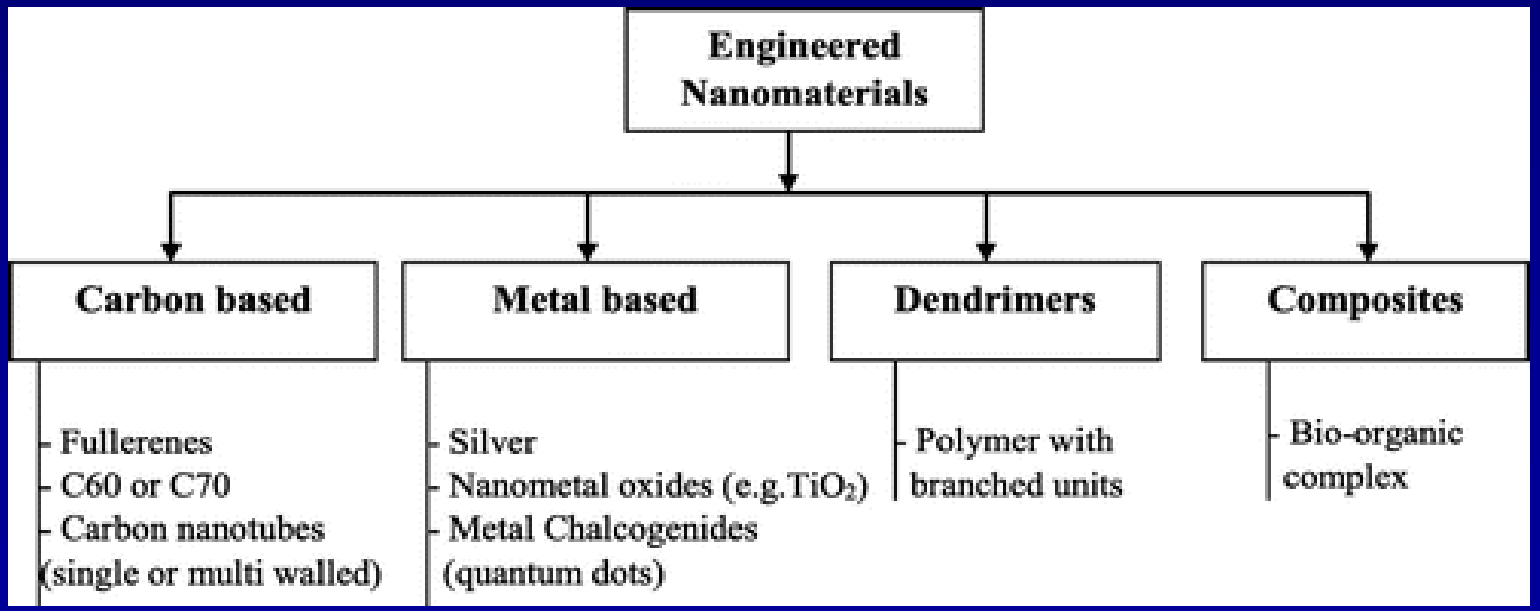
Energy conversion and use

Automobile and aerospace industry

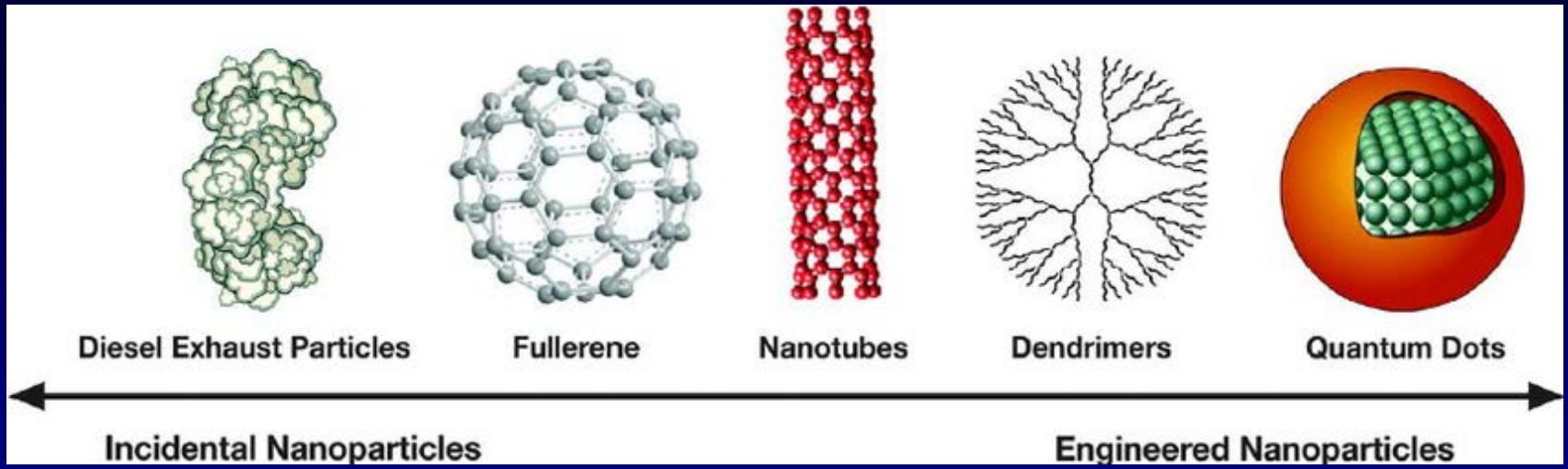
Electronics, communication

Manufacturing of instruments

Agriculture



Nanoparticles: engineered or incidental



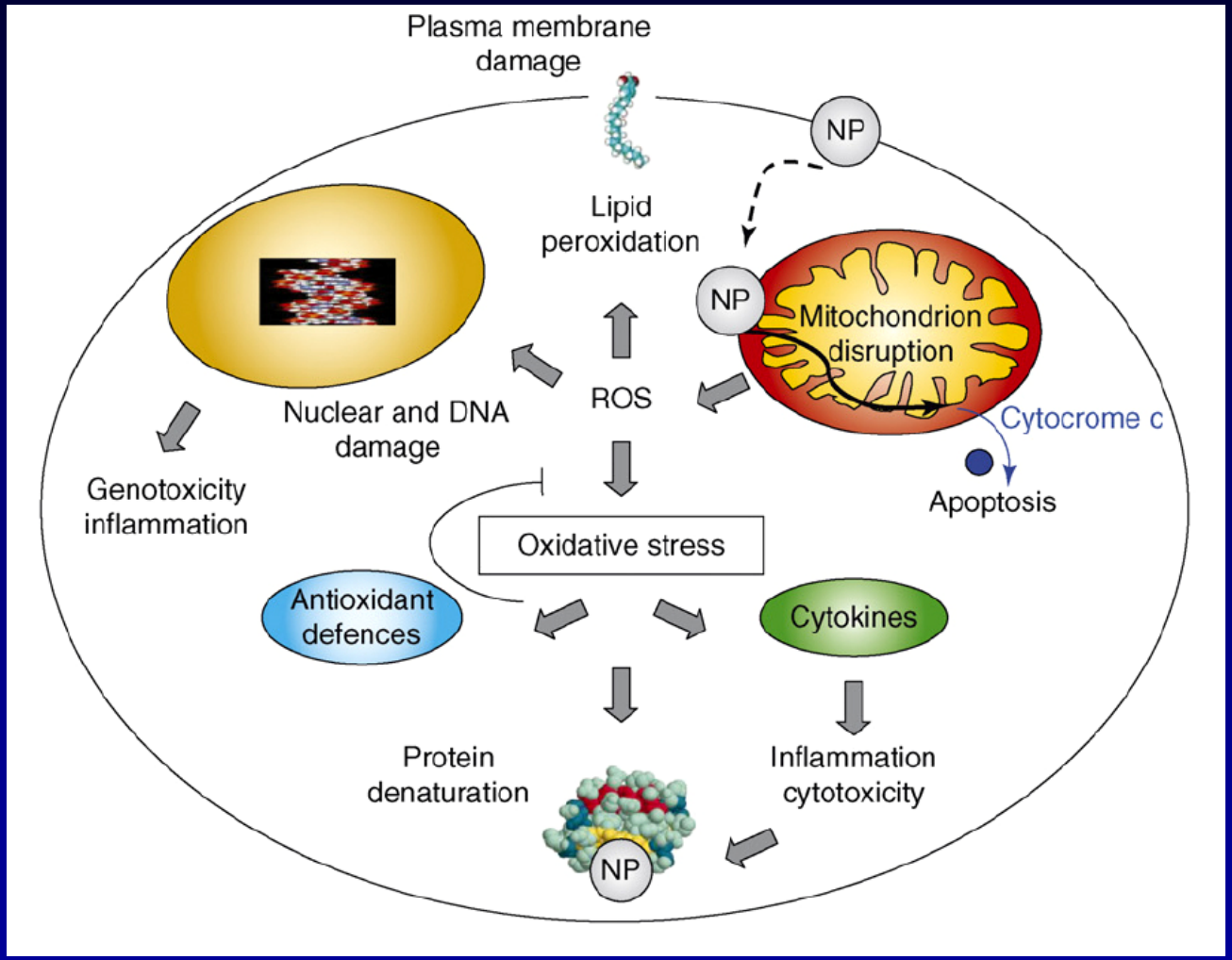
Sources of incidental nanoparticles

- Ambient air particulate
- Environmental tobacco smoke
- Wood smoke
- Diesel exhaust

Effects of Nanoparticles in Biological Systems.

- Surface reactivity (ROS generation, oxidative stress, inflammation, cytotoxicity, genotoxicity, blood contact changes)
- Interaction with macromolecules (e.g. protein corona)
- Size/shape-dependent toxicity
- Aggregation/agglomeration tendency

Role of Reactive Oxygen Species (ROS) in Nanoparticle Toxicity.



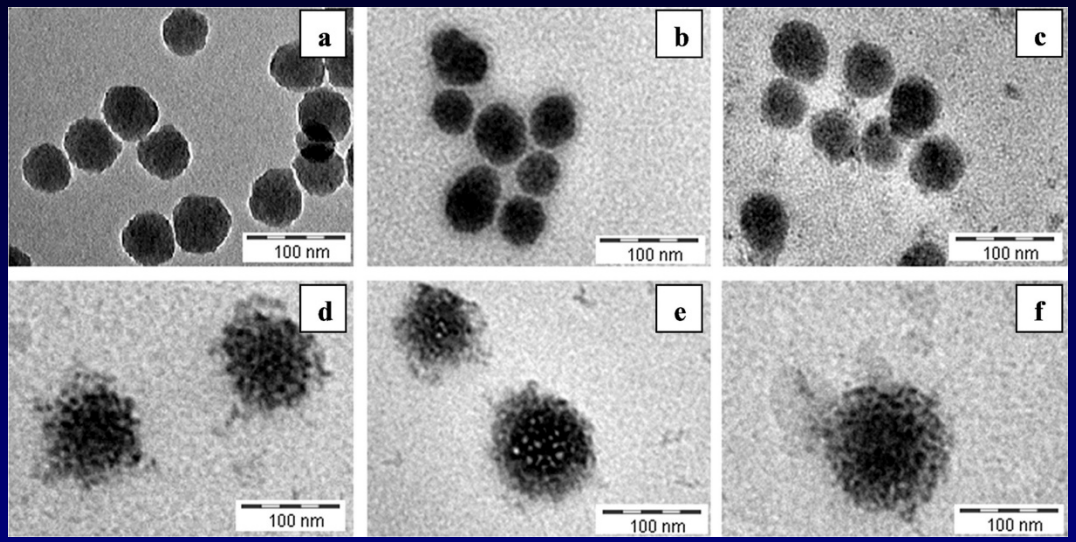
Nanoparticles are able to target mitochondria directly, which can lead to mitochondrial disruption and, in turn, to ROS production. Oxidative stress owing to excess ROS generation induces over-expression of antioxidant enzymes in an attempt to control ROS levels. At high levels of oxidative stress, antioxidant defences are overwhelmed, which leads to inflammatory and cytotoxic responses. Oxidative stress might induce collateral damage, such as lipid peroxidation, protein denaturation, nuclear and DNA damage, immune reactivity, and blood contact changes.

Adapted from Sanvicens & Marco, Trends Biotechnol (2008).

Effects of Nanoparticles in Biological Systems.

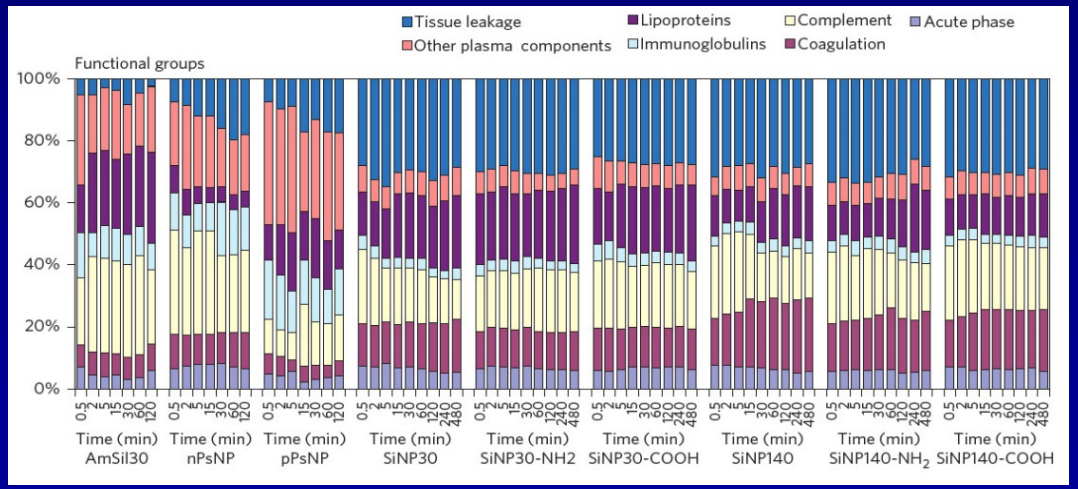
- Surface reactivity (ROS generation, oxidative stress, inflammation, cytotoxicity, genotoxicity, blood contact changes)
- Interaction with macromolecules (e.g. protein corona)
- Size-shape dependent toxicity
- Aggregation/agglomeration tendency

Proteins in biological fluids bind to the surface of nanoparticles to form a coating known as the protein corona.This process can critically affect the interaction of nanoparticles with living systems.



Silica NPs: (a) 0 min, (b) 10 min, (c) 6 h, (d) 48 h, (e) 1 week, (f) 2 weeks incubation in Dulbecco medium + 10% fetal bovine serum.

Bioinformatic classification of corona components grouped according to biological processes of the blood system



Sources: Izac-Nau et al, Part Fibre Toxicol, 2013. Tenzer et al, Nature Nanotechnol, 2013

Top 20 most-abundant corona proteins (ppm) detected after 0.5 min of plasma exposure to polystyrene nanoparticles.

1	Serum albumin
2	Complement C3
3	Complement factor
4	β2-glycoprotein 1
5	Kininogen- 1
6	Inter-α-trypsin inhibitor heavy chain H4
7	Ig γ-1 chain C region
8	Vitronectin
9	Complement C1r subcomponent
10	Ig γ-3 chain C region
11	Lipopolysaccharide-binding protein
12	Gelsolin
13	Complement C5
14	Complement C1s subcomponent
15	Apolipoprotein A-I
16	Ig μ chain C region a
17	Complement C4-B
18	Ig κ chain C region
19	C4b-binding protein α chain
20	Histidine-rich glycoprotein

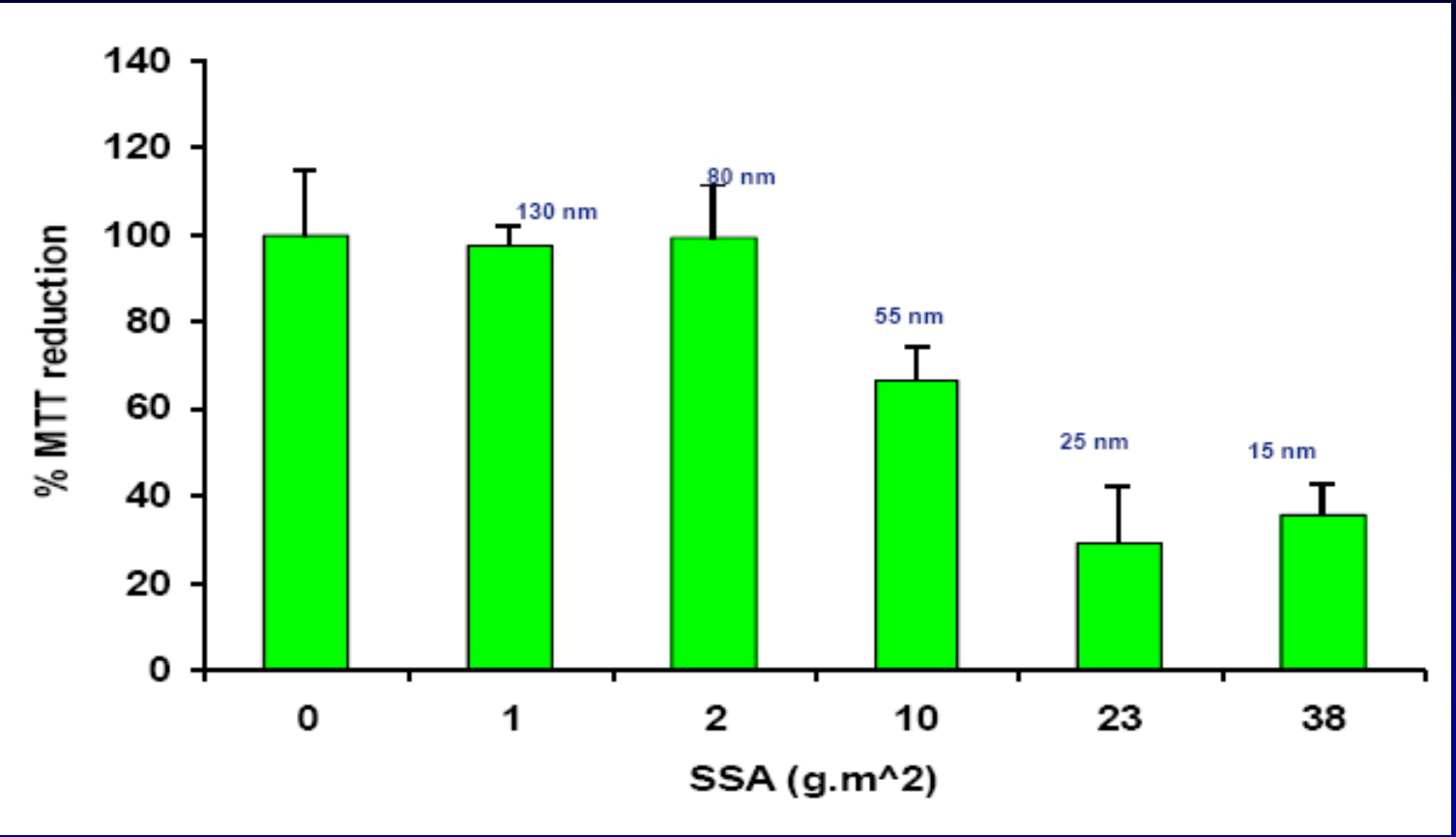
"Protein corona" occurs with proteins known to play an important role in acute-phase response, complement activation, and immune-mediated events.

Tenzer et al. Nature Nanotechnol, 2013.

Effects of Nanoparticles in Biological Systems.

- Surface reactivity (ROS generation, oxidative stress, inflammation, cytotoxicity, genotoxicity, blood contact changes)
- Interaction with macromolecules (e.g. protein corona)
- Size/shape-dependent toxicity
- Aggregation/agglomeration tendency

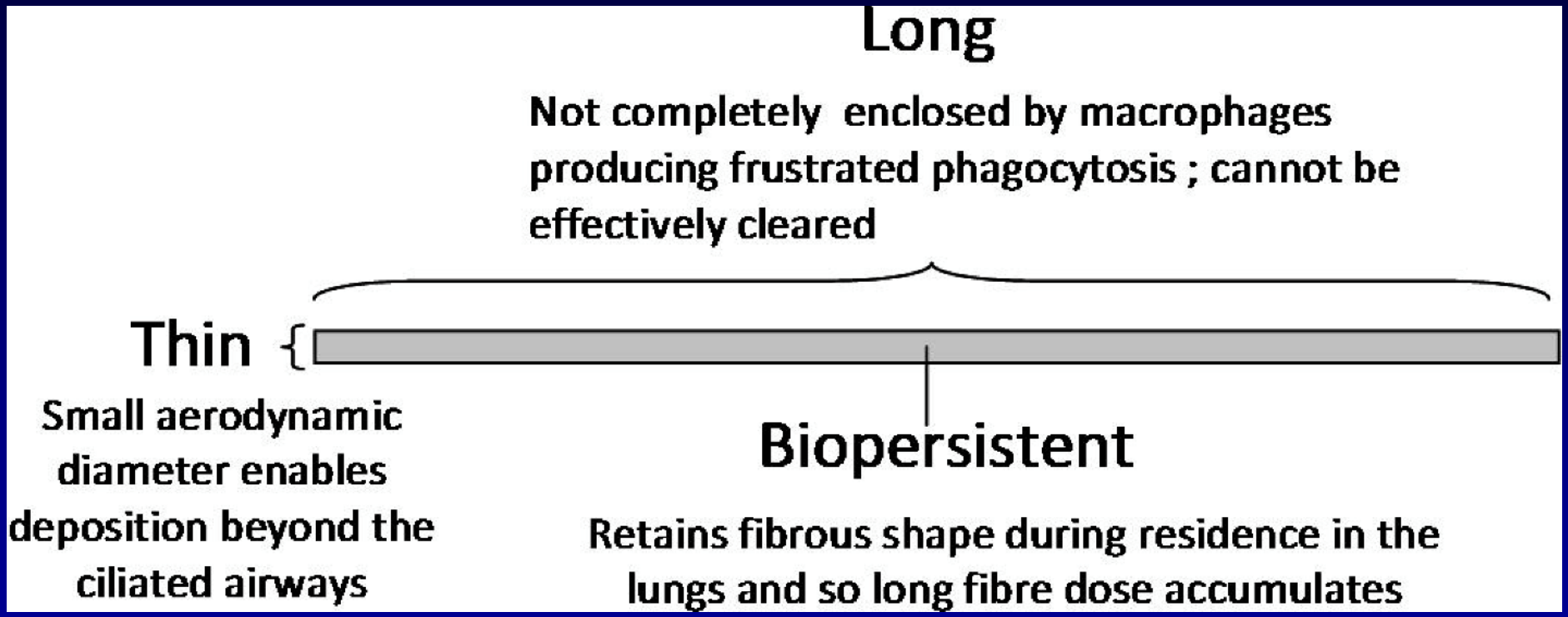
Size and Surface Area Dependent Toxicity of Silver NPs.



Cytotoxicity observed in cell cultures exposed to 50 µg/ml Ag nanoparticles, size from 15 to 130 nm

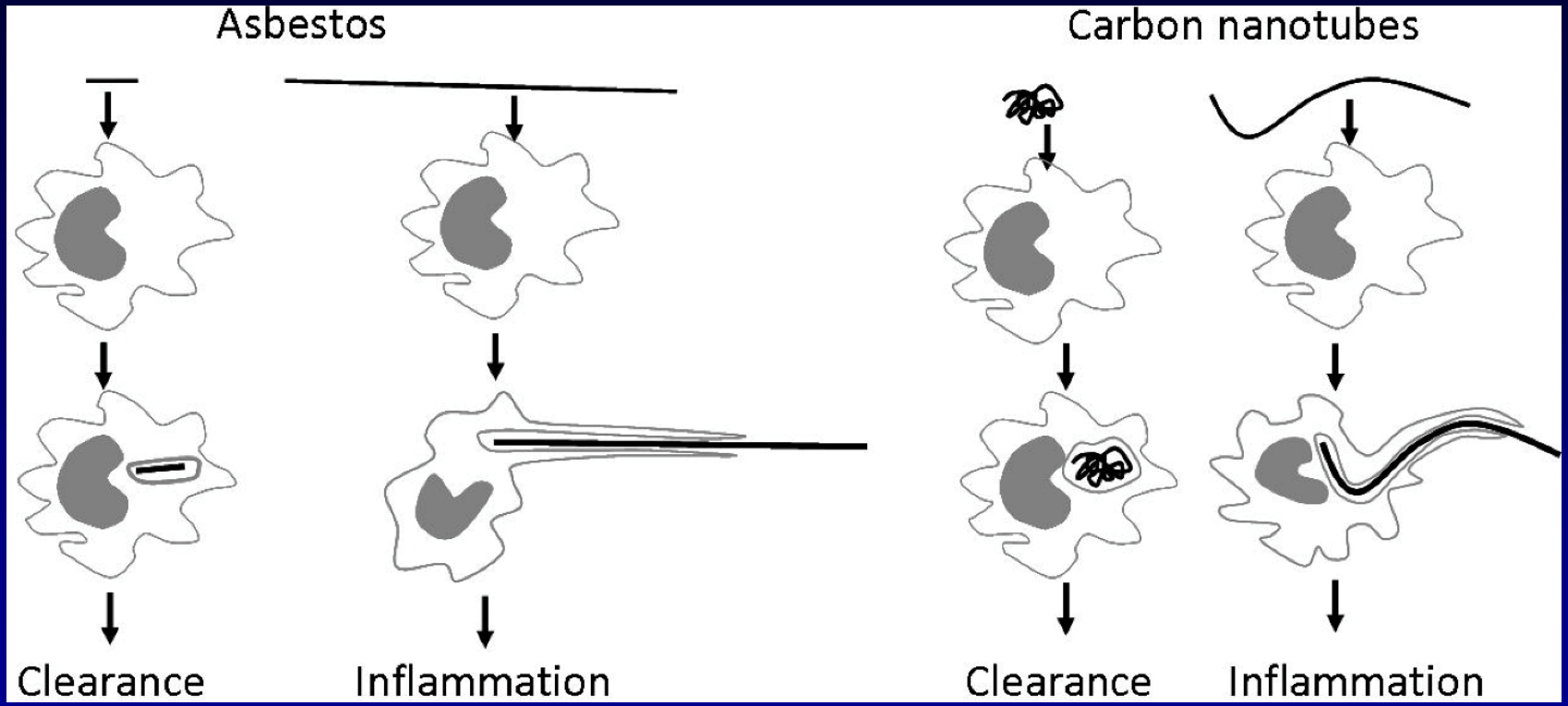
Hussain et al., 2008

Diagram illustrating the pathogenicity paradigm of fibres according to their shape characteristics.



(K. Donaldson et al, Part Fibre Toxicol, 2010)

The frustrated phagocytosis paradigm as it relates to various forms of carbon nanotubes and asbestos.



When confronted by short asbestos fibres or tangled, compact CNT particles, the macrophage can enclose them and clear them. However the macrophage cannot extend itself sufficiently to enclose long asbestos or long nanotubes, resulting in incomplete or frustrated phagocytosis, which leads to inflammation.

K. Donaldson et al. Part Fibre Toxicol, 2010.

Effects of Nanoparticles in Biological Systems.

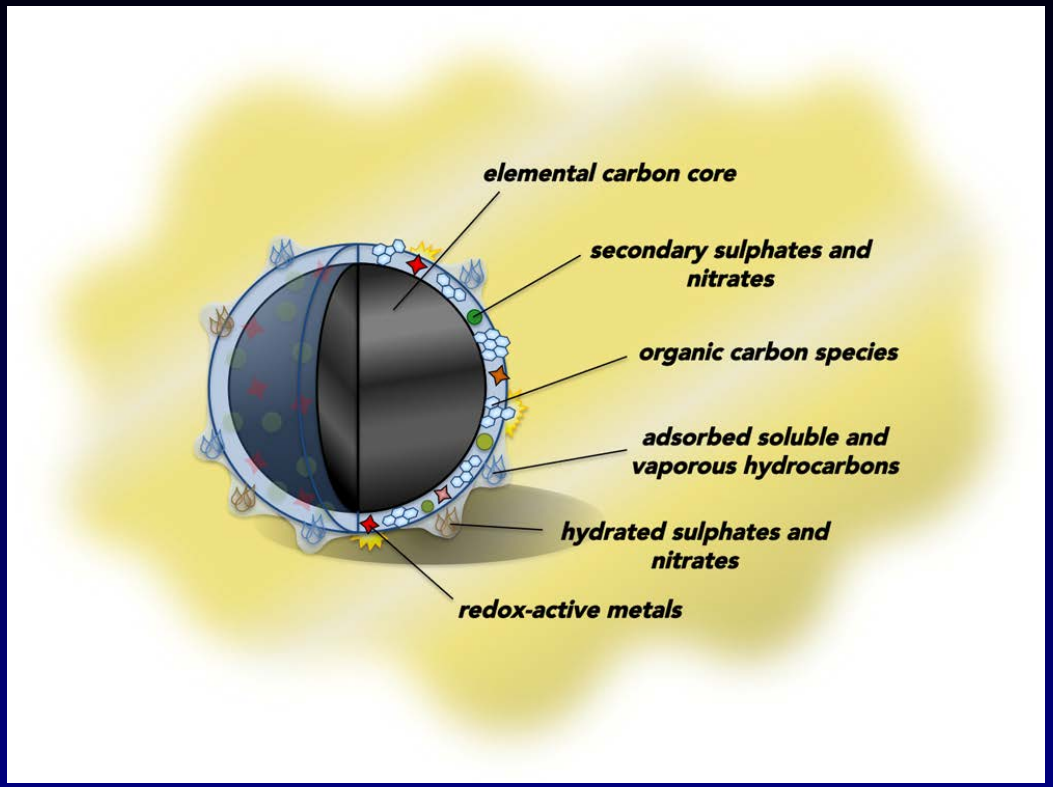
- Surface reactivity (ROS generation, oxidative stress, inflammation, cytotoxicity, genotoxicity, blood contact changes)
- Interaction with macromolecules (e.g. protein corona)
- Size/shape-dependent toxicity
- Aggregation/agglomeration tendency

Agglomeration-Aggregation

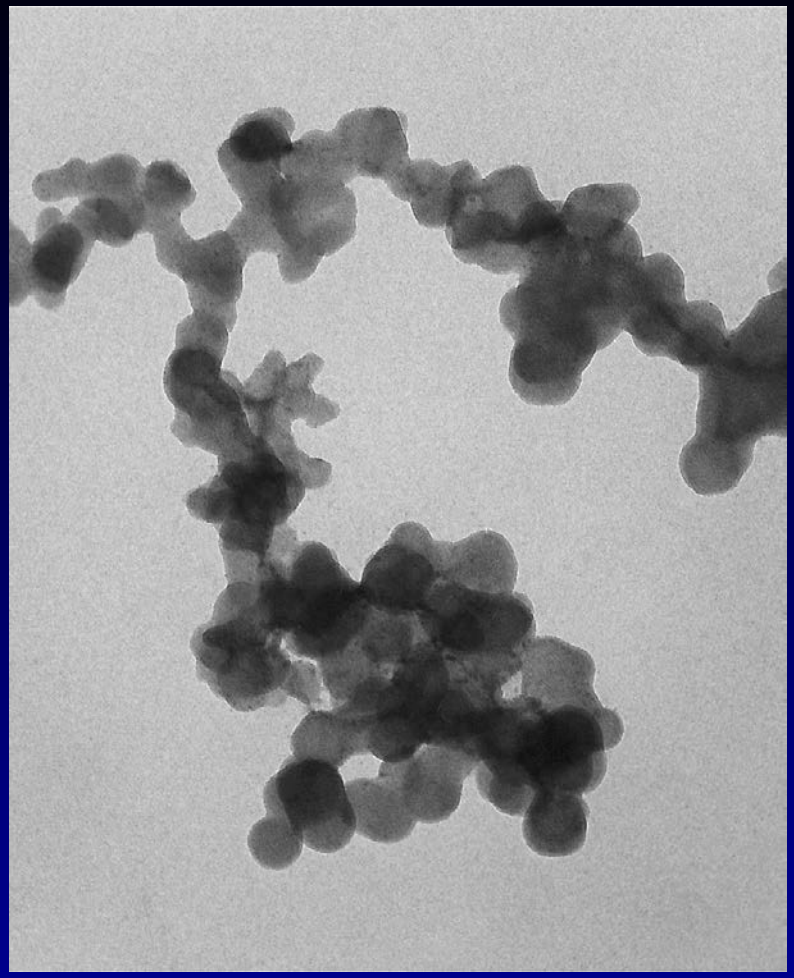
Unpredictable dose-response relationships, in terms of reactivity, macromolecular binding, tendency to cross biomembranes, cellular uptake, phagocytosis, etc

Agglomeration-aggregation may either reduce bioactivity of nanoparticles (by reducing surface area and reactivity) or mediate some of their adverse effects (e.g. generation of microemboli, endothelial damage)

Effects mediated by nanoparticle components and impurities



NPs from vehicle exhaust



NPs from wood smoke

Examples of complex composition of ultrafine particles (UFPs)

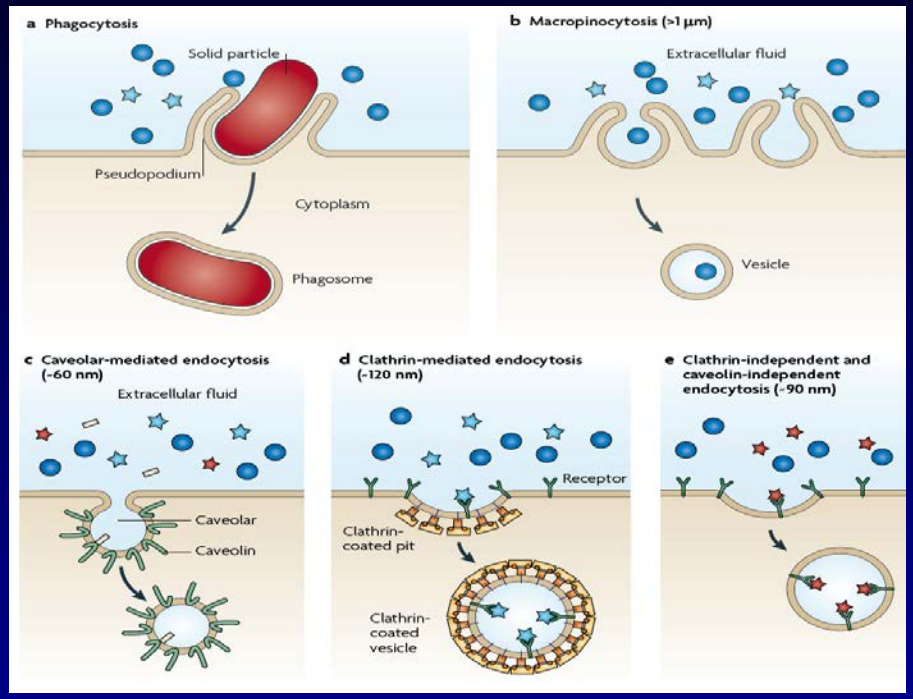
C. Arnold EHP (2017); V. Stone et al, EHP (2017).

Size-Dependent Biokinetic Properties of Nanoparticles.

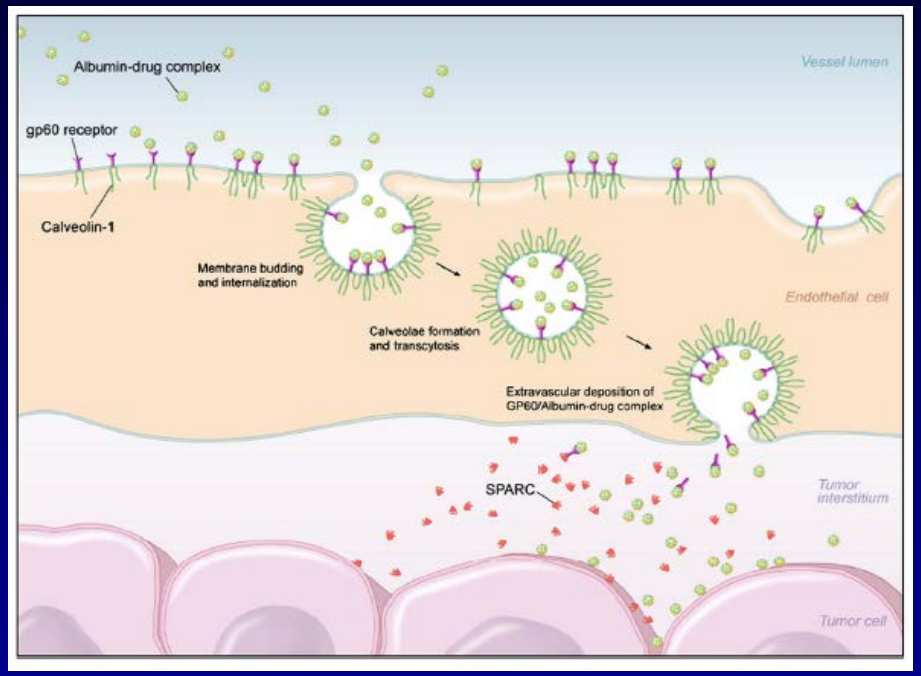
Nanoparticles can migrate from portal of entry in the body to systemic circulation, escape phagocytosis, and avoid detection by the immune system.

Implications: adverse effects of inhaled nanoparticles may extended to remote organs.

Size-Dependent Cellular Internalization of Nanoparticles and their Implications.



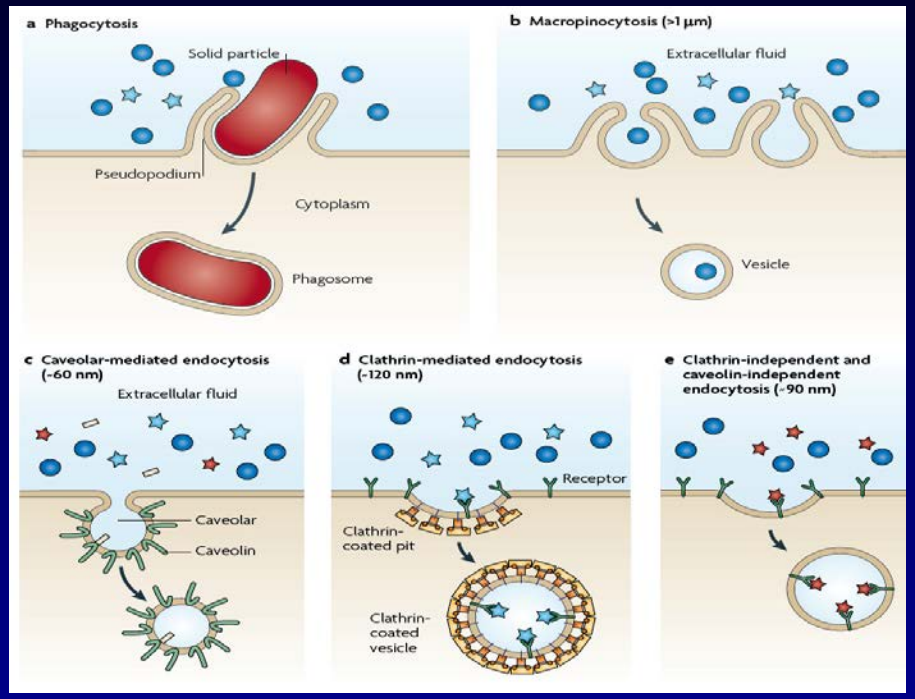
Size-dependent modes of particle cellular uptake.



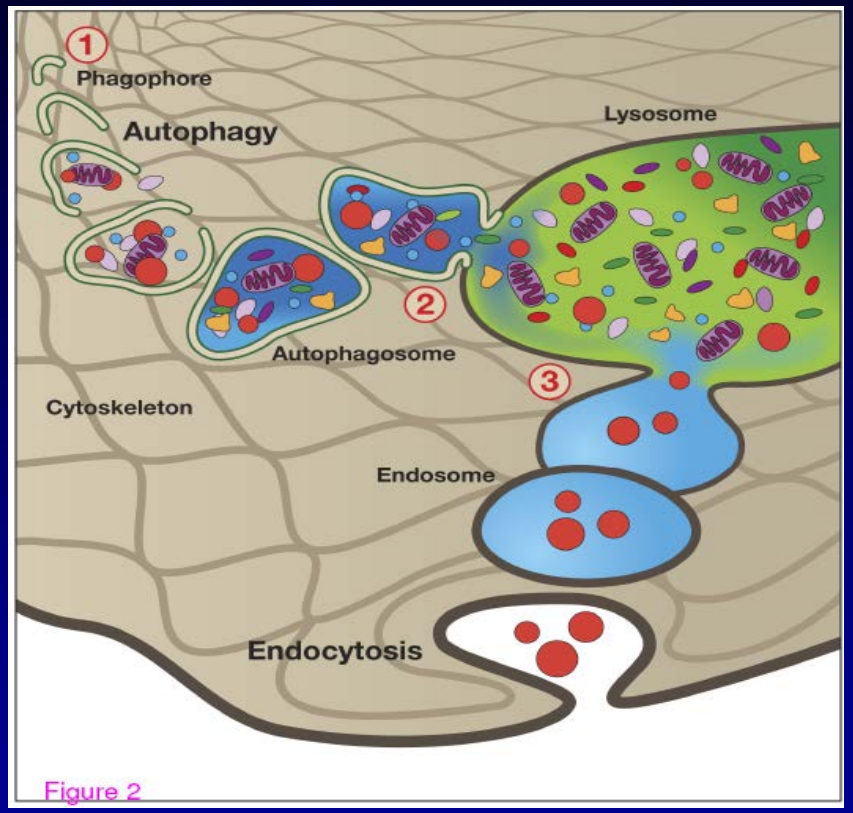
Role of the gp60 transcytosis pathway in uptake of albumin paclitaxel nanoparticles

Petros & De Simone, Nature Rev Drug Disc, 2010. Stern ST *et al.* Part Fibre Toxicol 2012; R. Hassan, Natl Cancer Institute.

Mechanisms of Cellular Internalization of Nanoparticles and their Implications.



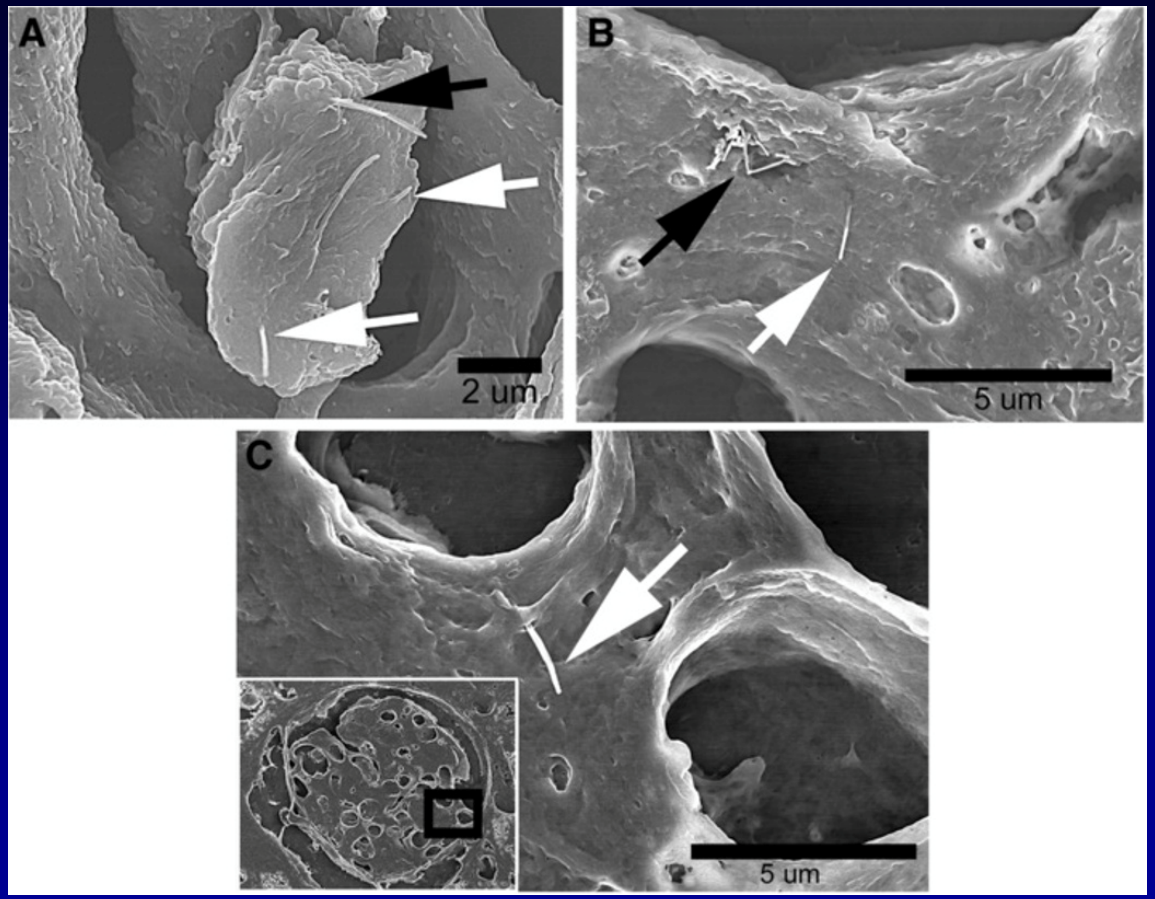
Size-dependent modes of particle cellular uptake.



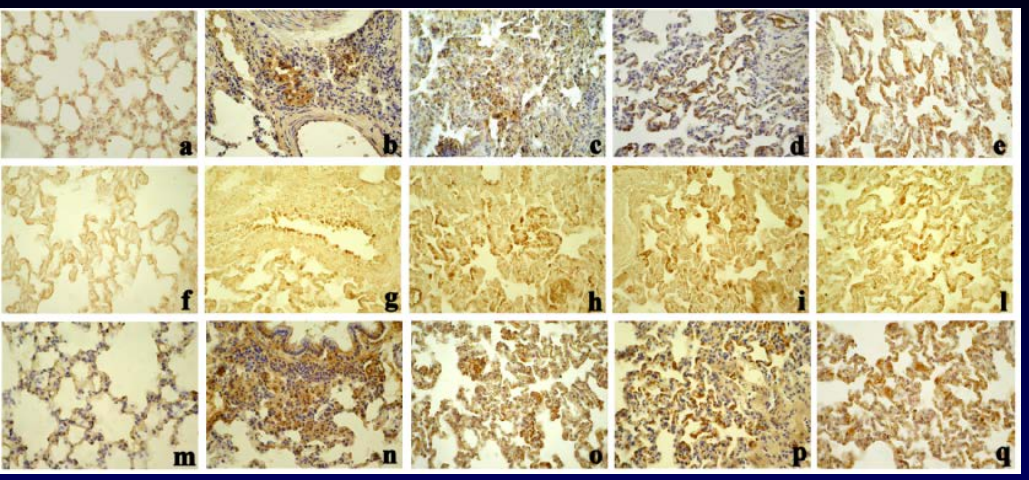
Unsuccessful attempt to degrade biopersistent NPs by lysosomes may cause free radical generation, protein aggregation, aberrant authophagy, and lysosomal dysfunction.

Petros & De Simone. Nature Rev Drug Disc, 2010. Stern ST *et al.* Part Fibre Toxicol 2012.

MWCNTs in Lung and Kidney after MWCNT Inhalation Exposure.



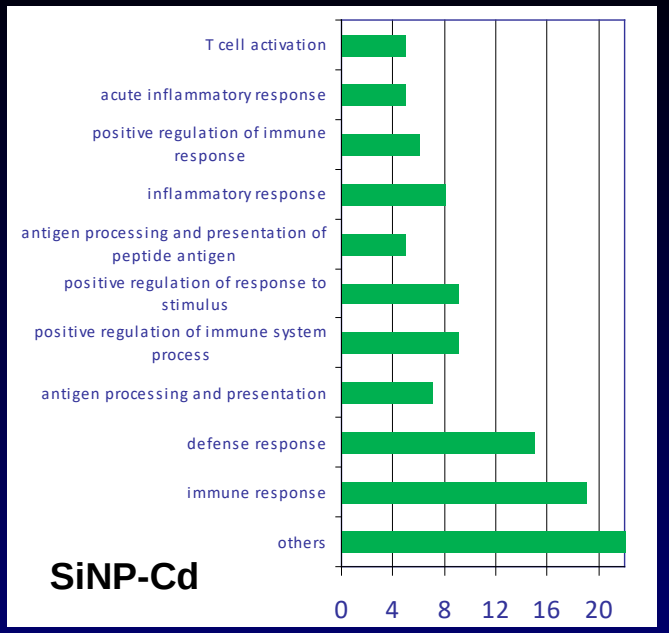
MWCNT fibers protruding from the surface of alveolar macrophage 1 day post exposure (1A) or found in the alveolar interstitial space 336 days post-exposure (1B). Figure 1C shows a MWCNT found in the kidney 336 days post-exposure. Source: Mercer et al, Part Fibre Toxicol (2013).

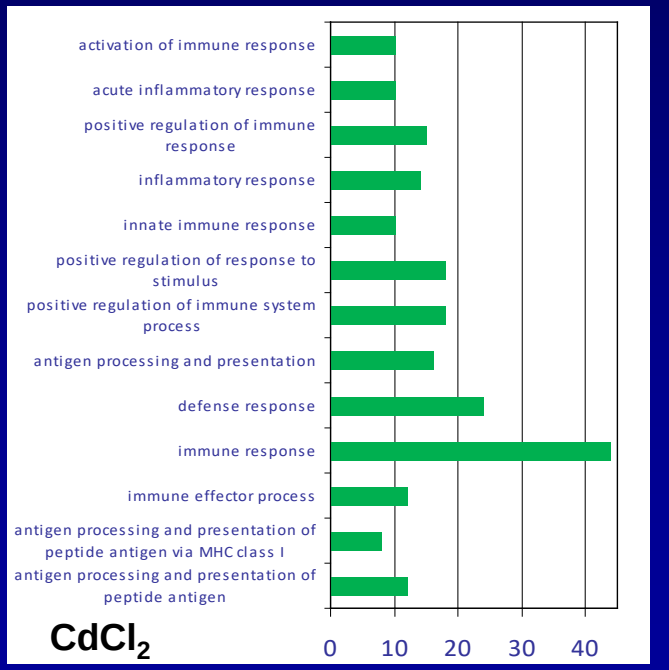


LUNG - Immunostaining patterns of *IL-6*, *IP-10*, *TGF-β1 expression*

Pro-inflammatory effects observed in rat lung and kidney 30 days after a single dose of SiNP-Cd given by i.t. instillation.

KIDNEY – Cluster gene categories linked to acute inflammation, immunity and defense processes.





Number of genes with GO

Coccini et al, *J Nanopart Res, 2012; Histol Histopathol, 2013.*

Extra-Pulmonary Targets Identified in Studies on Inhaled Nanoparticles.

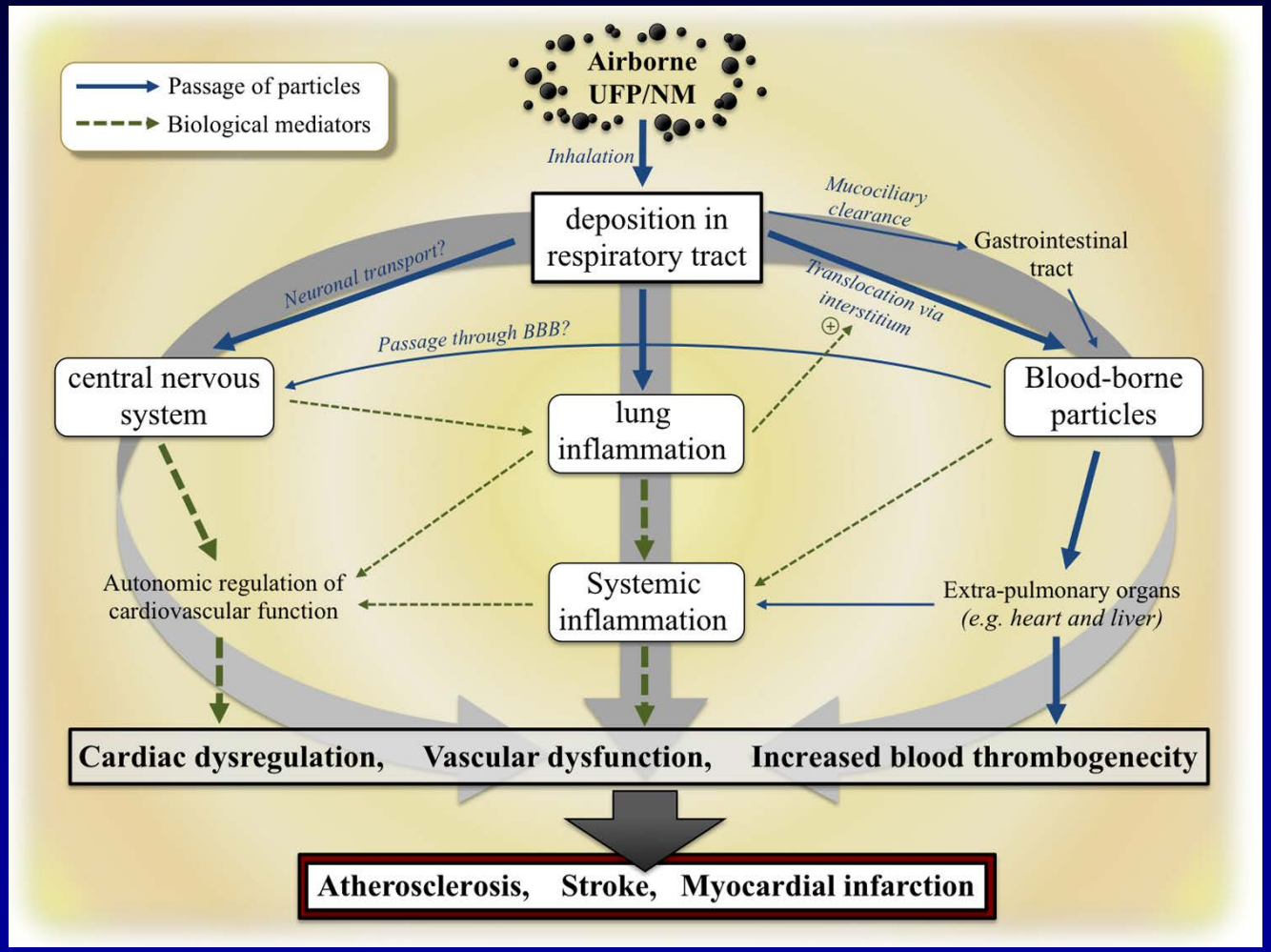
- Cardiovascular tract (myocardium, circulation, heart rhythm, hemostasis)
- Blood (pro-thrombotic effects)
- Kidney (nephrotoxicity)
- CNS (neurobehavioral alterations)
- Fetus (low birth weight)

Proposed Contribution of UFPs to Cardiovascular Effects of Particulate Air Pollutants.

TARGET	OUTCOMES
MYOCARDIUM, CORONARY VASCULATURE	Myocardial ischemia, chest pain, ECG ST segment changes
CIRCULATION	Vasoconstriction, increased systolic BP
HEART RHYTHM	Reduced heart rate variability, arrhythmias
SYSTEMIC INFLAMMATION, PRIMARY AND SECONDARY HEMOSTASIS	Hypercoagulability, changes in blood viscosity, thromboembolism, stroke, plaque progression, plaque rupture

Sources: R.J. Delfino et al., 2005; D.E. Newby et al, 2015; P.M. Mannucci et al, 2015.

Proposed Mechanisms of Cardiovascular Toxicity of Inhaled Ultrafine Particles.



V. Stone et al, Environ health Perspect (2017).

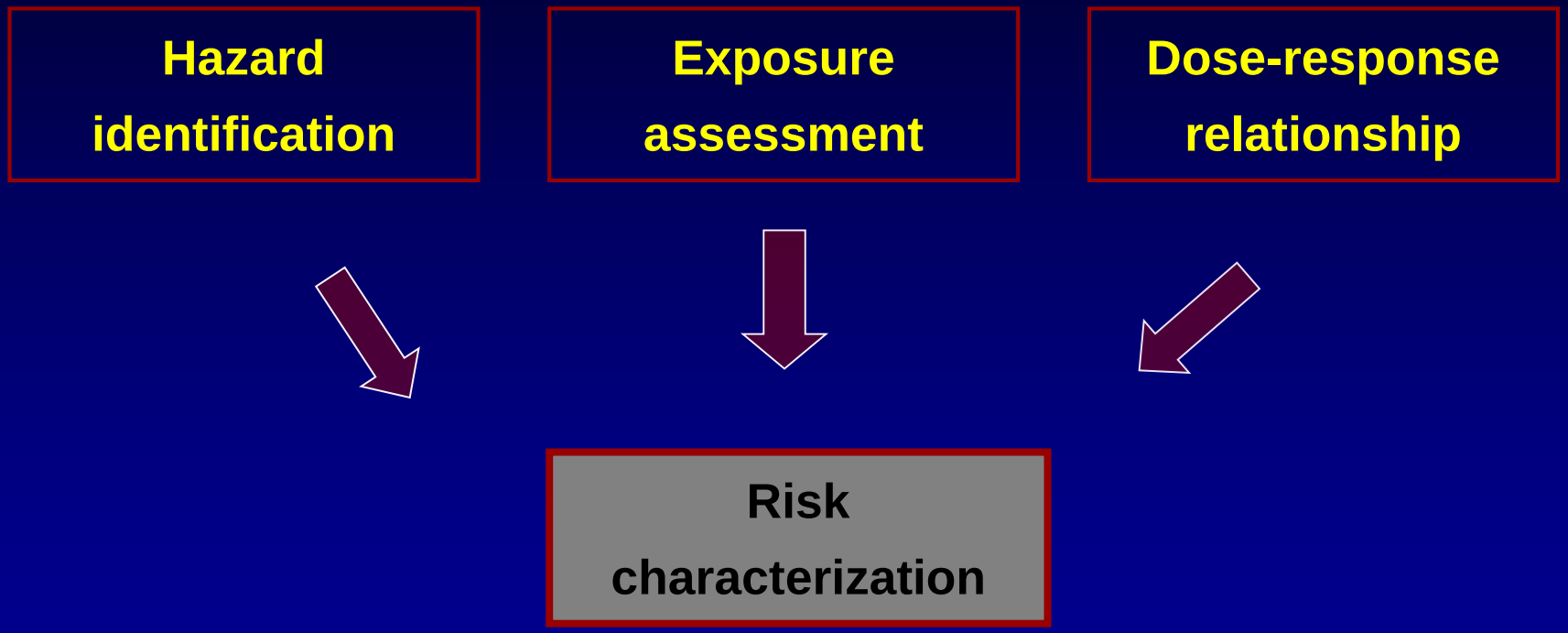
Summary of Effects of Nanoparticles in the Respiratory Tract.

In acute exposure, nanoparticles exhibit acute, neutrophil-driven, inflammatory and oxidative reactions, possibly resulting in cytotoxic effects, genotoxicity and fibrotic responses.

In chronic exposure, carcinogenic effects may develop under overload conditions, the response to nanoparticles often being more severe compared to microscale materials of the same chemical composition.

Translocation of inhaled NPs to circulation may either increase the toxic outcome (e.g. cardiovascular toxicity) or mitigate pulmonary toxicity due to easier removal from the lung.

NanoRisk Assessment



Current Challenges in Nanosafety Assessment

- Paucity of data in humans
- No availability of epidemiological studies
- Limited exposure data (workers, consumers…)
- Lack of standard procedures for risk analysis
- Long-term effects still unexplored

Dose(s) /route(s)
of
exposure / contact

Physico-chemical characterization

Tiered System

Cell-free assays

In vitro assays: primary cells, cell-lines, co-cultures (toxicity-target and secondary organs)

Ex vivo assays (diverse methodologies)

Minimum set of in vivo studies (diverse methodologies)

- **Solubility, dispersibility, agglomeration/aggregation, ROS generation**
- **Cytotoxicity, genotoxicity**
- **Immune system effects**
- **Biocompatibility, blood contact properties, biological surface adsorption**
- **Biokinetics**
- ***Receptogram* profiling, effects on "key" enzymes and ion channels**
- **"Omics", toxicity pathways**
- **Biomarkers**

DATA INTEGRATION

Conventional toxicology studies, Pattern recognition, ENM library

Preclinical Safety Evaluation

Nanomaterial Consumer Product Inventory

A total of 1827 consumer products from 622 companies in 32 countries are listed in the inventory:

- Goods for children
- Food and beverages
- Automotive
- Home and garden
- Health and fitness (supplements, sunscreens, sporting goods, cosmetics, clothing, personal care).

- ➢ Nanosilver is the most frequently used nanomaterial.
- ➢ For 49% of the products included in the Inventory the composition of the nanomaterial used is not declared.

Sources:
www.nanotechproject.org
M.E. Vance et al, Beilstein J. Nanotechnol. (2016)

Nanoparticelle in cosmetici e filtri solari.

- **Biossido di Titanio (TiO_2)**
- **Ossido di Zinco (ZnO)**

Usando TiO_2 o ZnO in nanoparticelle di 30-60 nm si ottiene un prodotto che blocca efficacemente gli UV (azione protettiva) e al tempo stesso non macchia, in quanto trasparente alla luce visibile.

Colloidal NanoSilver “Super Health Tonics”

«An all natural mineral supplement».

«Taken daily, this «miracle water» boosts your immune system, supports your body to overcome and resist infections and is known to be a remarkable catalyst in the reproduction of healthy, disease-free life».

Current Experience of Nanoparticle Safety/Toxicity in Humans

Studies on air pollution

Nanomedicine

The Effect of Fine and Coarse Particulate Air Pollution on Mortality (Zanobetti & Schwartz, 2009).

Percent increase in mortality for 10-μg/m³ increase in PM coarse or PM2.5 across 47 US cities.

	PM 2.5	PM coarse
All-cause mortality	0.94 (0.65 to 1.22)	0.47 (0.21 to 0.73)
Cardiovascular disease	0.97 (0.51 to 1.43)	0.29 (–0.04 to 0.61)
Myocardial infarction	1.18 (0.43 to 1.93)	0.04 (–0.72 to 0.81)
Stroke	1.96 (0.88 to 3.07)	0.71 (0.02 to 1.41)
Respiratory disease	1.92 (1.08 to 2.78)	1.14 (0.43 to 1.85)

Particle number and particle surface area per 10 pg/cm^3 airborne particles

Particle diameter (nm)	Particles number /cm^{-3}	Particle surface area (µm^2 /cm^{-3})
5	153 000 000	12 000
20	2 400 000	3 016
250	1 200	240
5 000	0,15	12

The ultrafine size range comprises the major proportion (about 80%) of the total number of ambient particles per unit volume, but negligible mass concentration.

G. Oberdörster et al (2009).

nab Paclitaxel vs Conventional Paclitaxel Therapy in Patients with Metastatic Breast Cancer

CLINICAL OUTCOME: moderate/minor advantage

Results obtained in a clinical trial on 454 patients: greater response rate (33% vs 19%, P < 0.001), longer time to tumor progression (21.9 vs 16.1 wks, P < 0.029), longer median survival (65.0 vs 55.3 wks)

TOLERABILITY: major advantage

Minimal local irritation, rare hypersensitivity reactions

SYSTEMIC TOXICITY: no advantage

Similar incidence of severe (grade 3-4) neutropenia; more frequent sensory neuropathy with *nab*-paclitaxel

JL Blum, Commun Oncol 2005

JM Hawkins et al, Adv Drug Deliv Rev, 2008.

Study of nab-Paclitaxel plus Gemcitabine vs Gemcitabine Monotherapy in Pancreatic Cancer Patients.

	nab-Paclitaxel plus Gemcitabine	Gemcitabine monotherapy
Median overall survival (months)	8.5	6.7
Median progression-free survival (months)	5.5	3.7
Neutropenia, grade 3 or higher (patients, %)	38	27
Peripheral neuropathy (patients, %)	17	1

Von Hoff et al, N Engl J Med, 2013.

Carbon Nanotubes

- Toxicity observed in a large number of experimental studies (oxidative stress, inflammatory reactions, lung fibrosis, asbestos-like effects in rodents)
- High-volume production (several workers exposed)
- Proposed for many technological applications including application in medicine (drug delivery systems, biosensors, tissue engineering, etc.)

www.advmat.de

ADVANCED MATERIALS

Water-Miscible Liquid Multiwalled Carbon Nanotubes

By *Maurizio Fagnoni, Antonella Profumo, Daniele Merli, Daniele Dondi, Piercarlo Mustarelli,* and Eliana Quartarone*

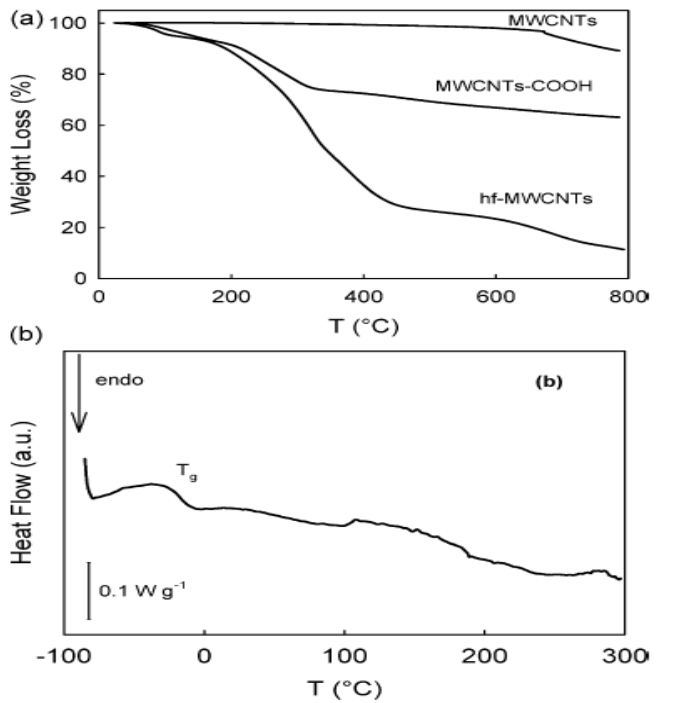


Figure 3. TGA and DSC plots of hf-MWCNTs. a) TGA thermograms of the liquid hf-MWCNTs obtained at 10 °C min^{-1} in a N_2 purge. The TGA plots of pristine MWCNTs and MWCNT–COOH are shown for comparison. b) DSC heating plot of hf-MWCNTs with a scan rate of 5 °C min^{-1}. The deviation from the baseline displayed above 100 °C is related to the starting weight loss shown in the TGA curve.

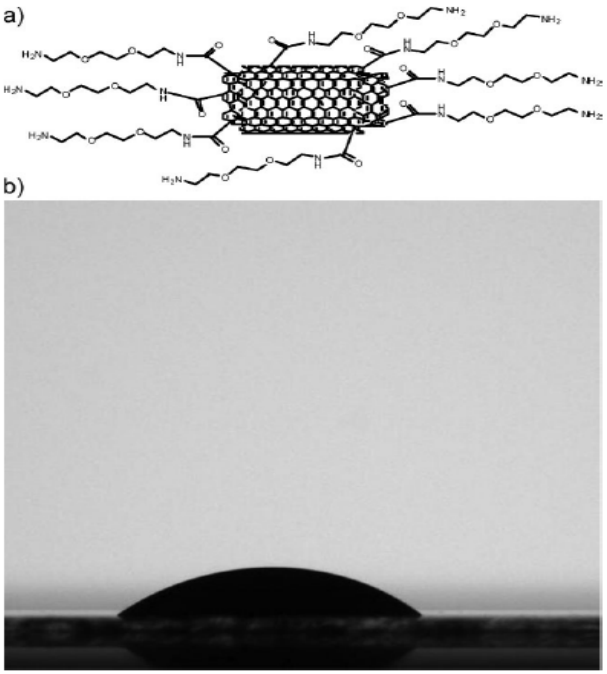
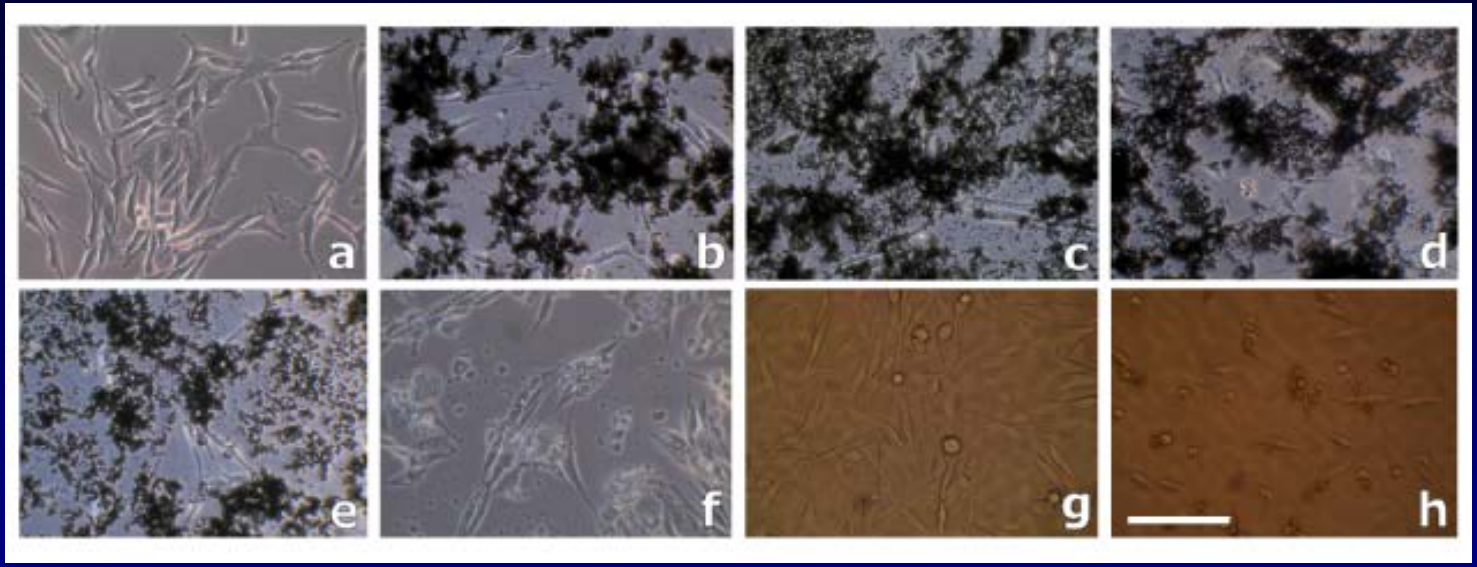


Figure 1. Highly modified liquid hf-MWCNTs. a) Proposed structure of the hf-MWCNTs. b) A photograph of a drop of hf-MWCNTs on sylanized silica. The liquid nanotubes behave like water when deposited on a hydrophilic substrate. The contact angle (17.8°) is comparable to that of water (18°), but is reached after a longer time, as a result of the higher sample viscosity (see Supporting Information).

Fagnoni et al, Adv Mat 21:1761 (2009)

Functionalized MWCNTs are easily dispersible in biological media.



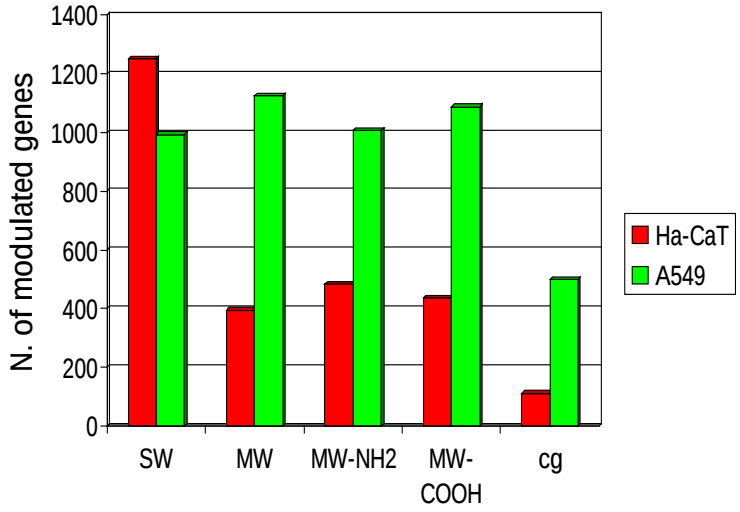
Phase contrast microscopy images of D383 cell culture

Bundle-like agglomerates cover cell surface of cells exposed for 24 h to 100 µg/ml of MWCNTs (**b**), MW-COOH (**c**), MW-NH2 (**d**), or CB (**e**).
No agglomeration in cell cultures exposed to 100 µg/ml SiO_2 (**f**) or highly-functionalized MW-NH_2 (**g**). In samples treated with 800 µg/ml highly-functionalized MW-NH_2 only slight agglomeration occurred (**h**).

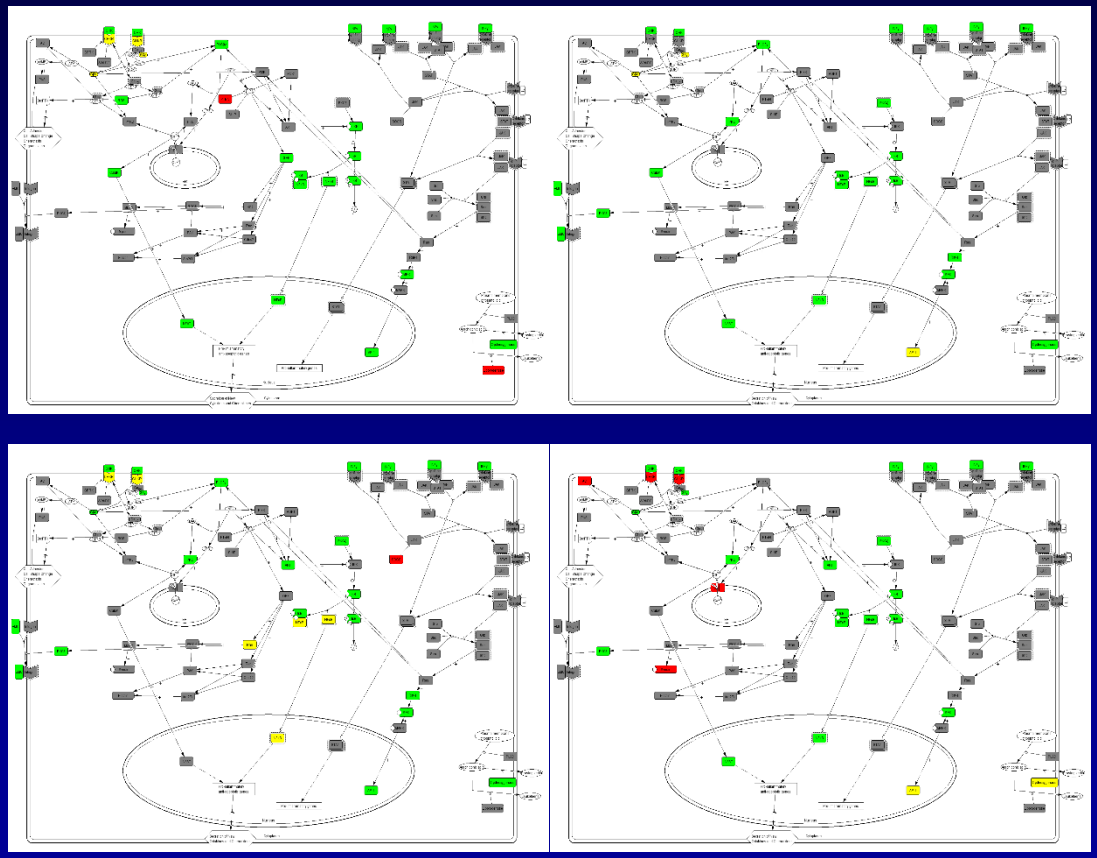
Coccini et al, Toxicology, 2010

Toxicogenomic Assay of Carbon Nanotubes in Ha-CaT and A549 Cell Lines*

Gene expression changes

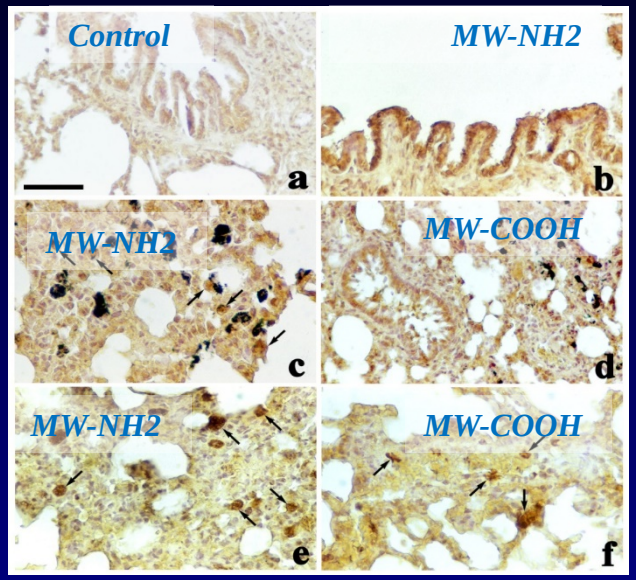


Inflammation mediated by chemokine and cytokine signaling pathways.

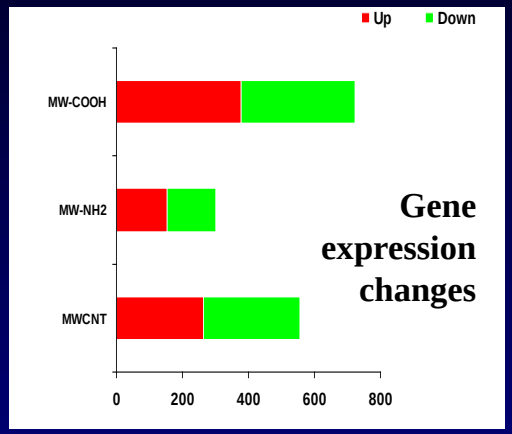


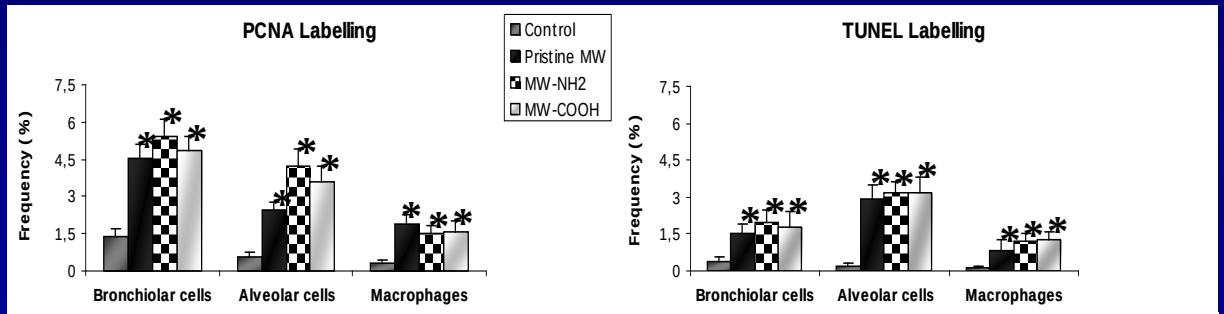
***Total gene expression assessed by DNA-microarrays and quantitative real-time PCR. 48 h exposure**

Pulmonary Effects of Functionalized MWCNTs 16 Days after a Single it Administration (200 µg/rat).



Immunostaining patterns of *IL-6* (a-d) and *TGF-β1* (e-f) expression in controls (a) and rats treated with MW-NH2 (b, c, e) or MW-COOH (d, f).





Changes in % of TUNEL and PCNA labelling Index of bronchiolar, alveolar and macrophagic cells.

Fagnoni et al, Adv Mat (2009). Coccini et al, Toxicology (2010). Roda et al, Histol Histopathol (2011).

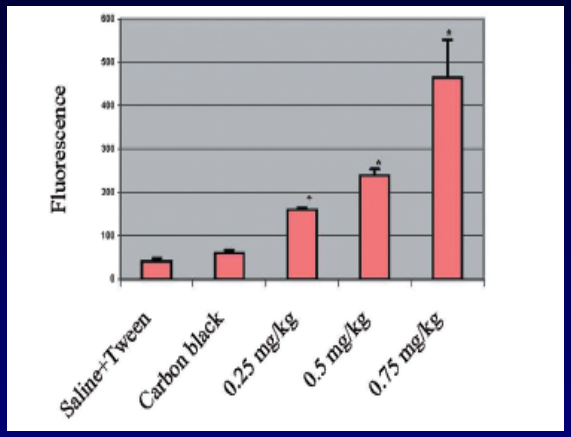
Immunohistochemical Effects of f-MWCNTs in Rat Lung 16 Days after Treatment (200 µg/rat i.t).

	Bronchiolar cells	Alveolar cells	Stromal cells
IL-6	++++	++	+++
TGF-beta1	++	+	++++
Collagen-I	- +	- +	- +

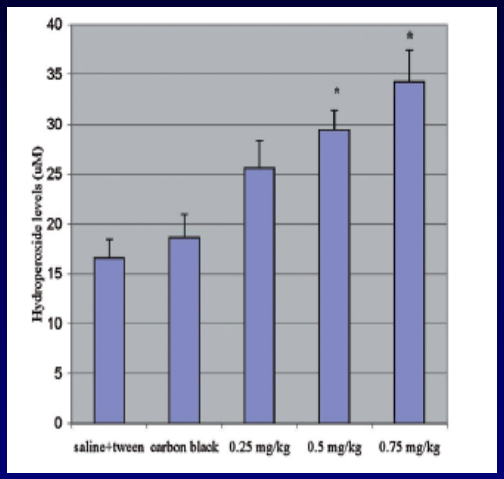
Effects examined 16 days after treatment.
Staining intensity: from undetectable (-) to intense (++++).
CNTs: outer diameter 20-30 nm; wall thickness 1-2 nm; particle length 100-200 nm.

E. Roda et al., Histol Histopathol 2011

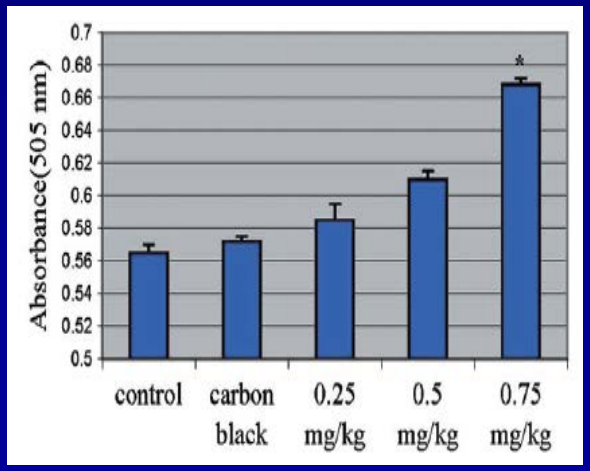
Hepatic Changes Observed 24 h after i.p. Injection of Functionalized CNTs (0.25-0.75 mg/kg) in Mice (Patlolla et al, J Appl Toxicol 2010.



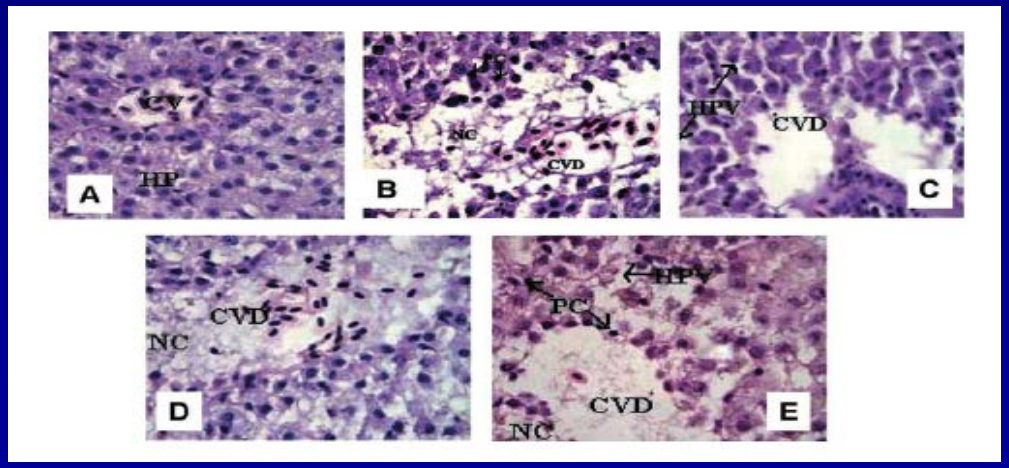
ROS generation



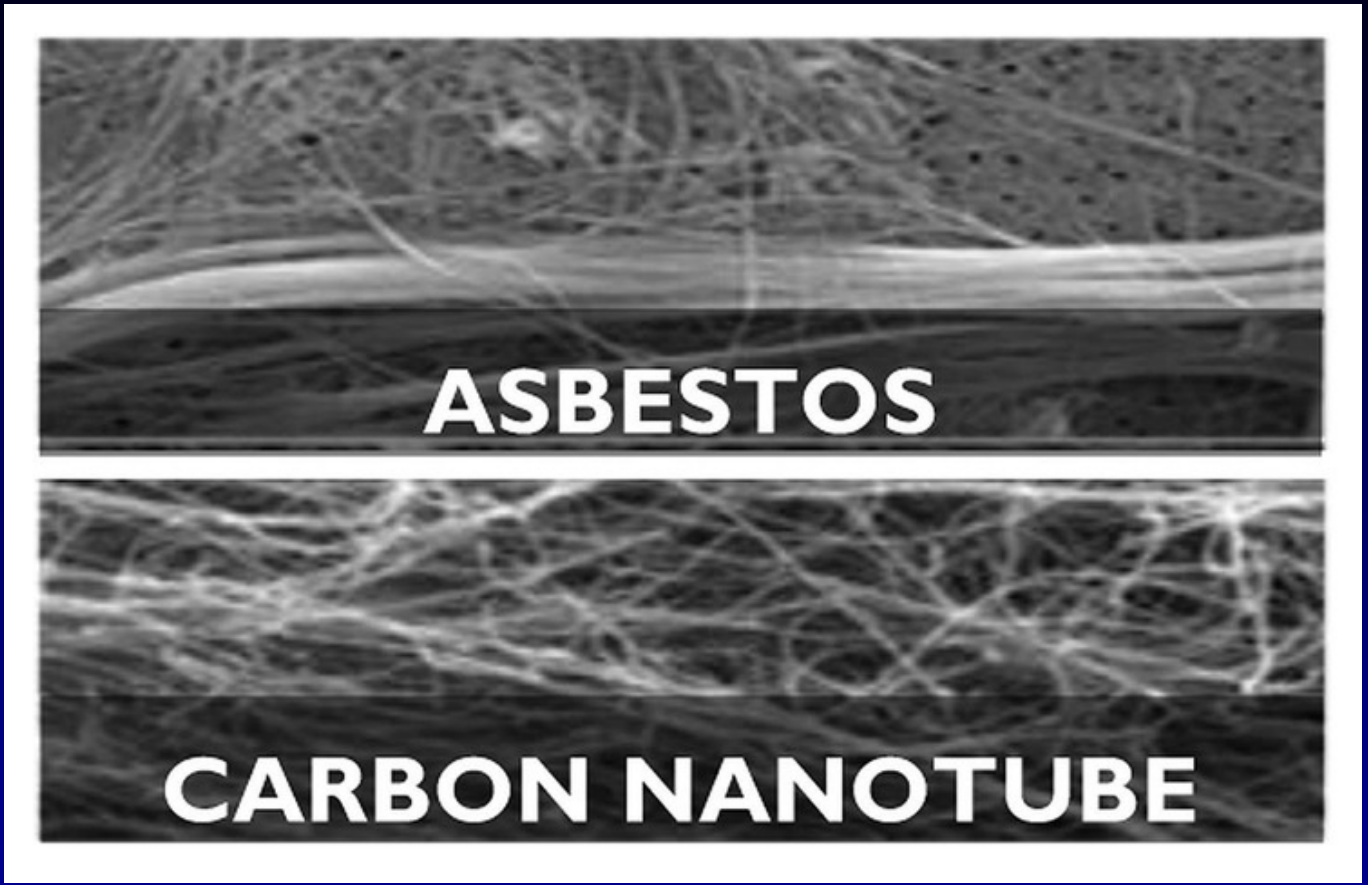
Lipid hydroperoxides



Serum ALT



Histopathology, H&E staining x 1000



Long-Fiber Carbon Nanotubes (CNTs) Replicate Asbestos-Induced Mesothelioma

Long-Fiber Carbon Nanotubes (CNTs) Replicate Asbestos-Induced Mesothelioma

Highlights

Instillation of either long CNTs or long asbestos fibers into the pleural cavity of mice induces mesothelioma.

By 12-20 months, up to 25% of animals exposed to CNTs and 9% of animals exposed to asbestos developed pleural mesothelioma, with identical disease latency for both fiber types.

Both asbestos- and CNT-induced tumors exhibit histopathology and immuno-histochemical markers consistent with human pleural mesothelioma, including mesothelial lineage markers, cytokeratins, and WT1.

Chernova et al, Current Biology 27: 3302-14 (2017)

Long-Fiber Carbon Nanotubes (CNTs) Replicate Asbestos-Induced Mesothelioma

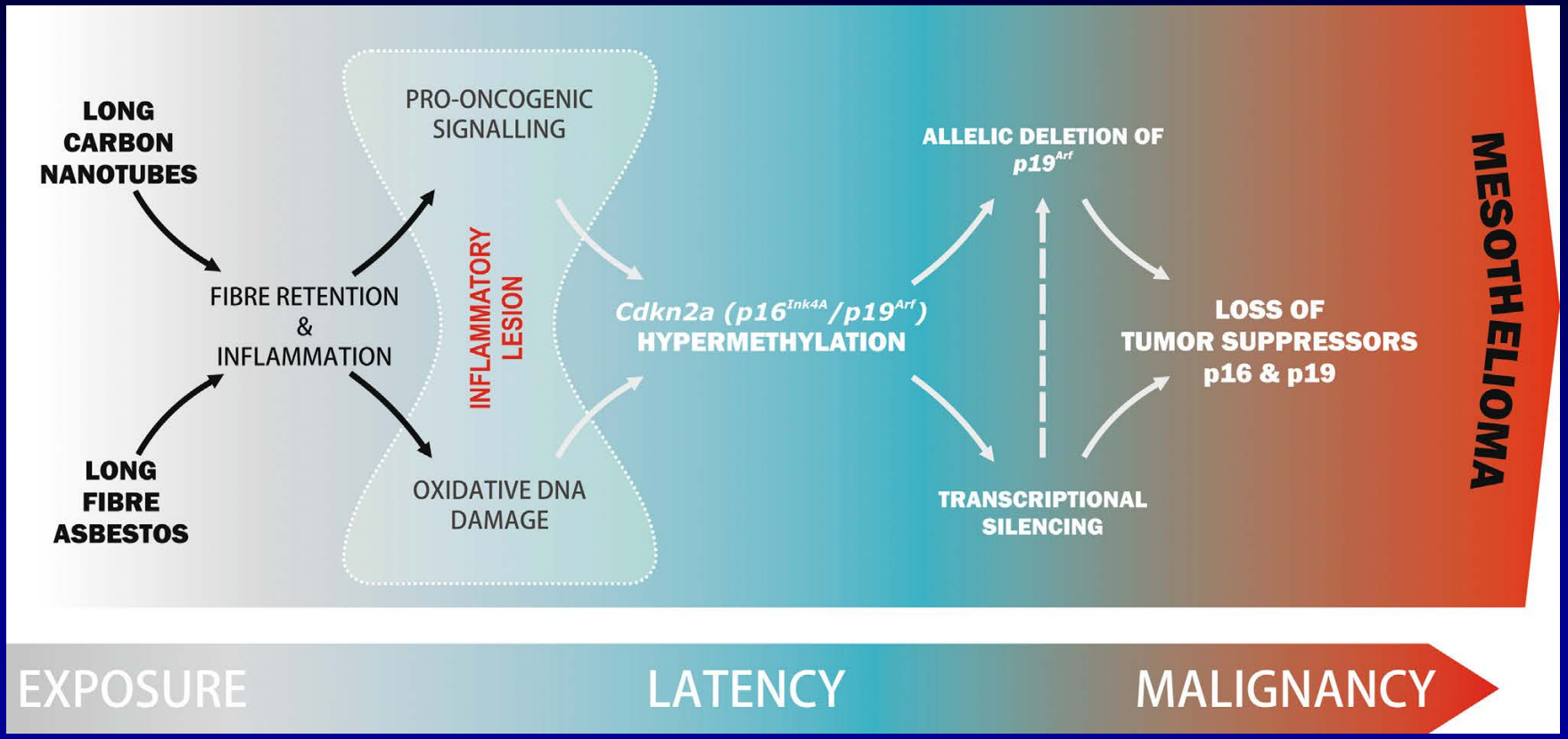
Highlights

CNT- and asbestos-induced mesotheliomas exhibit common key molecular events (activation of pro-oncogenic signaling pathways, increased proliferation, oxidative damage) throughout the latency period of disease progression.

Mesothelioma is preceded by hypermethylation of molecular targets (*p16/Ink4A* and *p19/Arf*) resulting in silencing of *Cdkn2A*, a locus that shows a high-frequency of loss-of-function mutation in human pleural mesothelioma.

Chernova et al, Current Biology 27: 3302-14 (2017)

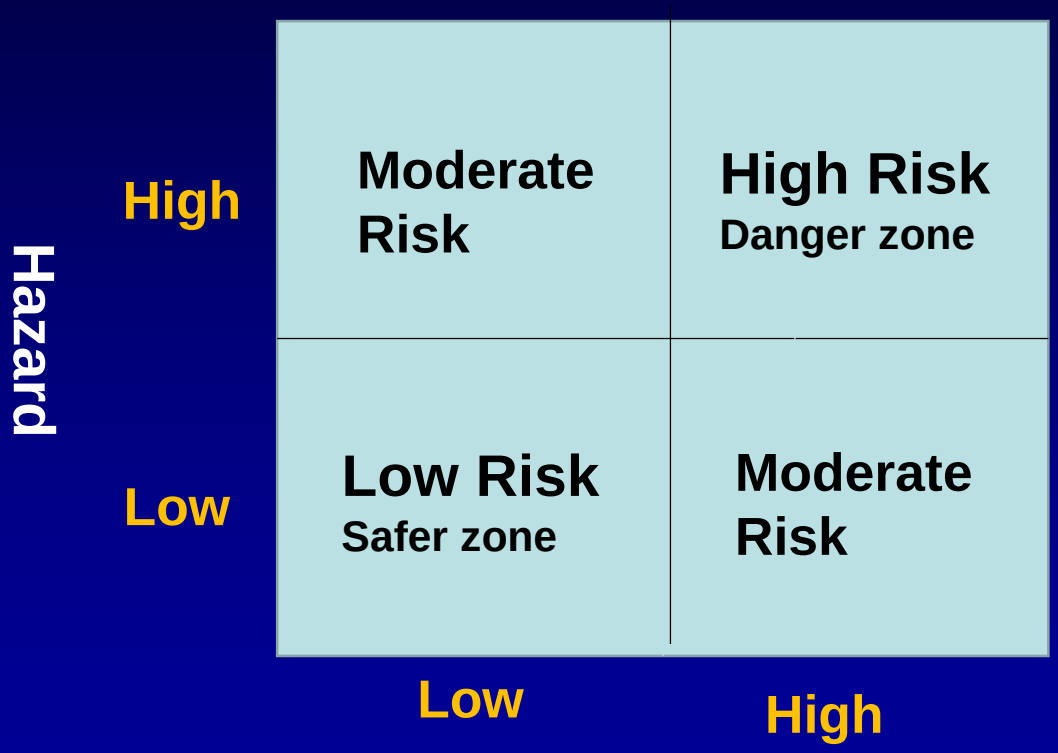
Long carbon nanotubes replicate asbestos-induced mesothelioma with disruption of the tumor suppressor gene *Cdkn2a (Ink4a)/Arf*



Chernova et al, Current Biology 27: 3302-14 (2017)

MANAGEMENT OF NANO RISK

Risk Mitigation Matrix for Engineered Nanomaterials

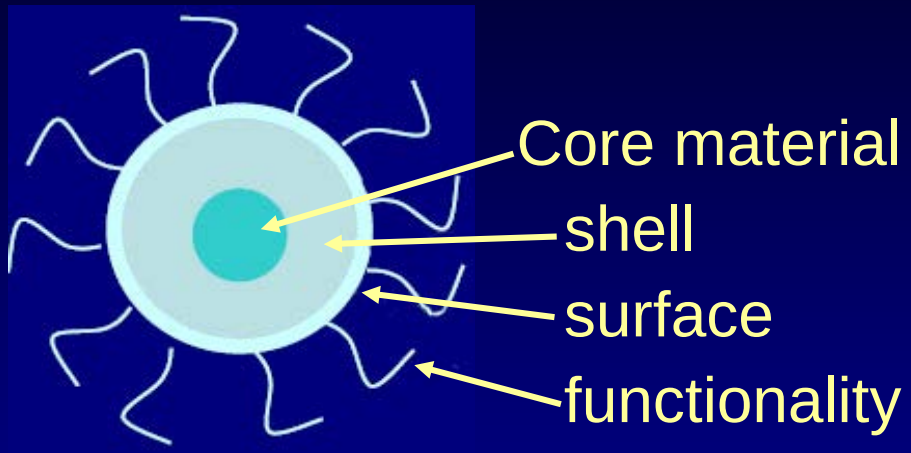


Principles of safer nanotechnology

1. Structure, size, surface
2. Composition
3. Functionality
4. Encapsulation
5. Reduce the quantity

Adapted from C. Morose
J Clin Product, 2010.

Nanotechnology-based safe-by-design strategies for circumvention of toxicity



Modulable determinants

MORPHOLOGY: size, shape
COMPOSITION: metal content, impurities.
PHYSICO-CHEMICAL: solubility, dispersibility, stability, agglomeration.
BIOCHEMICAL: surface bioreactivity, ROS generation, protein corona
BIOKINETIC: intracellular penetration, organ distribution, biodegradation, clearance, release of constituents
FUNCTIONALITY: stealth-like properties, targeting features, stimulus-sensitive component release.

Proposed Occupational Exposure Limits (OEL) for Manufactured Nanomaterials.

Twenty studies proposing a total of 56 OELs for manufactured nanomaterials (MNMs) have been identified (PubMed, Embase).

For carbon nanotubes the proposed values differ with a factor ranging from 30 to 50 and for metals with a factor from 100 to 300.

Exposure to MNMs measured in selected workplaces exceeds even the highest proposed OEL.

Limited applicability of the proposed OELs in the absence validated approaches to standard limit derivation. However, these OELs may be useful as reference values in occupational hygiene practice.

Mihalache et al, Nanotoxicology (2017)

Proposed Occupational Exposure Limits (OEL) for Engineered Nanomaterials.

Benchmark Exposure Levels adjusted by applying defined safety factors (SF) to existing OELs for agents with identical chemical composition.

- SF = 0.5 for soluble NMs
- SF = 0.66 for poorly soluble NMs
- SF = 0.16 for NMs presumed to be mutagenic asthmatogenic, or reproductive toxins

British Standards Institute, 2007

ASSESSING SUBCLINICAL EFFECTS OF AIR POLLUTION. BIOLOGICAL MARKERS

PLASMA

- Interleukin-6 (SI)
- Tumor necrosis factor-α, TNF- α (SI)
- Soluble TNF-α receptor II, sTNF-RII (SI)
- Soluble platelet selectin (sP-selectin) (PA)
- Acute-phase protein C-reactive protein, CRP (SI)

ERYTHROCYTE LYSATE

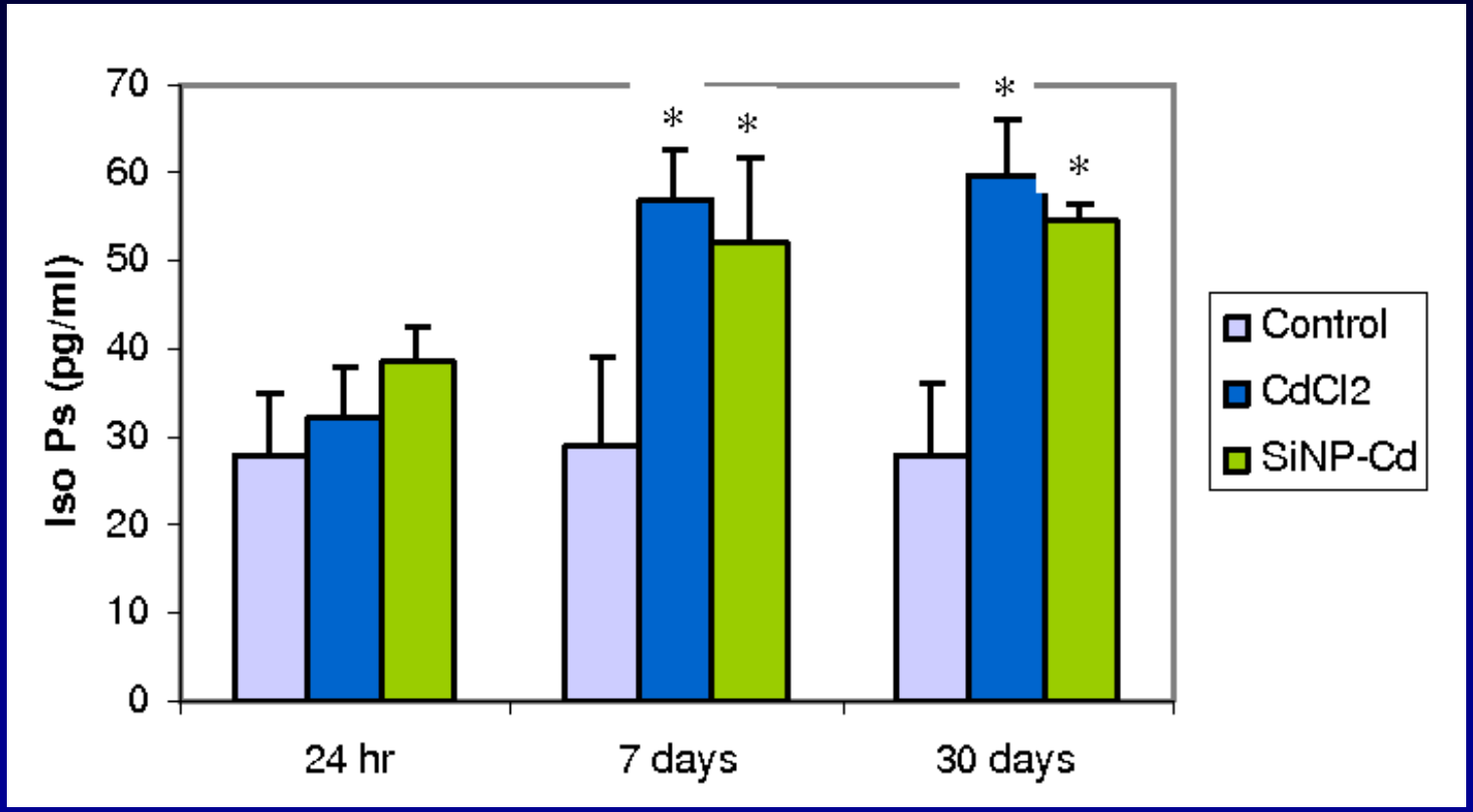
- Cu,Zn-superoxide dismutase (SAD)
- Glutathione peroxidase, GPx-1 (SAD)

SI, Systemic inflammation

PA, Platelet activation

SAD, Systemic antioxidant defence

F_2-Isoprostanes as Biomarkers of Nanoparticle-Induced Oxidative Stress In Vivo.

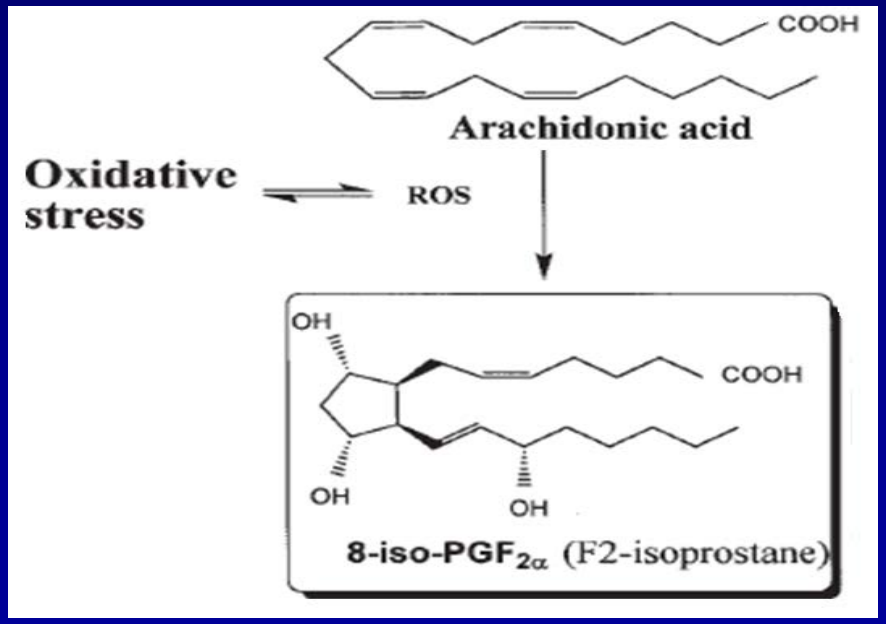


Plasma isoprostane levels in mice treated with a single dose of cadmium-doped silica nanoparticles (250 µg Cd, it).

T. Coccini et al, Toxicology, 2012.

F_2-Isoprostanes as *In Vivo* Biomarkers of Nanoparticle-Induced Oxidative Stress.

Attack of ROS on AA in membranes/ lipoproteins → Esterified F_2-IsoPs → (PLA_2, PAF-AH) → Free F_2-IsoPs → *Metabolism* → *Excretion* → *plasma* / *urine* → F_2-IsoPs and metabolites



AA: Arachidonic Acid
F_2-IsoPs: F_2-Isoprostanes
PLA_2: Phospholipase A_2
PAF-AH: Platelet Activating Factor Acetyl Hydrolase

Adapted from Halliwell and Lee, 2010.

Occupational Exposure to Nanoparticles. Cumulated Health Risks

STRESSOR	RISK
Air pollution, cigarette smoking, wood smoke, environmental tobacco smoke, radon	Lung cancer
Air pollution, COPD, allergic asthma, cigarette smoking, wood smoke, environmental tobacco smoke	Acute respiratory events
Pollutants from air conditioning systems	Infectious respiratory diseases
Air pollution, ischemic heart disease, high blood pressure, sedentarity	Cardiovascular events