Overview:

dai metodi di detection e misura di NP

alla Nanotossicologia

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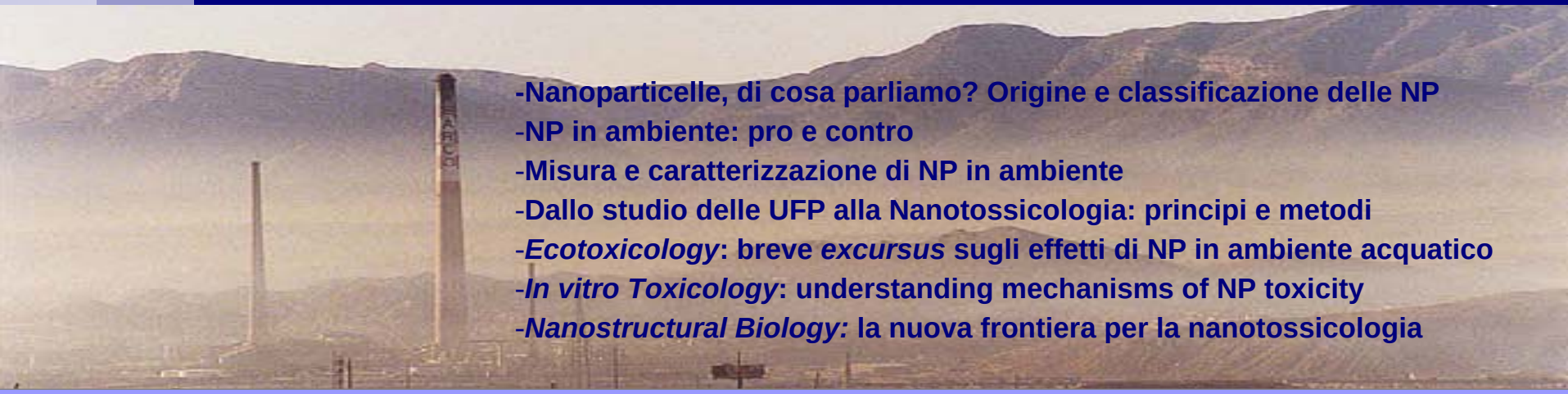

-Nanoparticelle, di cosa parliamo? Origine e classificazione delle NP
-NP in ambiente: pro e contro
-Misura e caratterizzazione di NP in ambiente
-Dallo studio delle UFP alla Nanotossicologia: principi e metodi
-*Ecotoxicology*: breve *excursus* sugli effetti di NP in ambiente acquatico
-*In vitro Toxicology*: understanding mechanisms of NP toxicity
-*Nanostructural Biology:* la nuova frontiera per la nanotossicologia

"*Nanoparticelle: Caratterizzazione e interazioni biologiche*"
Milano, 24-26 Marzo 2010

Shvedova et al., 2010. Close encounters of the small kind: adverse effects of man-made materials interfacing with the nano-cosmos of biological systems. *Annu. Rev. Pharmacol. Toxicol.* 50: 63-88

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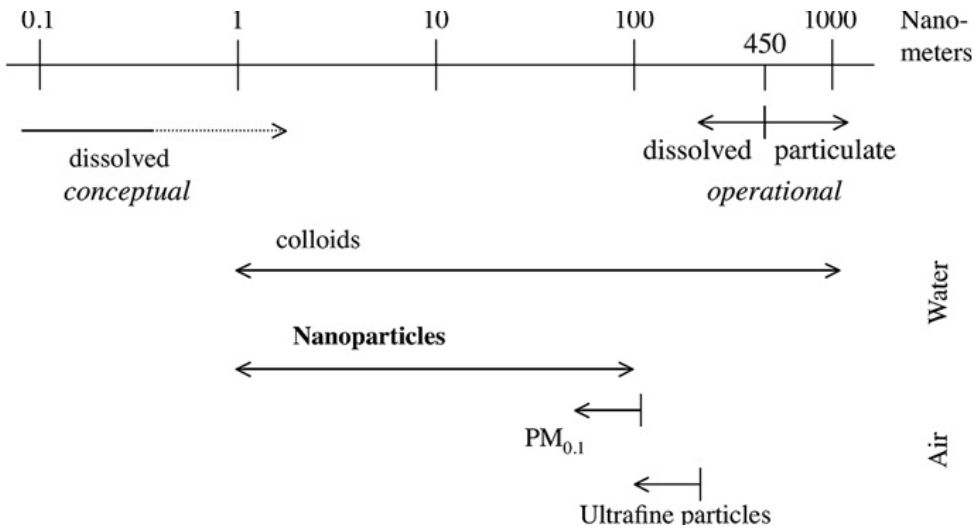


Fig. 1. Definitions of different size classes relevant for nanoparticles.

Nowack and Bucheli, 2007

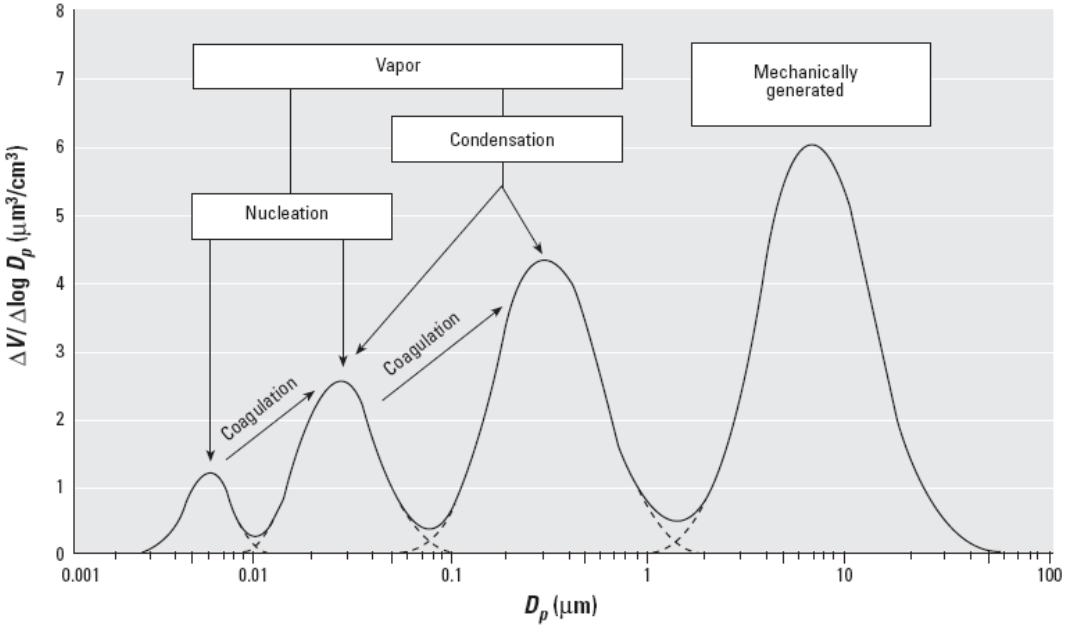


Figure 1. Idealized size distribution of traffic-related particulate matter (U.S. EPA 2004). Dp, particle diameter. The four polydisperse modes of traffic-related ambient particulate matter span approximately four orders of magnitude from < 1 nm to > 10 μm. Nucleation- and Aitken-mode particles are defined as UFPs (< approximately 100 nm). Source-dependent chemical composition is not well controlled and varies considerably. In contrast, NPs (1–100 nm) have well-controlled chemistry and are generally monodispersed (*Oberdorster et al., 2005*)

"Le nanoparticelle (NP) non le ha inventate l'uomo"

Evidenze di NP naturali nei ghiacci di decine di migliaia di anni e nei sedimenti del Cretaceo

Emissione di polveri in atmosfera a livello globale è stimata in ca 1 miliardo di ton/anno

Considerando emissione di UFP, diversi milioni di ton/anno NP

Produzione di Nanomateriali (NM) stimata in qualche migliaio di ton/anno

L'esposizione a NP naturali supera largamente quella a NP di origine antropica

Formazione di NP
- Meccanismi geologici → NP inorganiche
- Meccanismi biologici → NP organiche

Molte forme e abbondanza di NP in ambiente…

Assunto: ***"gli organismi si sono evoluti e adattati a vivere con questi materiali"***

Ma l'adattamento a NP naturali…

… è in funzione della dose di esposizione

…e della velocità di cambiamento dell'ambiente

Table 1. UFPs/NPs (< 100 nm), natural and anthropogenic sources.

Natural	Anthropogenic	
	Unintentional	Intentional (NPs)
Gas-to-particle conversions	Internal combustion engines	Controlled size and shape, designed for functionality
Forest fires	Power plants	
Volcanoes (hot lava)	Incinerators	Metals, semiconductors, metal oxides, carbon, polymers
Viruses	Jet engines	
Biogenic magnetite: magnetotactic bacteria protoctists, mollusks, arthropods, fish, birds human brain, meteorite (?)	Metal fumes (smelting, welding, etc.)	Nanospheres, -wires, -needles, -tubes, -shells, -rings, -platelets
	Polymer fumes	
Ferritin (12.5 nm)	Other fumes	Untreated, coated (nanotechnology applied to many products: cosmetics, medical, fabrics, electronics, optics, displays, etc.)
Microparticles (< 100 nm; activated cells)	Heated surfaces	
	Frying, broiling, grilling	
	Electric motors	

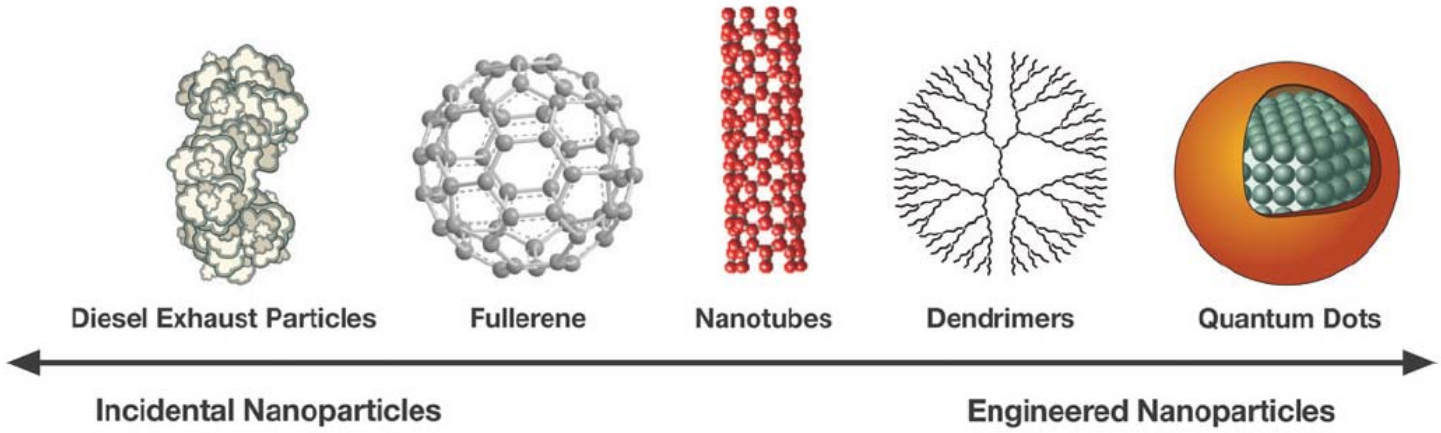


FIG. 1. Examples of incidental and engineered nanoparticles.

Perché NP possono essere pericolose

Anche alcune NP naturali sono dannose (es. polveri vulcaniche) → Anche NP antro possono essere tossiche

Molte NP naturali sono transienti in ambiente (… dissoluzione, aggregazione…) → Molte NP manufatte sono persistenti perché stabilizzate

→ NP possono contenere composti tossici in struttura e concentrazioni che non si verificano in natura

→ NP possono avere forme e strutture che non si ritrovano in natura

Overview of environmental NP

(Biswas & Wu, 2005)

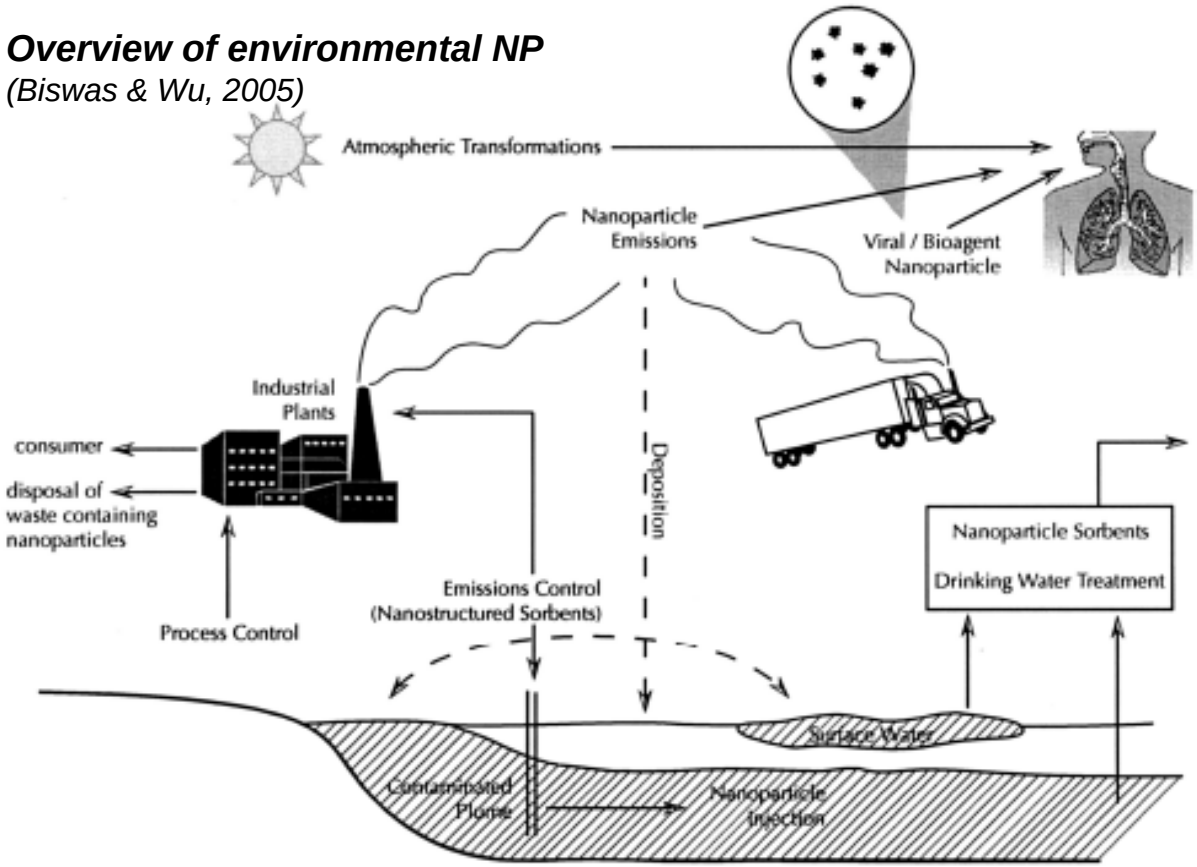


Figure 1. Schematic diagram illustrating nanoparticles in the environment.

Sources of NP

Stationary sources (industrial plants)

Mobile sources (vehicles)

Occupational Environ (welding)

Biological-Geological

Benefits of NP Science & Tech

Filtri nanostrutturati per la cattura di gas nocivi e scarichi

NMs come catalizzatori per ridurre emissioni da automobili

NPs per il rimedio di contaminazioni di acque di falda

Filtri a NP per la potabilizzazione delle acque

"Life history of NPs"

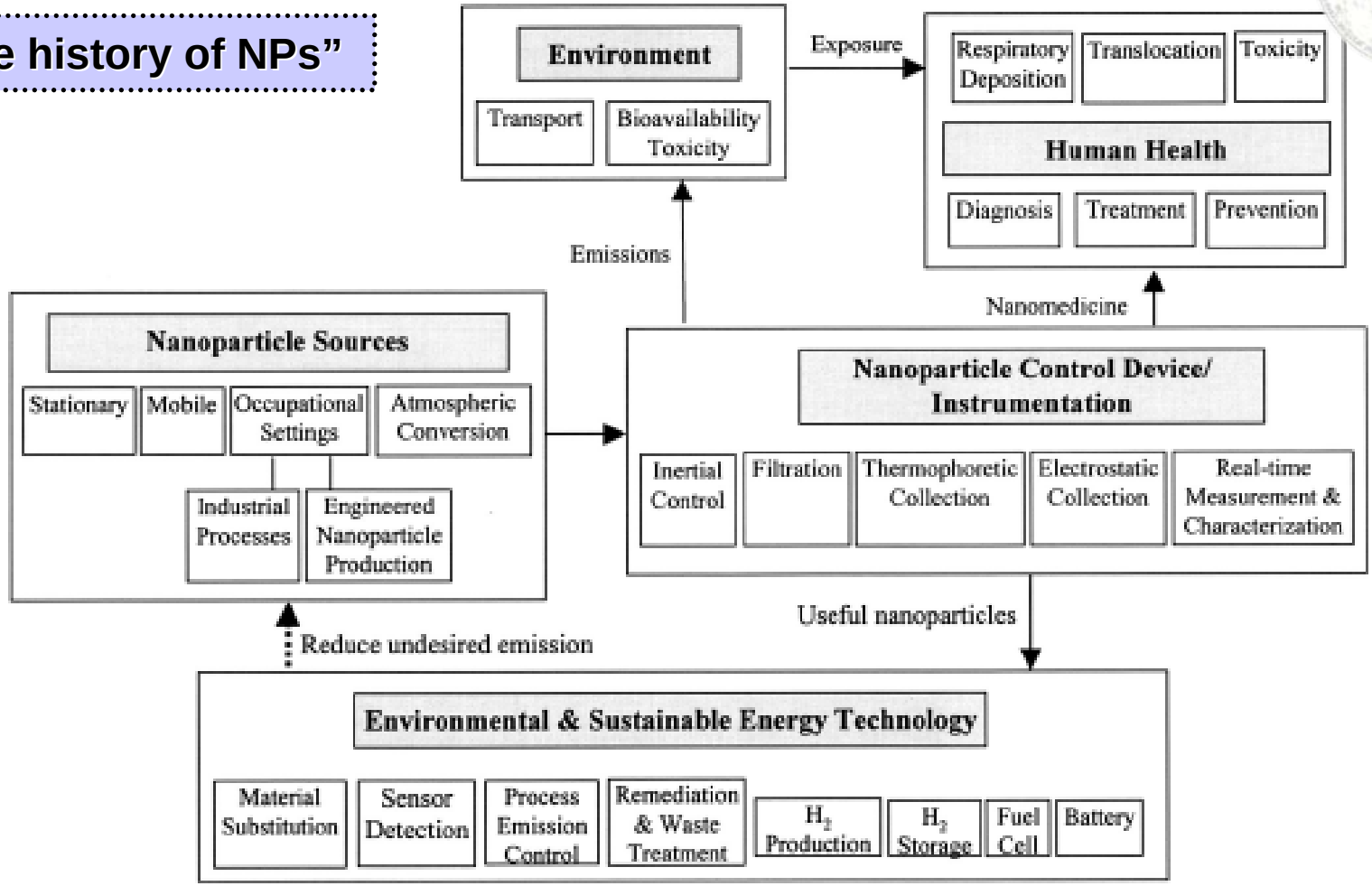


Figure 2. Nanoparticle system reviewed in this paper.

Biswas & Wu, 2005

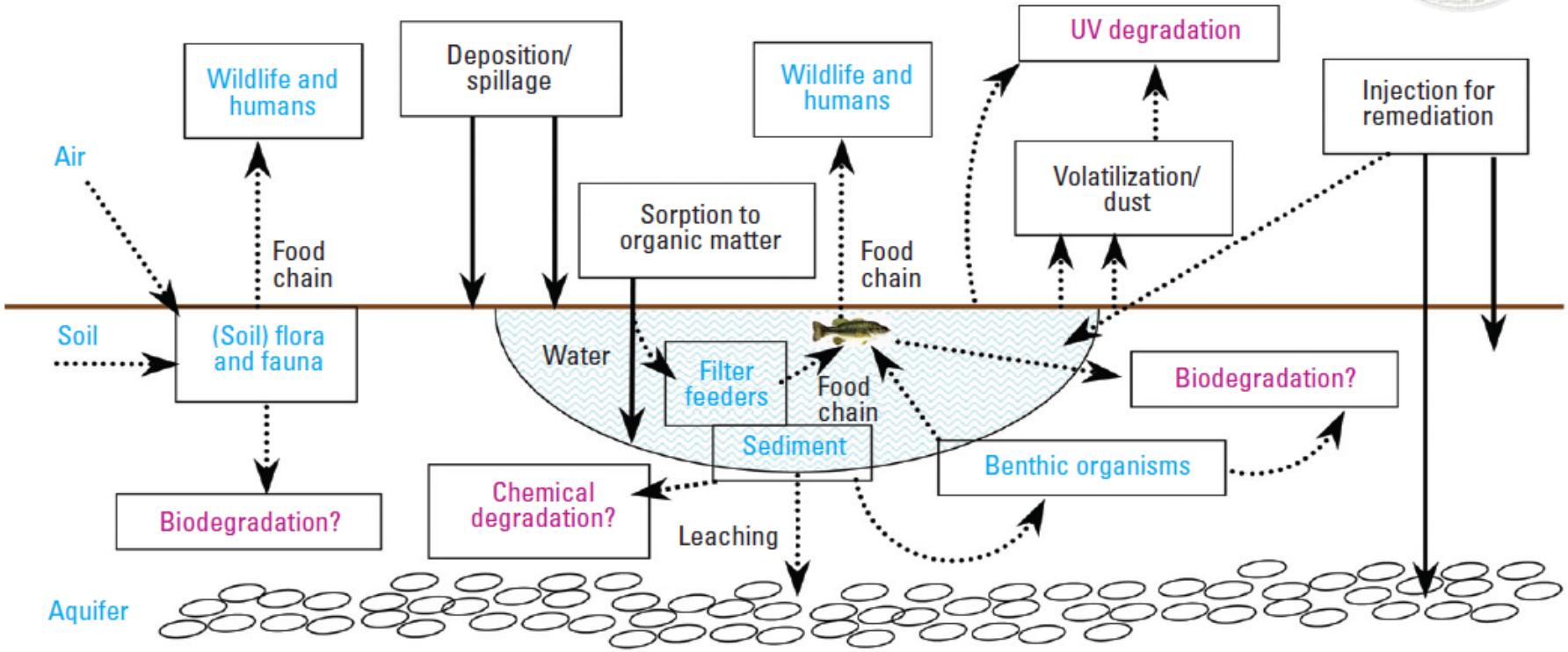


Figure 5. Routes of exposure, uptake, distribution, and degradation of NSPs in the environment. Solid lines indicate routes that have been demonstrated in the laboratory or field or that are currently in use (remediation). Magenta lettering indicates possible degradation routes, and blue lettering indicates possible sinks and sources of NSPs.

Durante i processi produttivi…

Formazione e emissione di NP indesiderate

Produzione di NP utili e funzionalizzate
(Nanomedicina inclusa)

In entrambi i casi, necessità di apparecchiature di controllo/raccolta e misura/caratterizzazione di NP

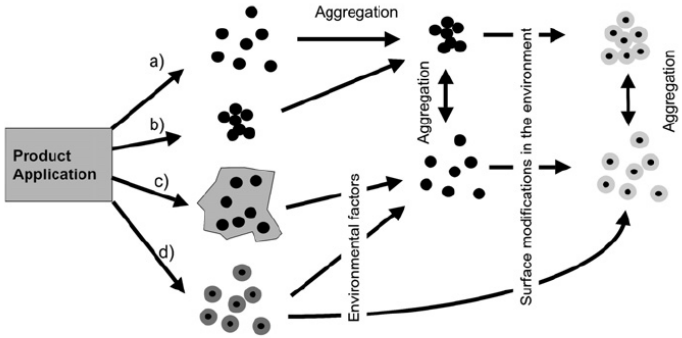


Fig. 3. Release of NP from products and (intended or unintended) applications: (a) release of free NP, (b) release of aggregates of NP, (c) release of NP embedded in a matrix and (d) release of functionalized NP. Environmental factors (e.g. light, microorganisms) result in formation of free NP that can undergo aggregation reactions. Moreover, surface modifications (e.g. coating with natural compounds) can affect the aggregation behavior of the NP.

Nowack & Bucheli, 2007

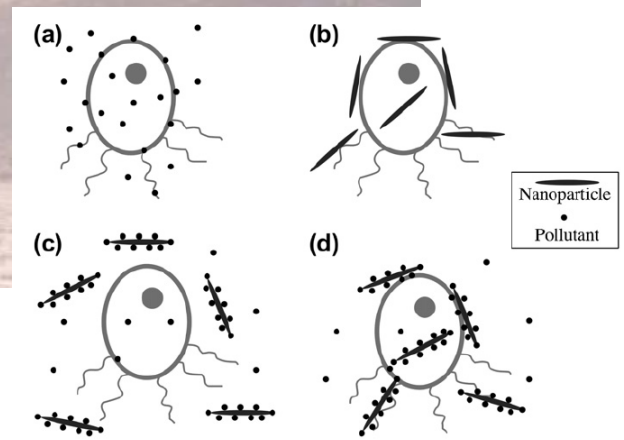


Fig. 4. Scheme of the interactions of pollutants, NP and organisms (algae as example). (a) Adsorption and uptake of pollutant, (b) adsorption and uptake of nanoparticle, (c) adsorption (or absorption) of pollutants onto NP and reduction in pollutant uptake by organisms and (d) adsorption of NP with adsorbed (or absorbed) pollutant and possible uptake of pollutant-NP.

Table 4. Comparison of collection devices for capture of airborne nanoparticles.

Device	Operational Principle	Size Range (Efficiency)	Configurations	Key Advantages	Recommendations
Low-pressure cyclone	Inertia (although enhanced by other methods)	100–60 nm (>98%), 50 nm (~50%)	Axial, tangential, low pressure	Low pressure drop; ease of operation and low cost	• Improve capture efficiencies for nanoparticles by using additional force fields
Filtration	Diffusion and inertia	Up to 5 nm (>95%)	HEPA, packed bed, bag	High capture efficiencies	• Fundamental study of filtration (understanding transition between molecules and nanoparticle behavior) • Develop low pressure drop filters with high capture efficiencies
Thermal precipitators	Thermophoresis	1–100 nm (>99%)	Plate	Capture independent of particle size	• Determine scale up criteria (used only for small scale applications)
Electrostatic precipitators	Electrical mobility	60–100 nm (>95%) efficiency drops below 60%	Tubular, parallel plate	High capture efficiency with low pressure drop; low operating costs	• Understand charging of nanoparticles • Design of systems with other forms of radiation to enhance capture • More detailed studies of pathways of inactivation of biological particles • Compact high voltage sources, reduce cost

Strumenti e tecniche di misura di NP in ambiente

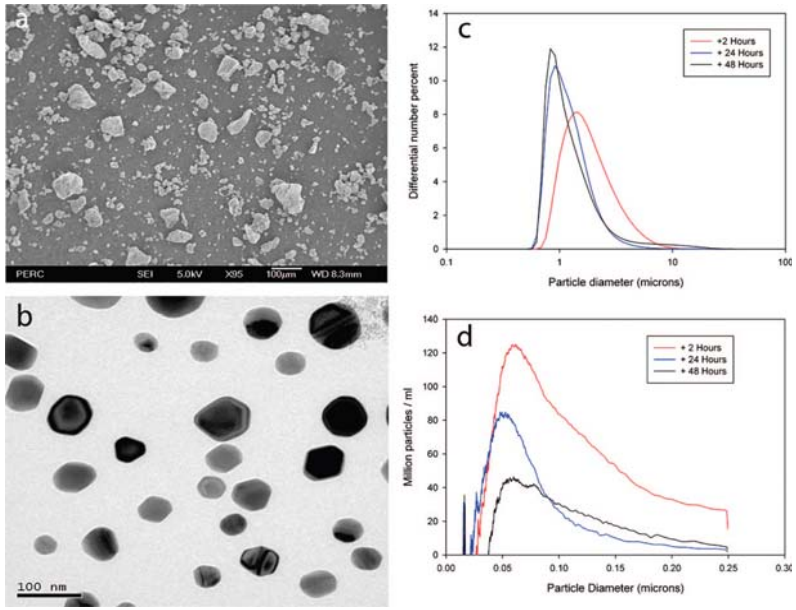
Per determinare la presenza e gli effetti di NP in ambiente vanno presi in considerazione diversi parametri

-Distribuzione dimensionale

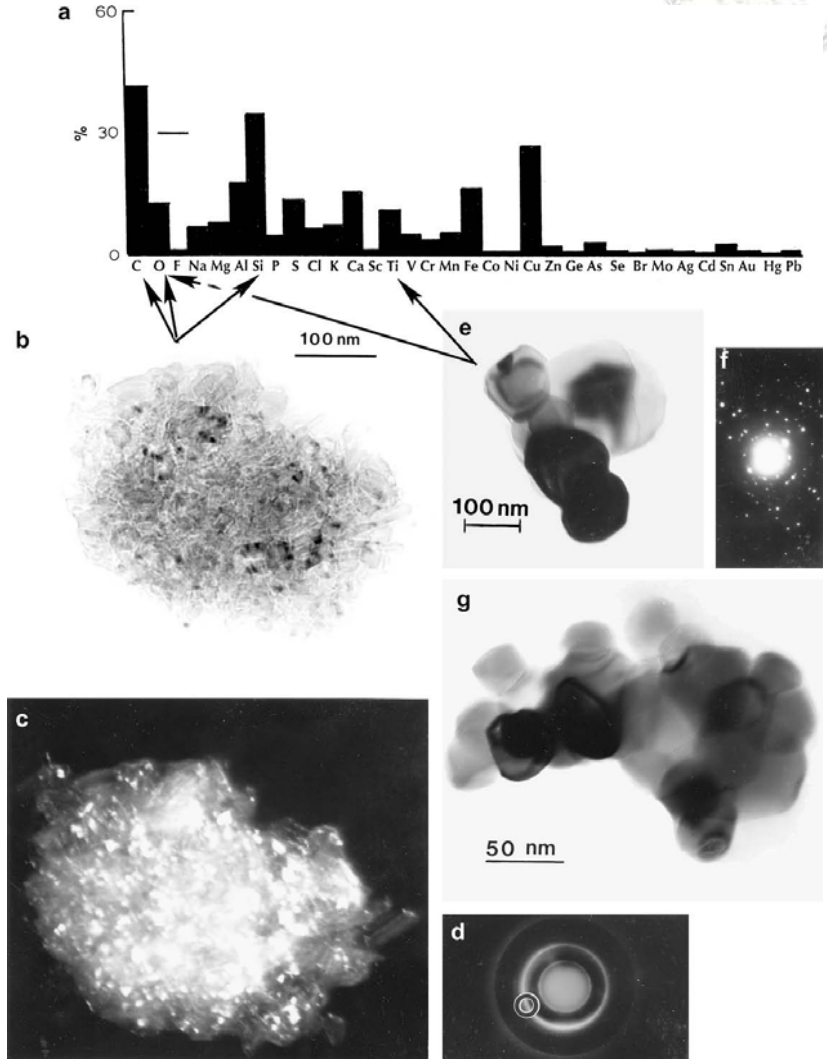
-Area superficiale

-Visualizzazione diretta delle NP

-Makeup chimico e/o fase minerale delle NP



Characterization of Cu NP suspension



Airborne PM characterized by analytical TEM

Tecniche analitiche disponibili per la caratterizzazione ambientale di NP

Table 2 Analytical tools and detection methods used to characterize environmental nanoparticles. See text for abbreviations and citations

		Sample analysis scale	
Parameter	Analytical tool	Whole sample	Single particle
Size fractionation	Centrifugation	X	
	Ultrafiltration	X	
	TFF	X	
	FFF	X	
Size distribution	LLS or DLS	X	
	LIBD	X	
	XRD	X	
	AFM		X
	TEM		X
Surface area	AFM		X
	TEM		X
	BET	X	
Chemical analysis	AAS	X	
	ICPMS/ICPAES	X	
	XRD	X	
	S/TEM EDS		X
	S/TEM EELS		X
	NanoSIMS		X
Direct visualization	AFM		X
	EM		X
Mineral phase/internal structure	TEM SAED		X
	FFT of HR-TEM image		X

Table 3. Nanoparticle characterization techniques.

Method	Observable
Electron microscopy (transmission and scanning)	Real space structure–particle size and morphology; particle morphology
X-ray diffraction	Phase and crystallite size measurements in the 4–40 nm range from Bragg peak linewidths using Scherrer formula[120]
BET surface area	Surface area and porosity of nanoparticles
UV-vis absorption spectroscopy	Fundamental optical gap; interpretation of band gap energies
Raman scattering	Phase analysis by phonons, crystallite size measurements by phonon linewidths; shifts as a function of size because of relaxation of selection rules
Mössbauer spectroscopy	Identification of magnetic behavior through internal fields: superparamagnetism by blocking temperature; identification of chemical shifts and quadrupole effects
FTIR spectroscopy	Vibrational spectra in infrared region. Analysis of surface adsorbed species such as OH radicals
Nuclear magnetic resonance	Localized bonding states (chemical shift and coupling constants) by detecting presence of specific nuclei
X-ray absorption spectroscopy EXAFS, XANES	Element-specific information on coordination environment to determine structure of nanocrystalline domains

Notes: BET = Brunauer-Emme H-Teller; FTIR = Fourtier transform infrared; EXAFS = edge X-ray absorption near edge structure; XANES = X-ray absorption fine structure.

Biswas & Wu, 2005

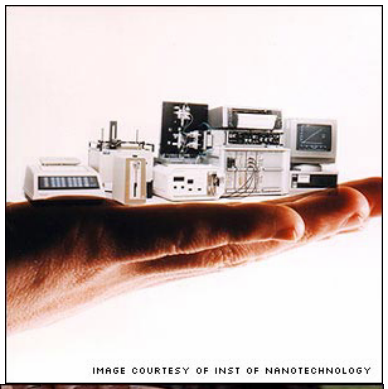


IMAGE COURTESY OF INST OF NANOTECHNOLOGY


Exposure Assessment
Materials Characterization
Hazard Identification & Toxicology
Risk Assessment
Risk Management

Table 7. Summary of overall recommendations.

Sources of nanoparticles	• Fundamental understanding of nanoparticle formation in a spectrum of systems, both natural and man-made • Quantitative description (measurement) of nanoparticle size distribution and composition of emissions; Developing guidelines for proper sampling protocols • Establishment of number based emission regulations and regulations for nanoparticle precursors (condensable species) • Understanding of the life-cycle of engineered nanomaterials
Control of nanoparticle emissions	• Design of high-efficiency nanoparticle emission control systems for specific applications • Systematic approaches to modify processes to tailor nanoparticle byproduct so it is readily controllable
Instrumentation and characterization	• Pushing the limits of real-time aerosol instrumentation to measure sub-3 nm (1 nm)-sized particles • Real-time composition characterization of nanoparticles • Creation of a database of properties of commonly encountered nanoparticles as a function of size
Exposure and health effects	• Development of a database of toxicological properties of nanoparticles as a function of size and composition • Accurate exposure and respiratory models need to be developed through integration of theoretical modeling and experimental measurement • Guidelines and criteria for workplaces and research laboratories • Understanding of transport and bioavailability of nanoparticles in the environment / ecosystem
Environmental nanotechnology	• Development of novel methodologies for remediation and establishing guidelines for implementation so that there is no adverse impact • Procedures for timely implementation and adoption of safe nanotechnologies • Enabling the development of alternative and sustainable energy sources

Metodi sperimentali mutuati dalla tossicologia e dalla farmacologia classica

Necessità di adattamento delle tecniche e dei protocolli a causa del particolare comportamento fisico-chimico di NP

Richiamo della CE alla nanotossicologia

Protocolli internazionali preliminari (OECD, ISO…)

Inserimento nel REACH di NP?

Nanomaterials and OECD test guidelines

Background

The scientific discussion regarding the properties of nanomaterials has raised the question of whether current Organisation for Economic Co-operation and Development (OECD) Test Guidelines are capable of appropriately addressing their toxicological profile and environmental behaviour. Therefore, the OECD 'Working Party on Manufactured Nanomaterials' established a project to review the existing guidelines and identify possible needs for development of new and/or revision of existing ones by the end of 2008.

Terms of reference

- Review existing OECD test guidelines for adequacy in addressing nanomaterials in the areas of effects on biotic systems (section 2), degradation and accumulation (section 3) and human health (section 4).
- Identify key endpoints, exposure routes and critical effects for each section and evaluate whether existing guidelines suitably address these.
- Develop recommendations for possible needs to generate new or revised guidelines in each of the sections.
- Develop guidance on how to prepare and administer dosing material for studies in each of the sections.
- Evaluate other currently used non-OECD methods (in vitro/in vivo) that have the potential to be used to refine the testing strategy for the hazard and risk assessment of nanomaterials.

Update March 2010

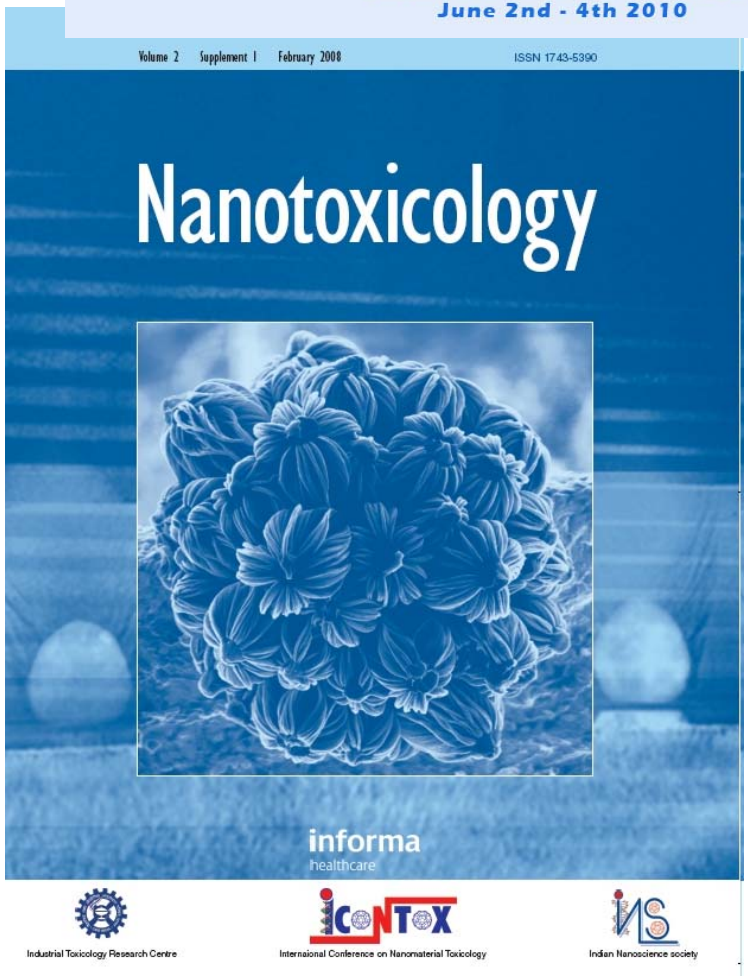
As soon as the respective OECD reports are released, they will be uploaded onto ECETOC's members' website. The task force is still kept alive to provide comments to the work programme and future report on alternative methods.

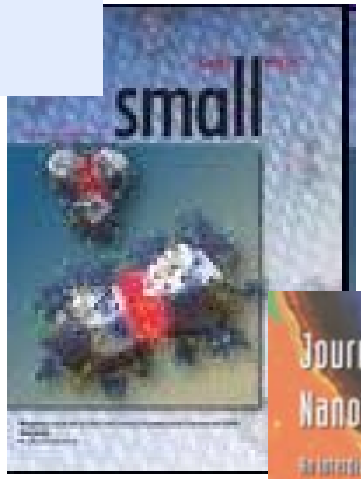
Further information from :

OECD Working Party on Nanotechnology

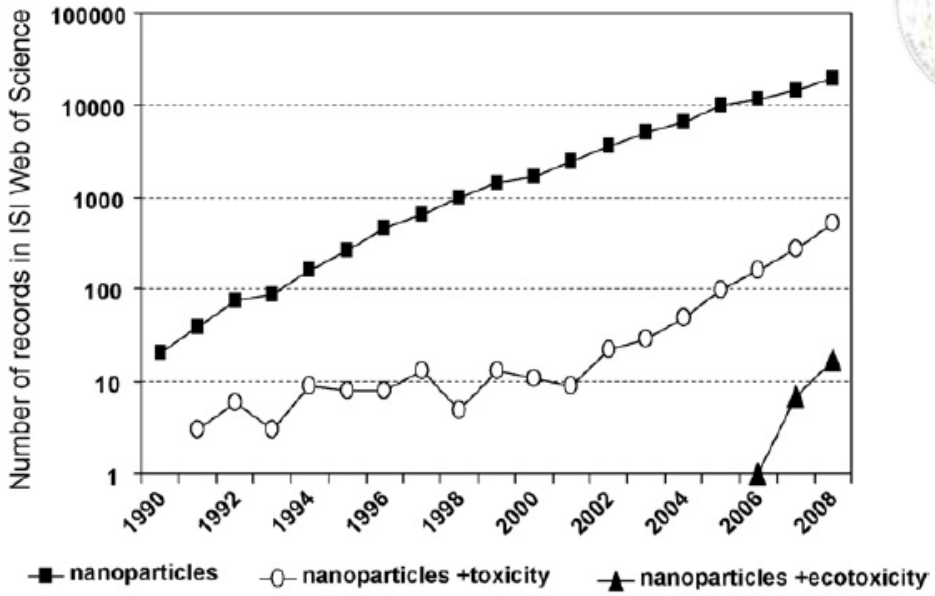
OECD Working Party on Nanotechnology (WPN): Vision Statement

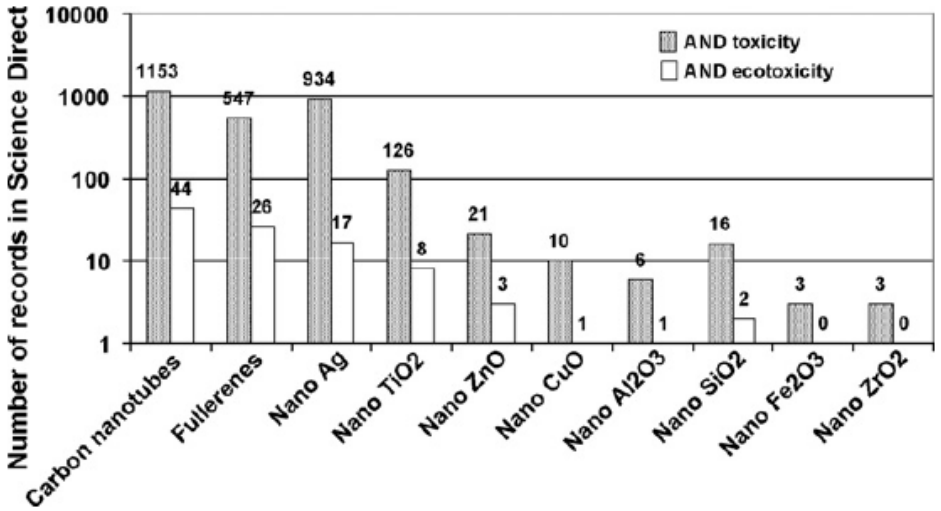
Nanotoxicology 2010
EDINBURGH
June 2nd - 4th 2010





Nanoparticelle,
Nano-tossicologia
e
Nano-ecotossicologia
nella letteratura scientifica





Exposures to airborne nanosized particles (NSPs; < 100 nm) have been experienced by humans throughout their evolutionary stages, but it is only with the advent of the industrial revolution that such exposures have increased dramatically because of anthropogenic sources such as internal combustion engines, power plants, and many other sources of thermodegradation.

The rapidly developing field of nanotechnology is likely to become yet another source for human exposures to NSPs—engineered nanoparticles (NPs)—by different routes: inhalation (respiratory tract), ingestion [gastrointestinal (GI) tract], dermal (skin), and injection (blood circulation).

…nasce la **Nanotossicologia** (termine coniato nel 2004-2005)
Quando, le caratteristiche chimico-fisiche uniche delle NP suggeriscono un'imprevedibile interazione con cellule e tessuti e portano un'evoluzione della tossicologia tradizionale di particelle e fibre

Donaldson et al., 2004 – *Occup. Environ. Med.* 61:727-28
Oberdorster et al., 2005 – *Environ. Health Perspect.* 113:823-39
Seaton and Donaldson, 2005 – *Lancet* 365:923-24

Dalle miniere di carbone alla nanotecnologia

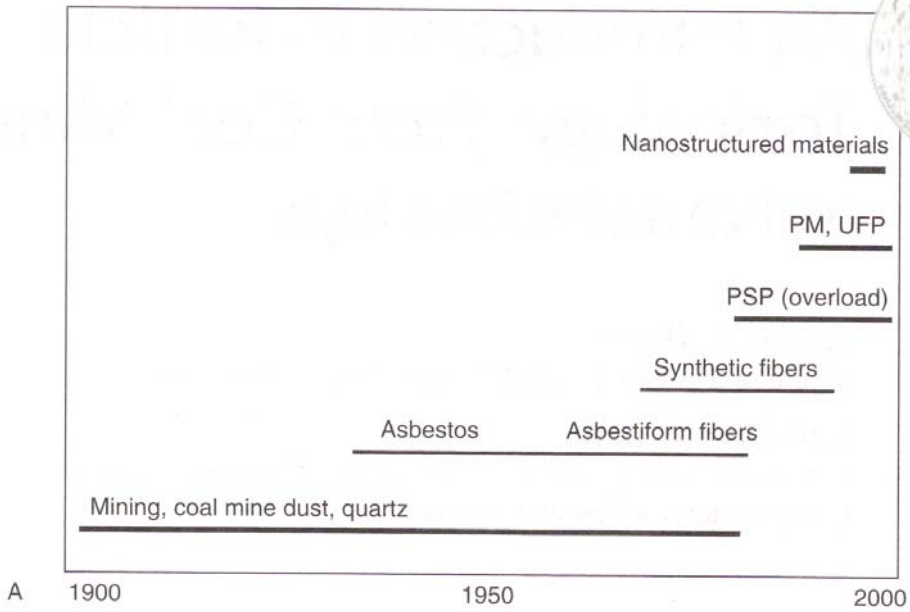
La storia della tossicologia delle particelle affonda le radici negli studi di tossicità di polveri sui lavoratori delle miniere di carbone…

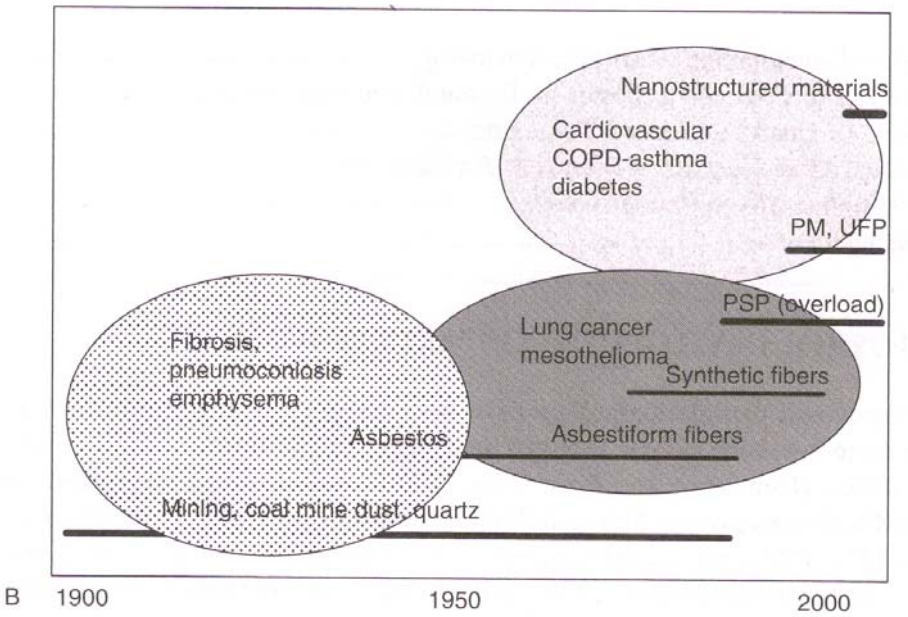
passa attraverso il problema dell'asbesto, alle particelle ambientali (PM),

per arrivare alle UFP

e infine alle NP ingegnerizzate.

(Borm and Donaldson, 2007. in "Particle Toxicology", CRC Press)



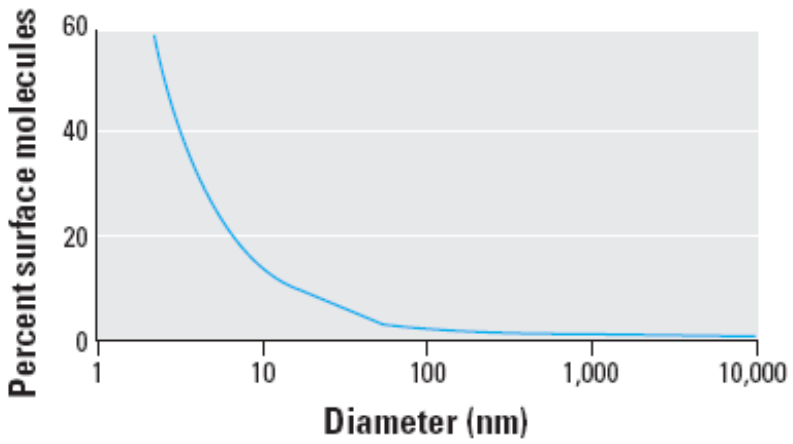


Caratteristiche delle NP e studi tossicologici

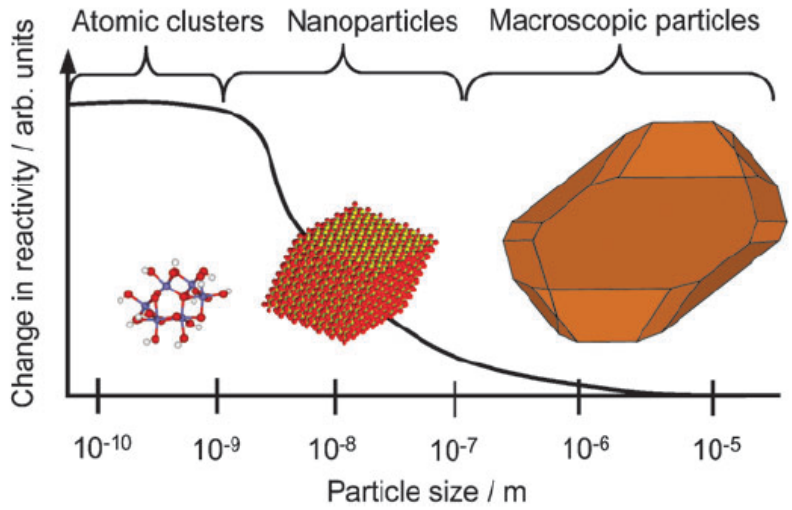
(è necessario caratterizzare a fondo il "sistema NP")

Table 2. Particle number and particle surface area per 10 µg/m^3 airborne particles.

Particle diameter (µm)	Particle no. (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



- Forma e dimensione
- Area superficiale
- Reattività superficiale
- Stato di aggregazione
- Comportamento idrodinamico



Nanomaterials properties driving adverse effects

Correlations between phisico-chemical properties of NMs and biological and toxicological outcomes

(Schvedova et al., 2010)

- **Dose-dependent toxicity**

not always NP effects are correlated with particle mass dose (high conc, high agglomeration?!)

- **Size-dependent toxicity**
- **Surface-area-dependent toxicity**
- **Crystalline-structure-dependent toxicity**
- **Surface-coating dependent toxicity**

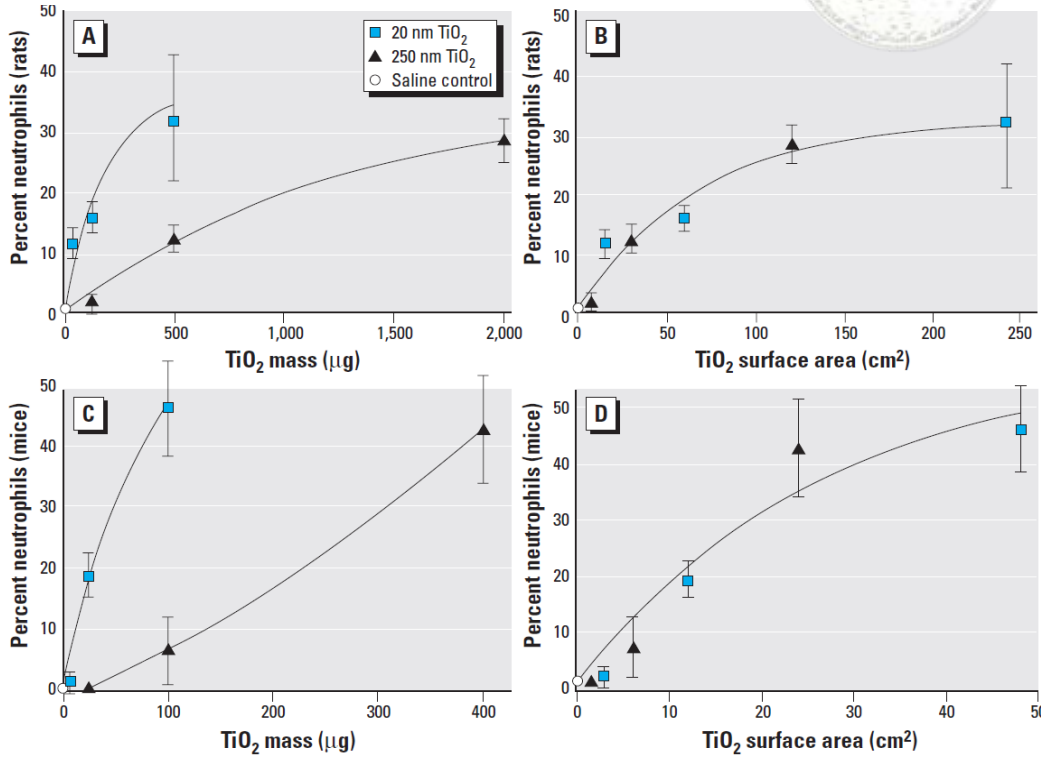


Figure 4. Percentage of neutrophils in lung lavage of rats (A,B) and mice (C,D) as indicators of inflammation 24 hr after intratracheal instillation of different mass doses of 20-nm and 250-nm TiO2 particles in rats and mice. (A,C) The steeper dose response of nanosized TiO2 is obvious when the dose is expressed as mass. (B,D) The same dose response relationship as in (A,C) but with dose expressed as particle surface area; this indicates that particle surface area seems to be a more appropriate dosemetric for comparing effects of different-sized particles, provided they are of the same chemical structure (anatase TiO2 in this case). Data show mean ± SD. *Oberdorster et al., 2005 (EHP)*

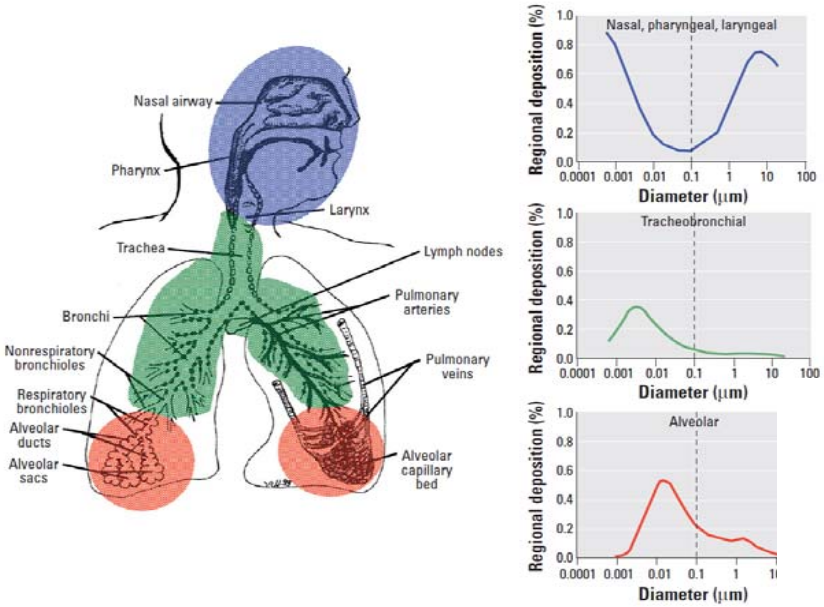


Figure 8. Predicted fractional deposition of inhaled particles in the nasopharyngeal, tracheobronchial, and alveolar region of the human respiratory tract during nose breathing. Based on data from the Internation Commission on Radiological Protection (1994). Drawing courtesy of J. Harkema.
Oberdorster et al., 2005 (EHP)

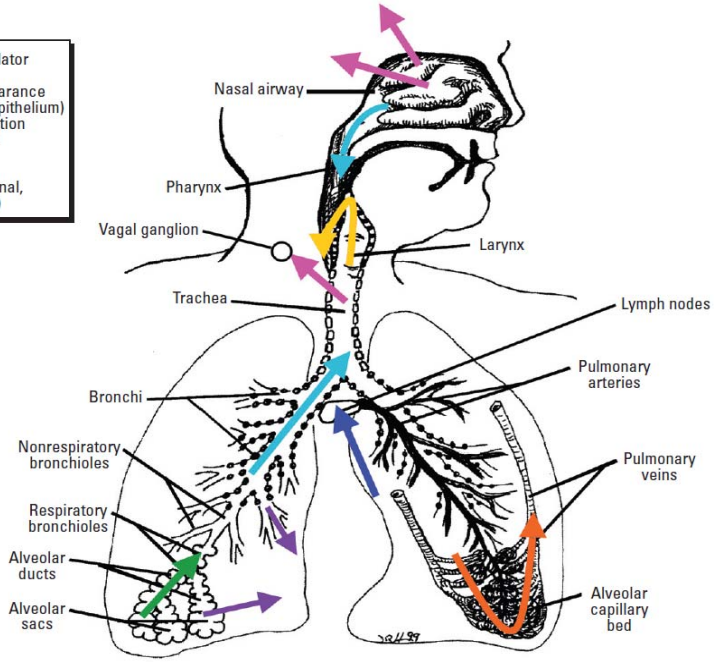
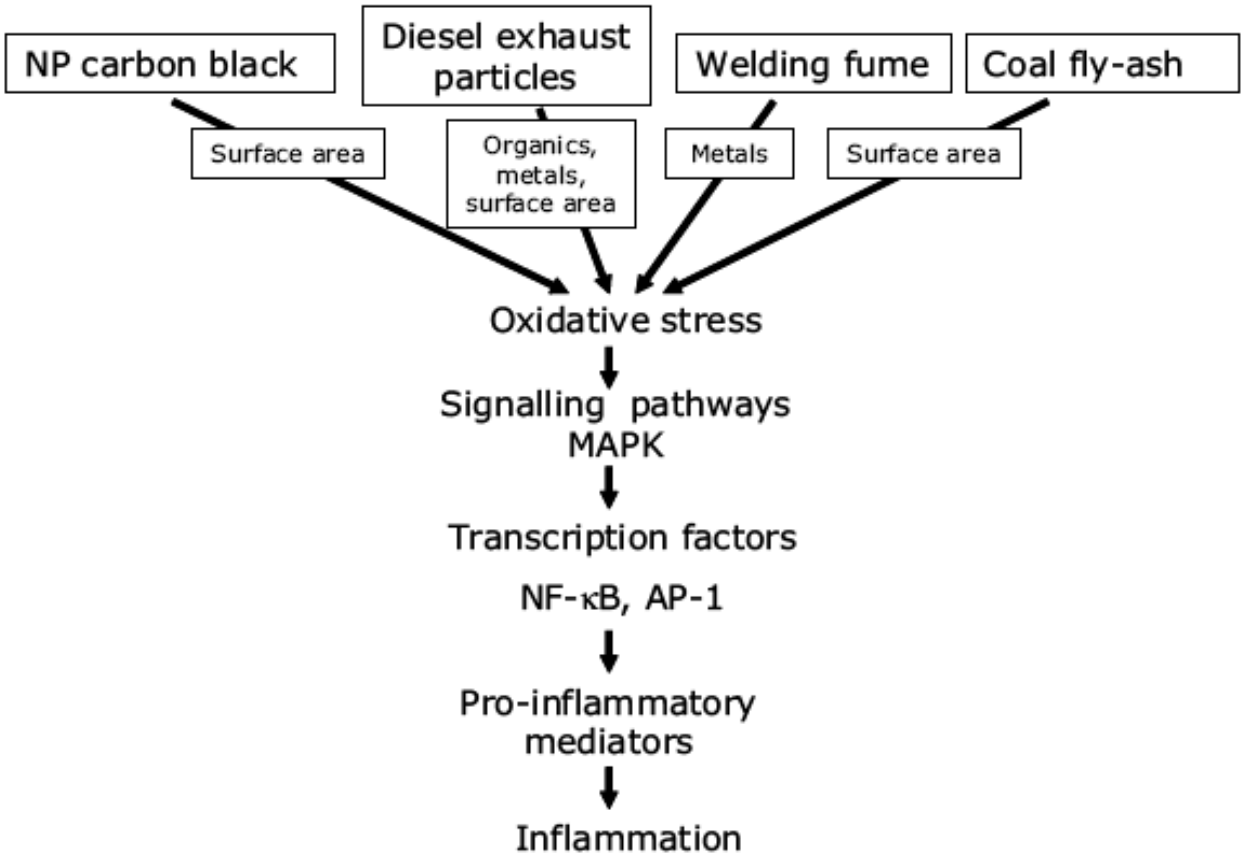
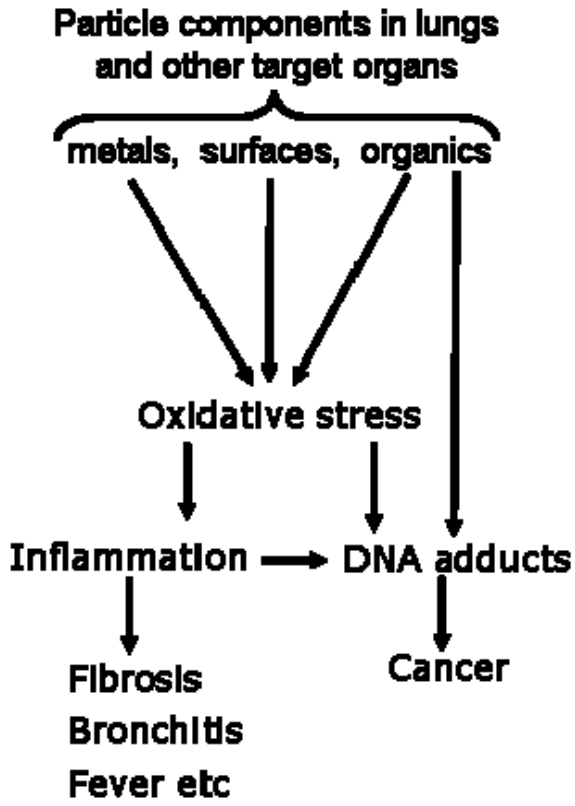


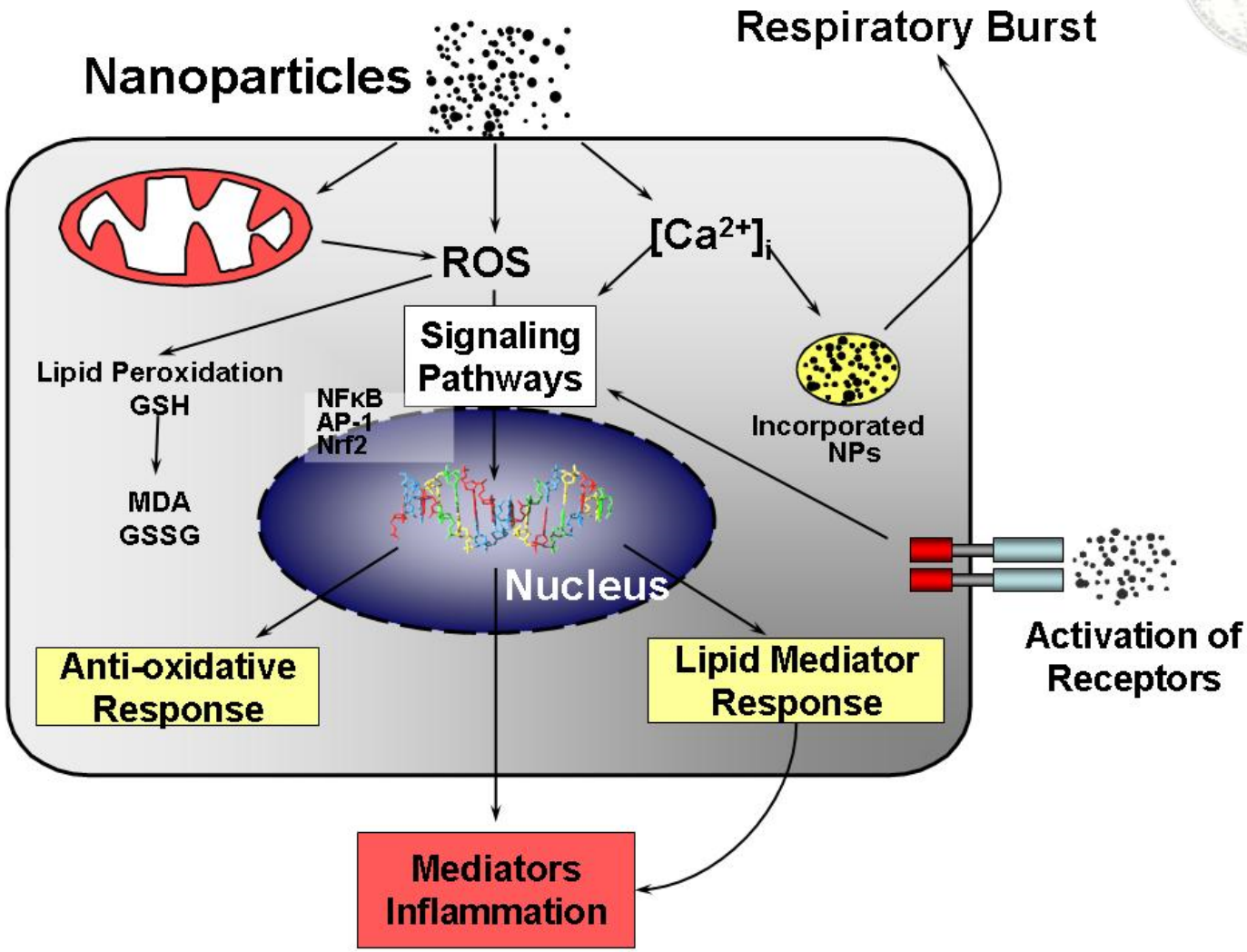
Figure 9. Pathways of particle clearance (disposition) in and out of the respiratory tract. There are significant differences between NSPs and larger particles for some of these pathways (see "Disposition of NSPs in the respiratory tract"). Drawing courtesy of J. Harkema.

Pathways ormai classici negli studi di inhalation toxicology di UFP e NP





Donaldson et al., 2005


Respiratory Burst
Nanoparticles
ROS
$[Ca^{2+}]_i$
Signaling Pathways
Lipid Peroxidation
GSH
MDA
GSSG
NFκB
AP-1
Nrf2
Incorporated NPs
Nucleus
Activation of Receptors
Anti-oxidative Response
Lipid Mediator Response
Mediators Inflammation

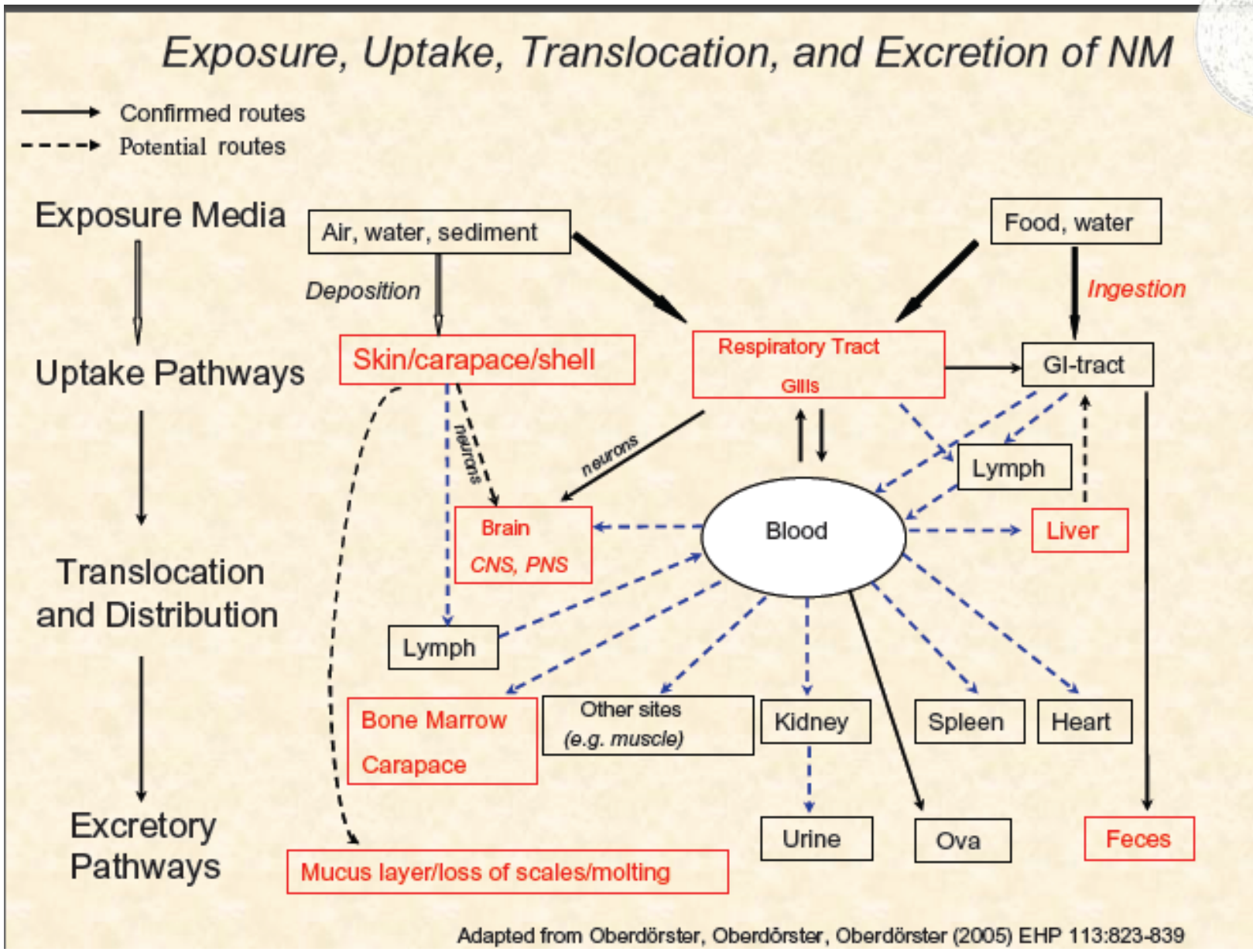
Impact of Particles in the Environment

•Toxicity of manufactured nanoparticles
•Mechanism of action
•Nanoparticlesof natural products versus macroparticles
•Will the organisms interact differently with nanoparticlesthan larger particles?
•Ecosystem impact?
–Bioaccumulation
–Fate
–Changes in species interactions-behavior

Manufactured nanoparticles: Traditional Toxicity Tests

•Toxicity tests
–Exposure to particles for 48 hours
–Determination of mortality rate

•Daphnia spp.
•Abundant in freshwater
•Filter feeders
•Crucial to food web


Exposure, Uptake, Translocation, and Excretion of NM
Confirmed routes
Potential routes
Exposure Media
Uptake Pathways
Translocation and Distribution
Excretory Pathways
Air, water, sediment
Food, water
Deposition
Ingestion
Skin/carapace/shell
Respiratory Tract
Gills
GI-tract
neurons
neurons
Lymph
Brain
CNS, PNS
Blood
Liver
Lymph
Bone Marrow
Carapace
Other sites
(e.g. muscle)
Kidney
Spleen
Heart
Urine
Ova
Feces
Mucus layer/loss of scales/molting
Adapted from Oberdörster, Oberdörster, Oberdörster (2005) EHP 113:823-839

Embrioni di *Xenopus laevis*

Cu++ | Zn++

CB <50 nm | CuO <50 nm | TiO_2<100nm (miscela commerciale) | ZnO <50 nm

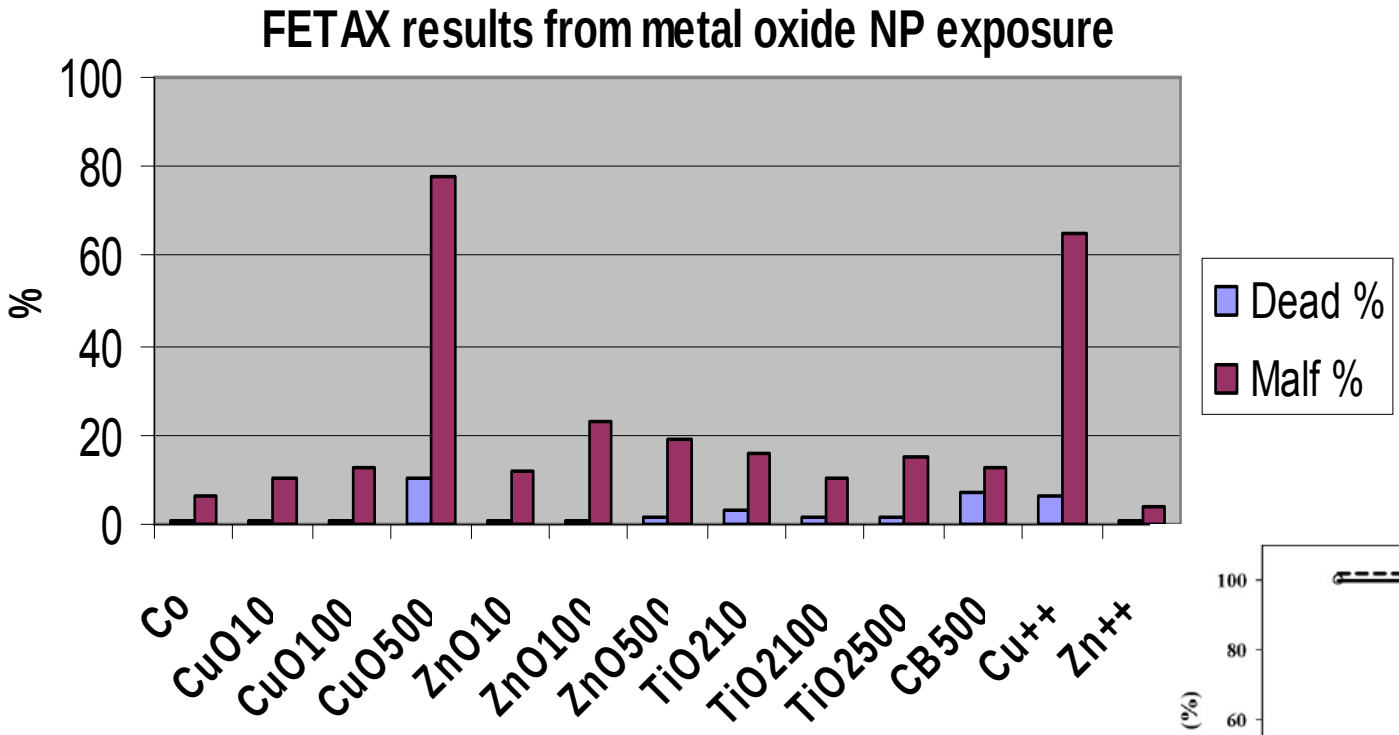
dose

Controllo | 10 mg/L | 100 mg/L | 500mg/L | 0,2 mg/L | 0,5 mg/L

96h

CONDIZIONI SEMI-STATICHE

% Mortalità | % Malformati | Frequenza malformazioni | Ritardo sviluppo | Analisi in microscopia



Embriotossicità di CuO NP, mimata da ione solubile

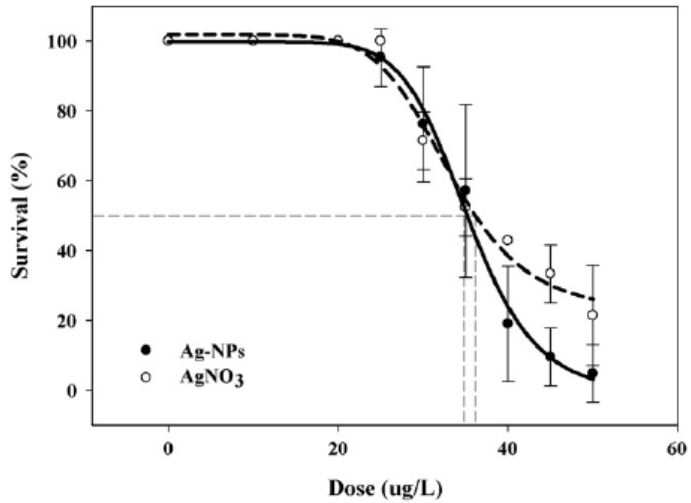
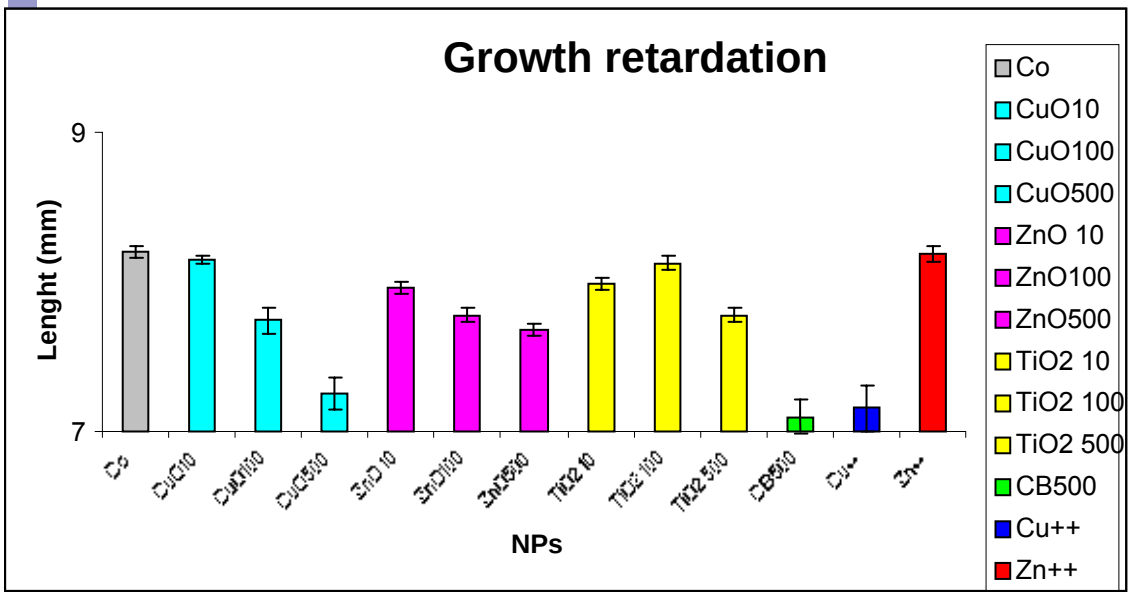
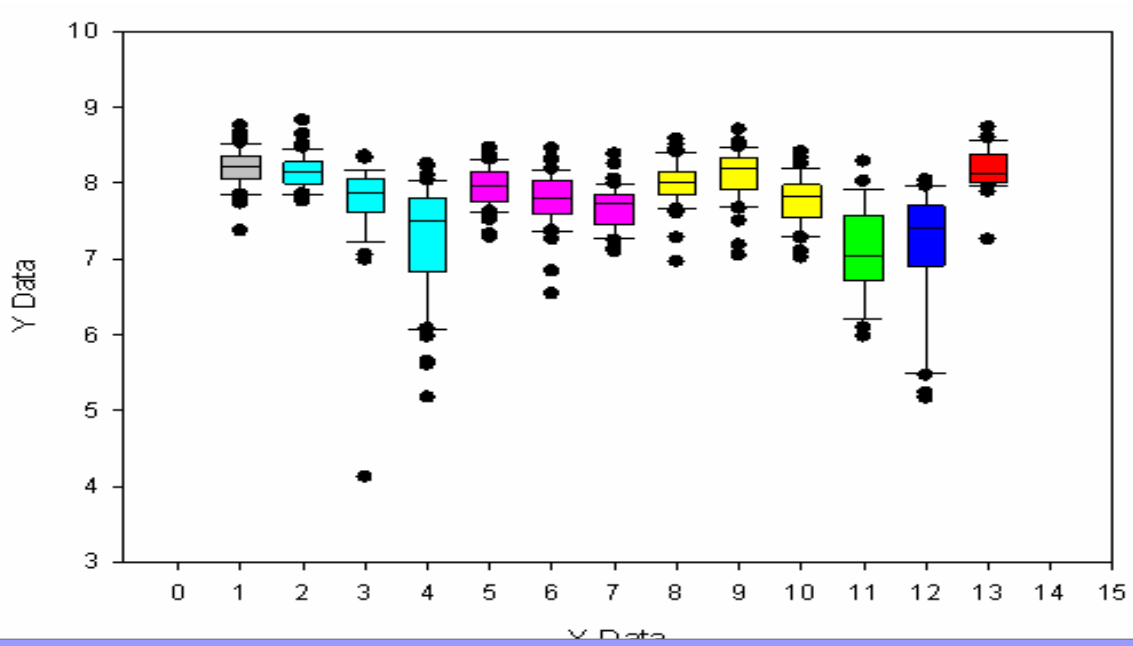


Fig. 2. Acute toxicity tests with the silver nanoparticles (●) and silver nitrate (○) on juvenile Medaka for 96 hrs. Data points indicate the percent survival (mean ± SEM of triplicate). Dashed drop lines indicate the LC_{50} concentrations for each chemical exposure.

Chae et al., 2009



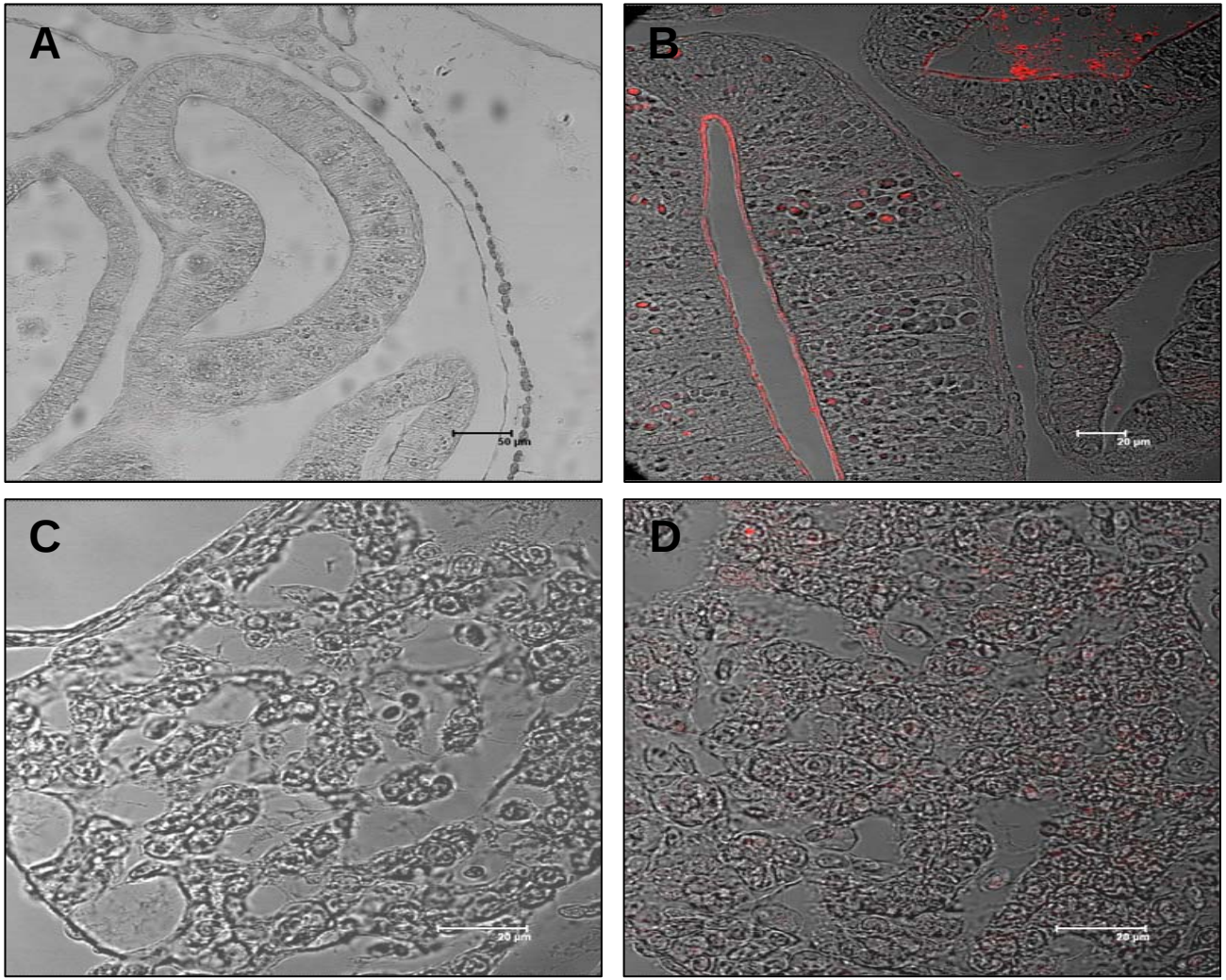
(Concentrazione di ioni Cu^{++} e Zn^{++} rilasciati da NP nel mezzo di coltura, determinata mediante **AAS**)



Effetti embriotossici di NP di ossidi di metallo in organismi acquatici sono mediati soprattutto da ioni solubili.

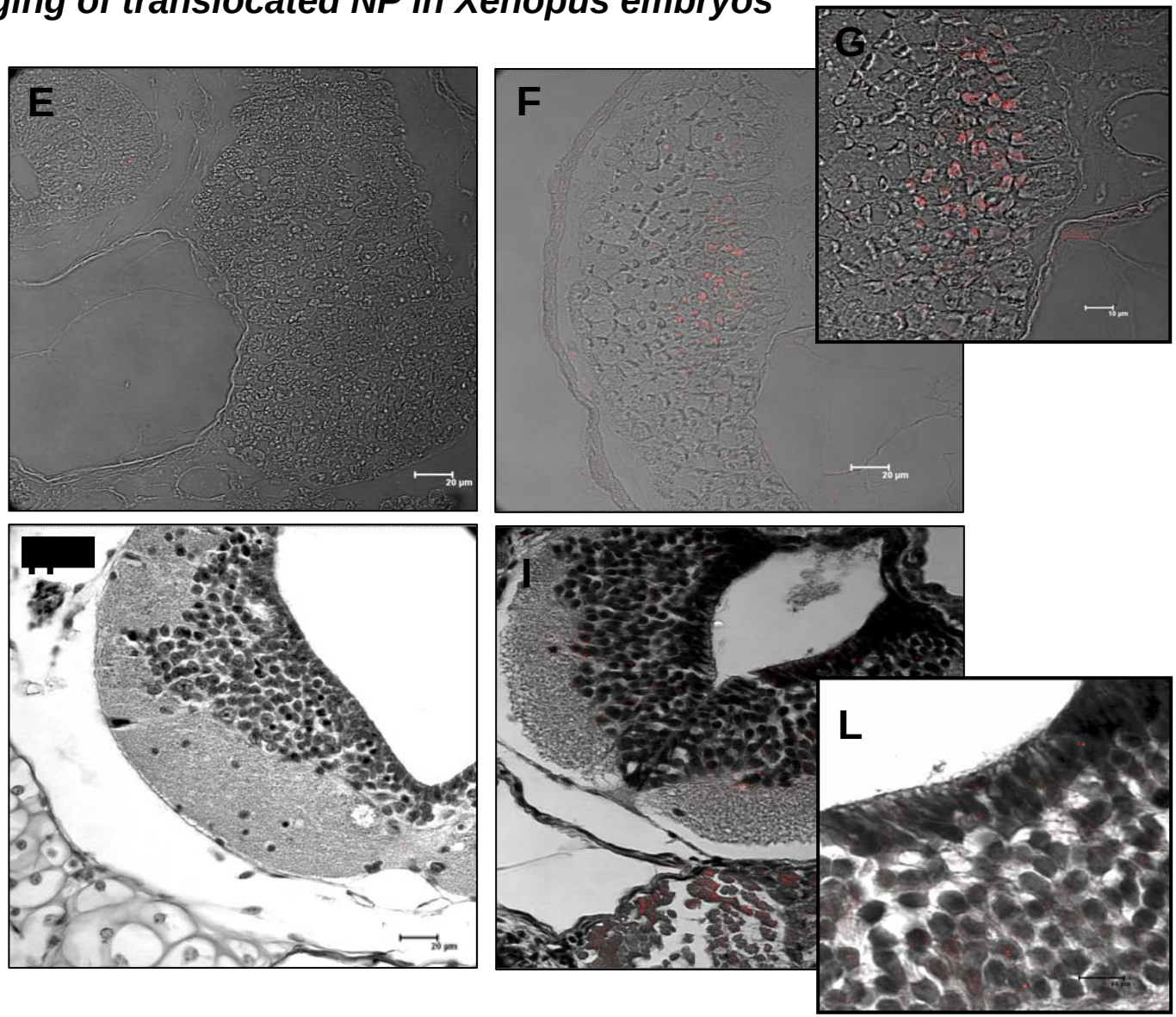
Non sono tuttavia trascurabili **effetti subletali e nascosti** delle NP stesse

NP imaging in embryo tissues



Imaging of NP tissue internalization by confocal laser reflection (red spots) in 100ppm CuO exposed embryos. (Gut and liver)

Imaging of translocated NP in Xenopus embryos



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Zebrafish as a correlative and predictive model for assessing biomaterial nanotoxicity ☆

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ABSTRACT

The lack of correlative and predictive models to assess acute and chronic toxicities limits the rapid pre-clinical development of new therapeutics. This barrier is due in part to the exponential growth of nanotechnology and nanotherapeutics, coupled with the lack of rigorous and robust screening assays and putative standards. It is a fairly simple and cost-effective process to initially screen the toxicity of a nanomaterial by using *in vitro* cell cultures; unfortunately it is nearly impossible to imitate a complimentary *in vivo* system. Small mammalian models are the most common method used to assess possible toxicities and biodistribution of nanomaterials in humans. Alternatively, *Danio rerio*, commonly known as zebrafish, are proving to be a quick, cheap, and facile model to conservatively assess toxicity of nanomaterials.

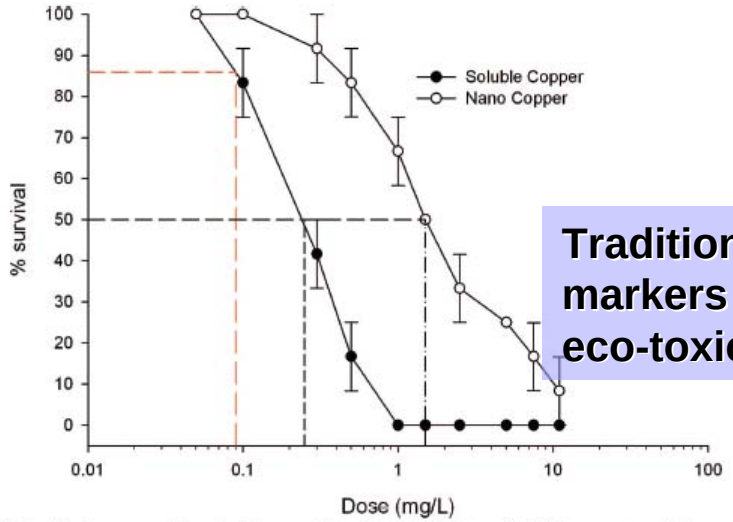
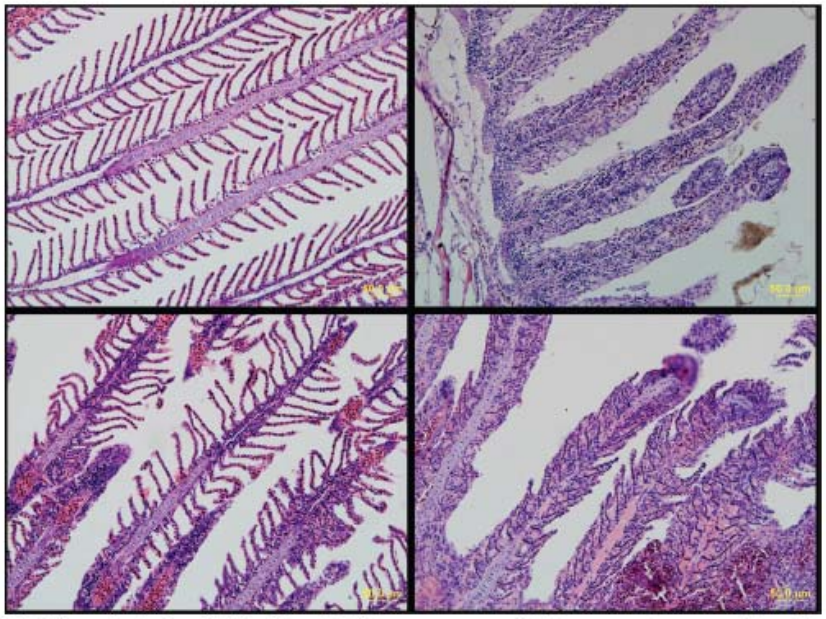
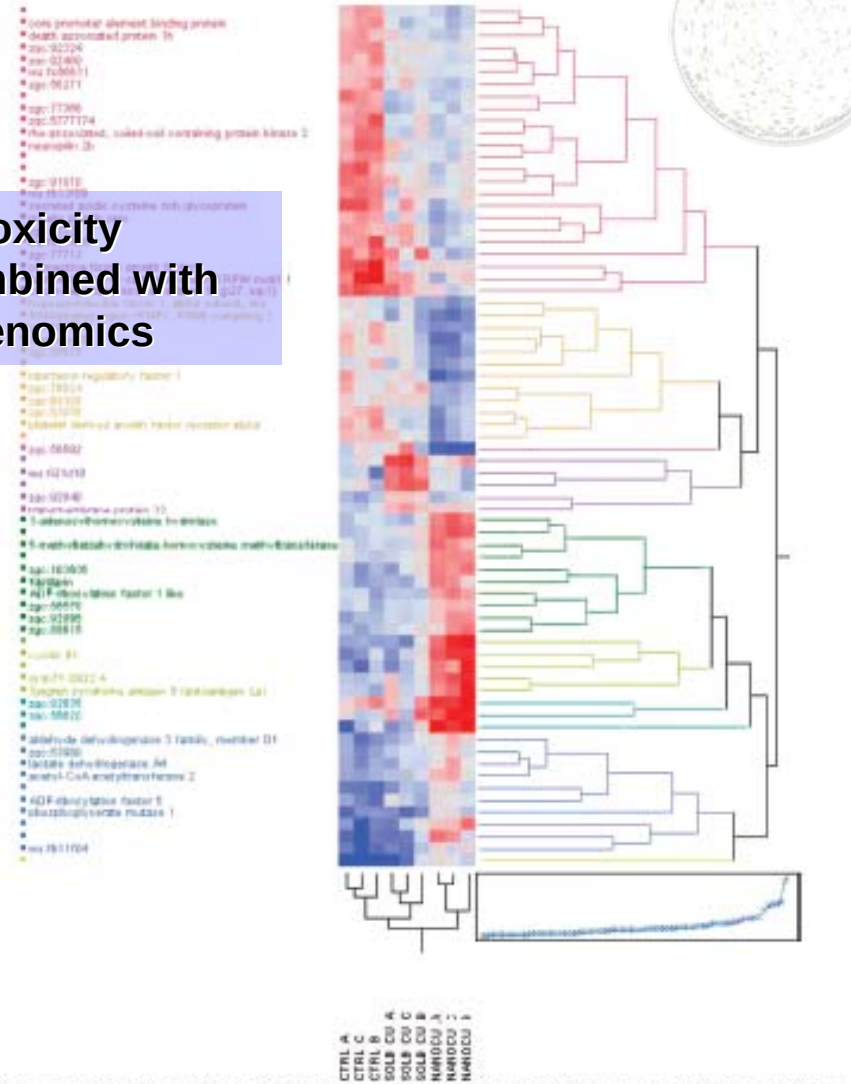


FIGURE 2. Toxicity of nanocopper (○) and soluble copper (•) to adult zebrafish. Data points indicate percent survival (mean ± SEM of three replicate experiments). Dashed black drop lines indicate LC_{50} concentrations for each exposure, as calculated by Trimmed Spearman Karber analysis. Red drop line indicates concentration and associated mortality of dissolved copper present in 1.5 mg/L nanocopper exposures, showing that the concentration of dissolved copper present in an LC_{50} nanocopper exposure is insufficient to explain the observed mortality.

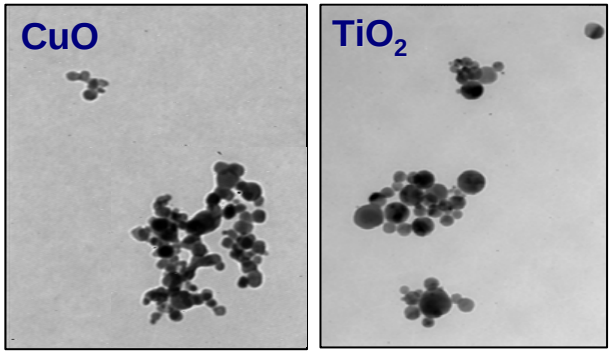
Traditional toxicity markers combined with eco-toxicogenomics



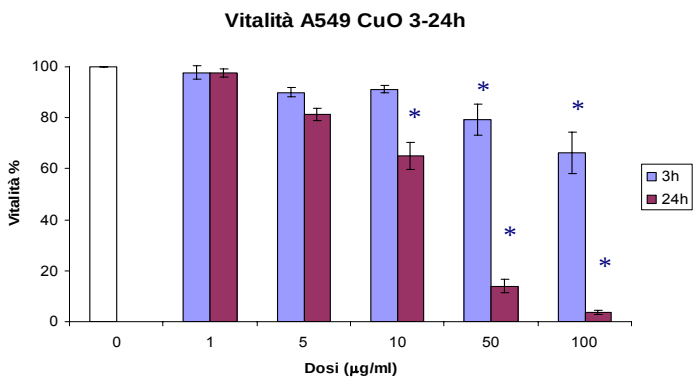


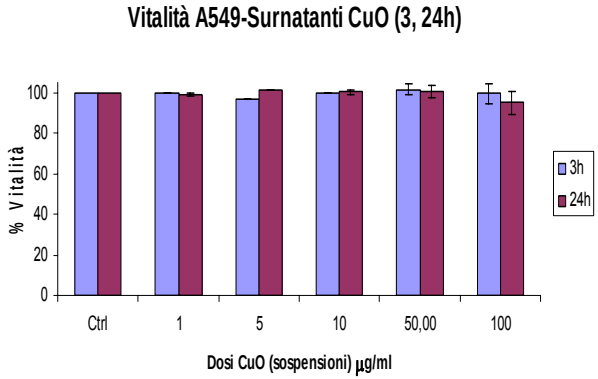
GURE 7. Hierarchical cluster analysis of significantly differentially expressed genes following exposure to sublethal concentrations of ionic or nanocopper. Gene expression values were clustered using Fast Ward hierarchical two-way clustering in JMP Genomics 4. Red indicates gene expression in the sample is greater than the pooled reference; blue indicates expression in the sample is

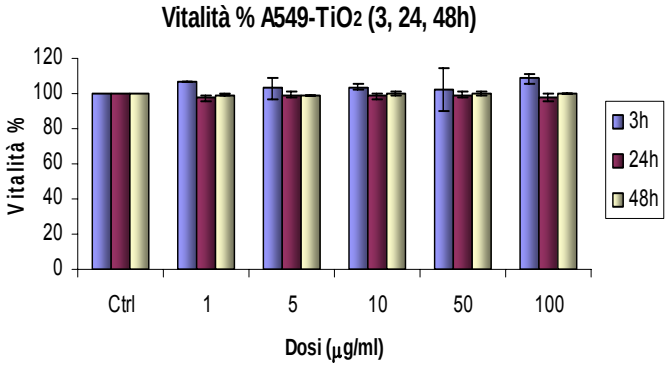
Griffitt et al., 2007. Environ. Sci. Technol. 41:8178-8186

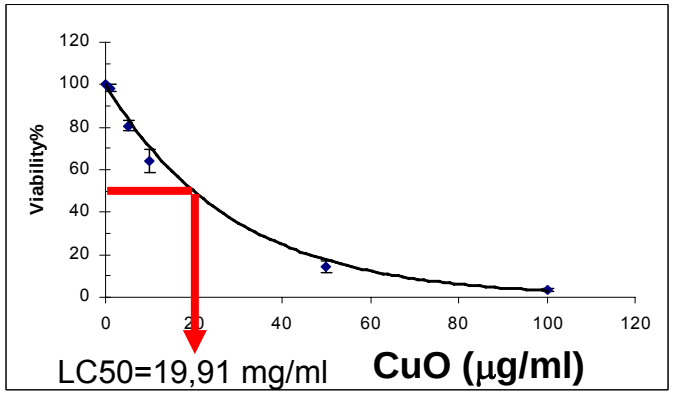


Nanoparticella	Forma	Diametro nominale (nm)	Diametro medio (nm) milliQ	PDI
CuO	Irregolare	<50	301,1	0,204
TiO2	Sferica	<100	351,1	0,251



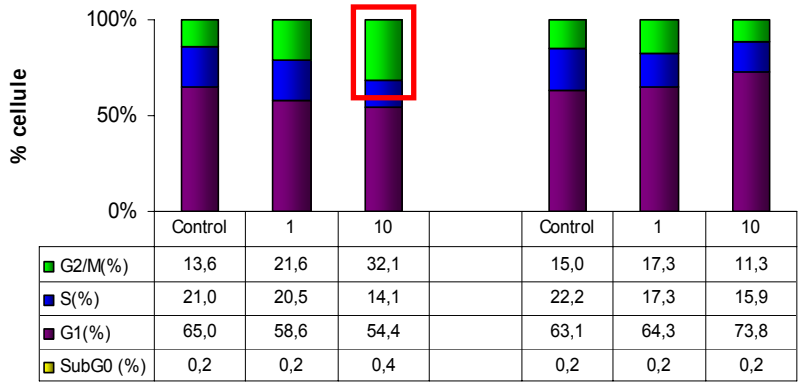




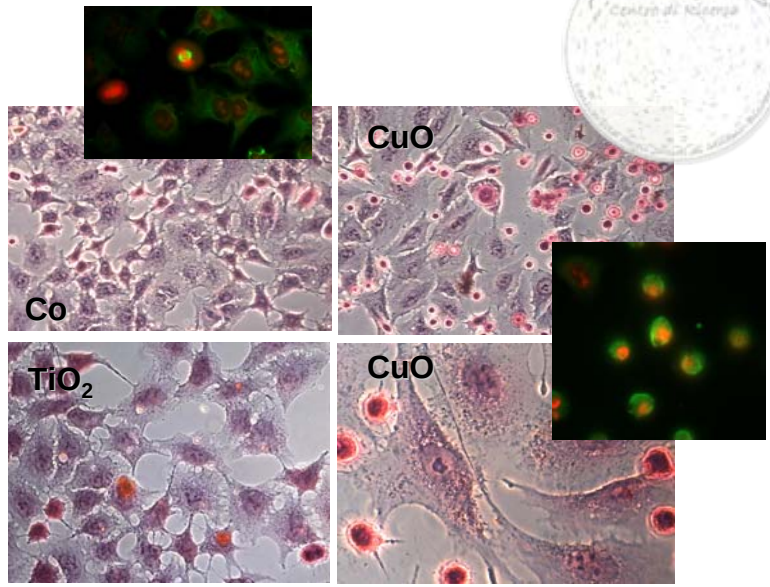


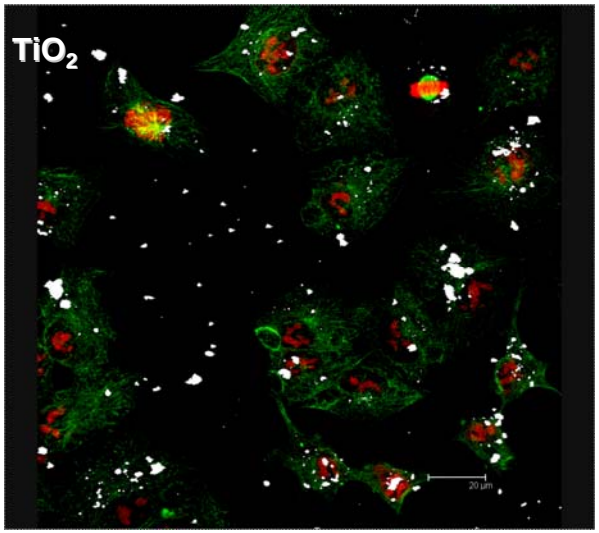
La citotossicità di NP di ossidi di metallo su cellule A549 dipende dalla natura fisico-chimica delle particelle

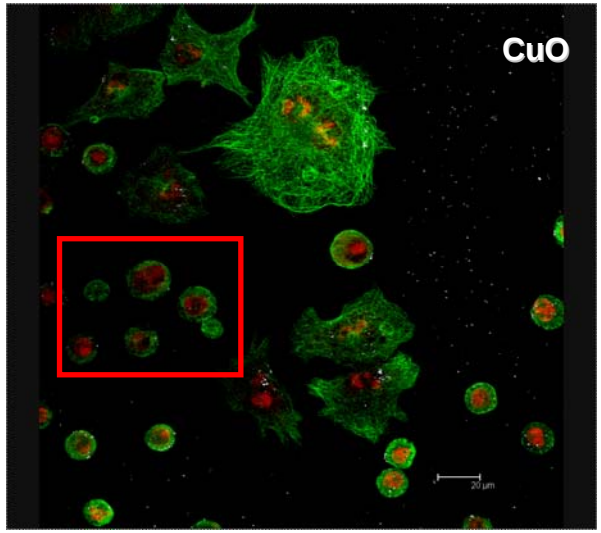
Ciclo cellulare A549 24h esposizione



	Control	1	10		Control	1	10
G2/M(%)	13,6	21,6	32,1		15,0	17,3	11,3
S(%)	21,0	20,5	14,1		22,2	17,3	15,9
G1(%)	65,0	58,6	54,4		63,1	64,3	73,8
SubG0 (%)	0,2	0,2	0,4		0,2	0,2	0,2

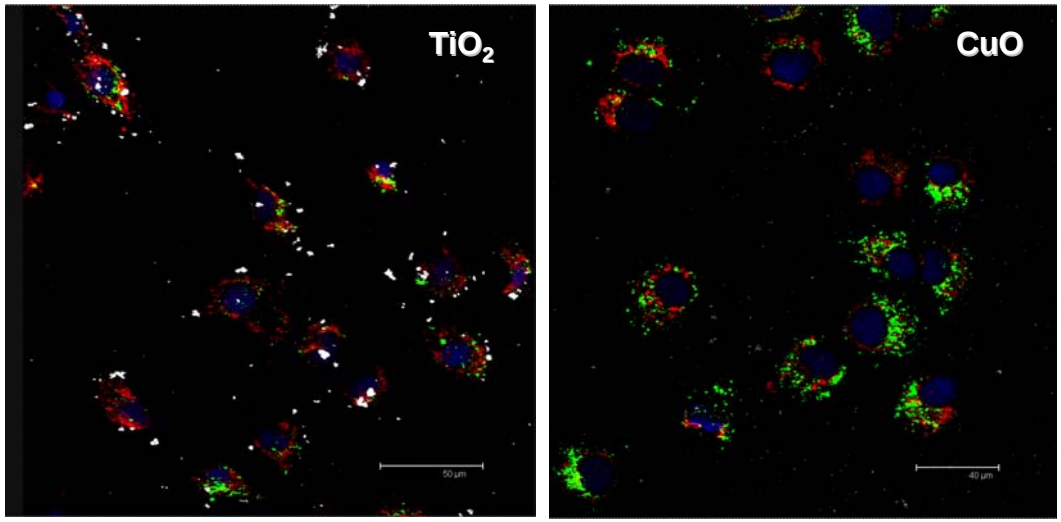






Immunostaining of B-tubulin in A549 cells. Nuclei counterstained with PI, NPs evidenced by confocal reflection

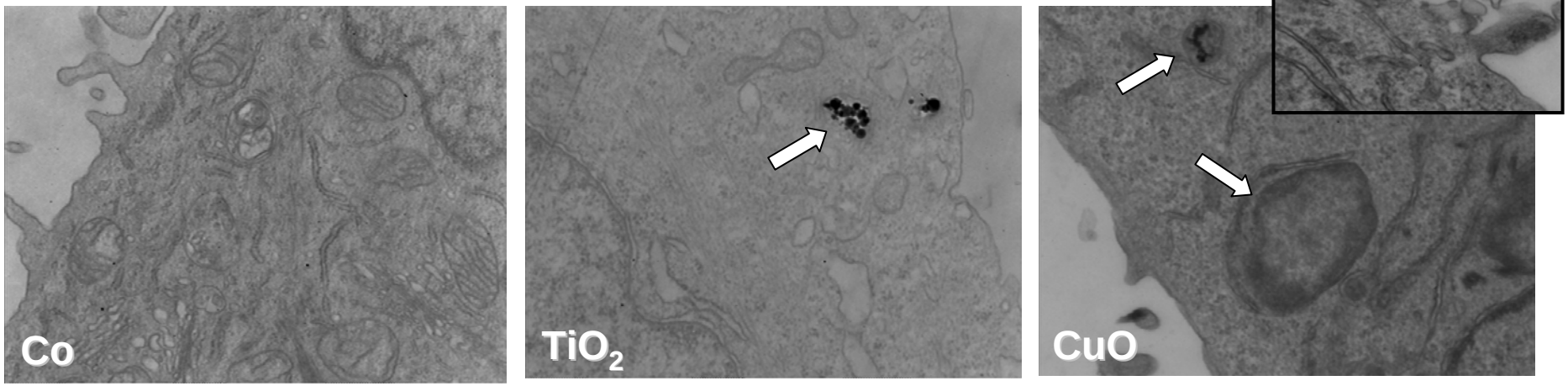
Anche il potenziale genotossico varia con la natura delle particelle



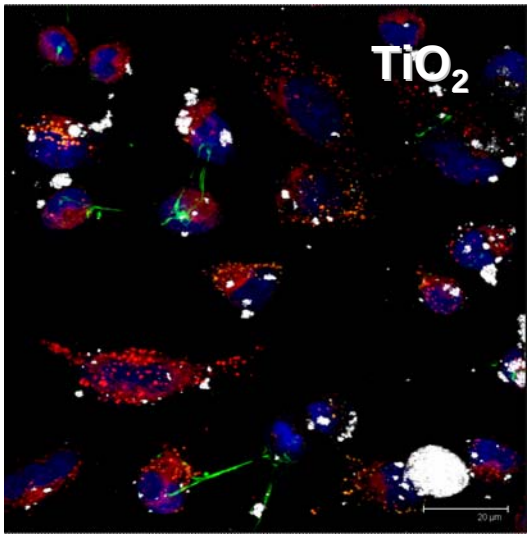
A549 probed with Mitotracker (red), DRAQ-5 (blue) and DCFH (green).
NPs evidenced by confocal reflection.

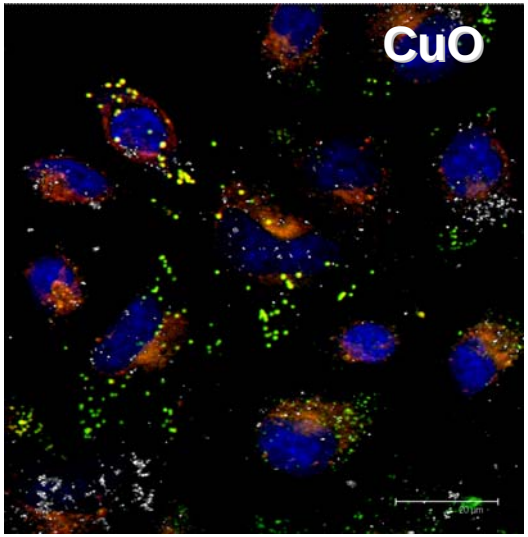
La tossicità in fase acuta dipende dalla reattività delle NP

E dalla tipologia di interazione con le strutture cellulari

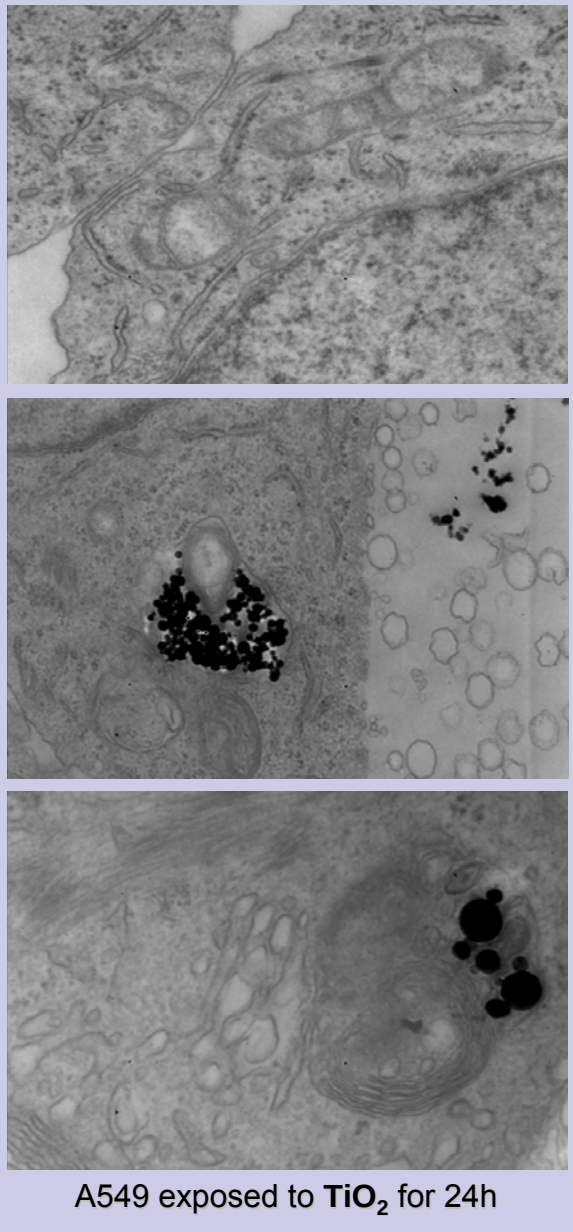


TEM images of A549 exposed to NP for 3h

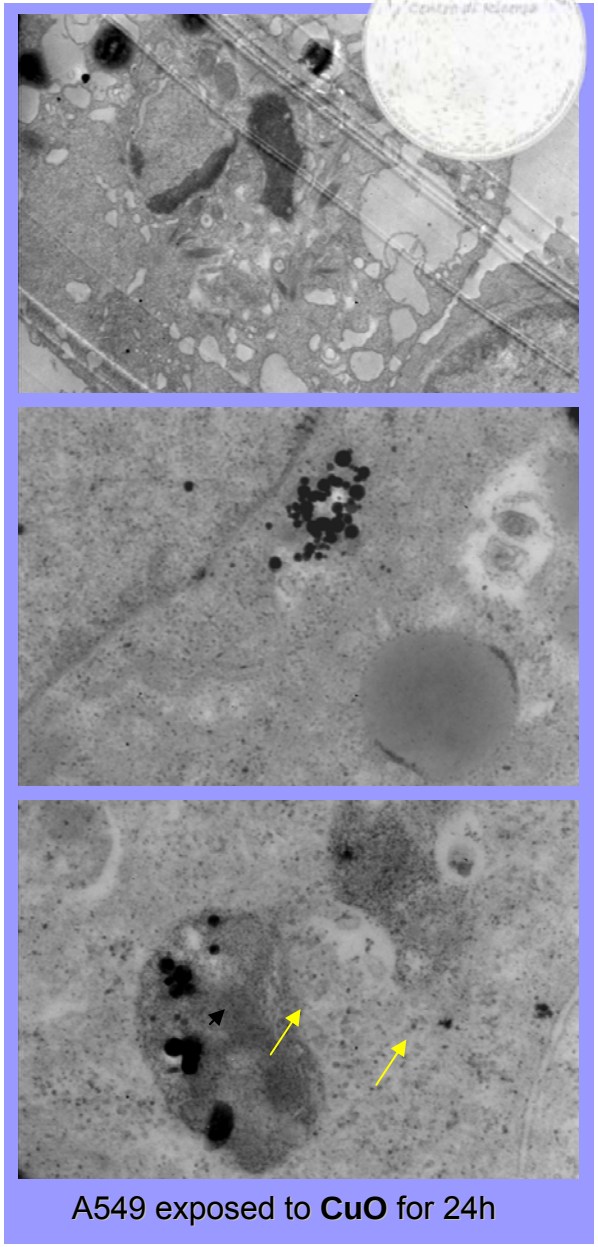




Lipid peroxidation visualized by oxidized BODIPY-C11 fluorescent probe (green); non-oxidized probe (red). Nuclei counterstained with DRAQ-5



A549 exposed to **TiO_2** for 24h



A549 exposed to **CuO** for 24h

The evolution of nanotoxicolgy into a predictive science as apposed to being merely descriptive science

Toward a biology of nanosystems

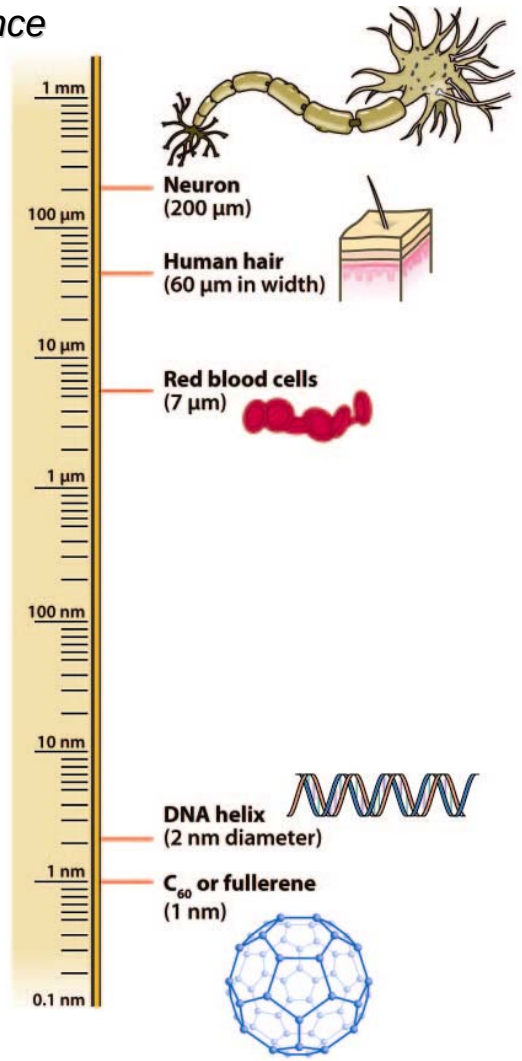
… where nanotoxicology is defined as the study of the interference of man-made nanomaterials with endogenous (cellular) nanostructures.

(Shvedova et al., 2010)

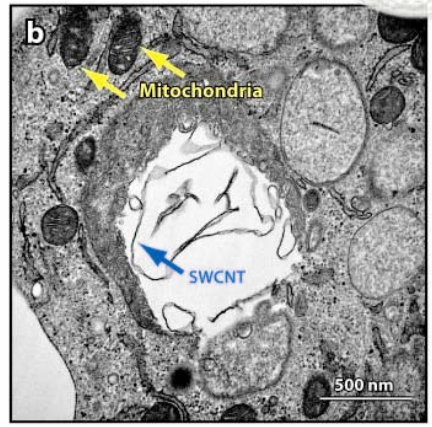
"Nanovision"

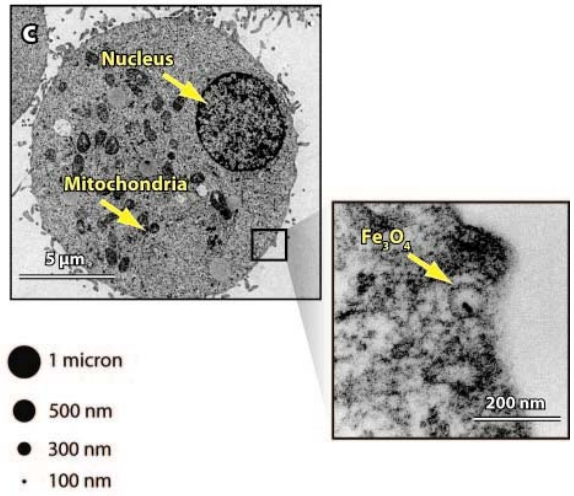
Living cells as a miniature factory that contain a large collection of dedicated protein machines of nano-scale dimensions, optimized by billions of years of evolution.

Alberts B., 1998. The cells as a collection of protein machines: preparing the next generation of molecular biologists. *Cell* 92:291-94



Shvedova AA, et al. 2010.
Annu. Rev. Pharmacol. Toxicol. 50:63–88





Do the artificial NMs interfere with the nanomachineries of the living cells?

1. Au_{55} of size 1.4 nm intercalates with the major groove of DNA – potent inducer of cell death (Tsoli et al., 2005)

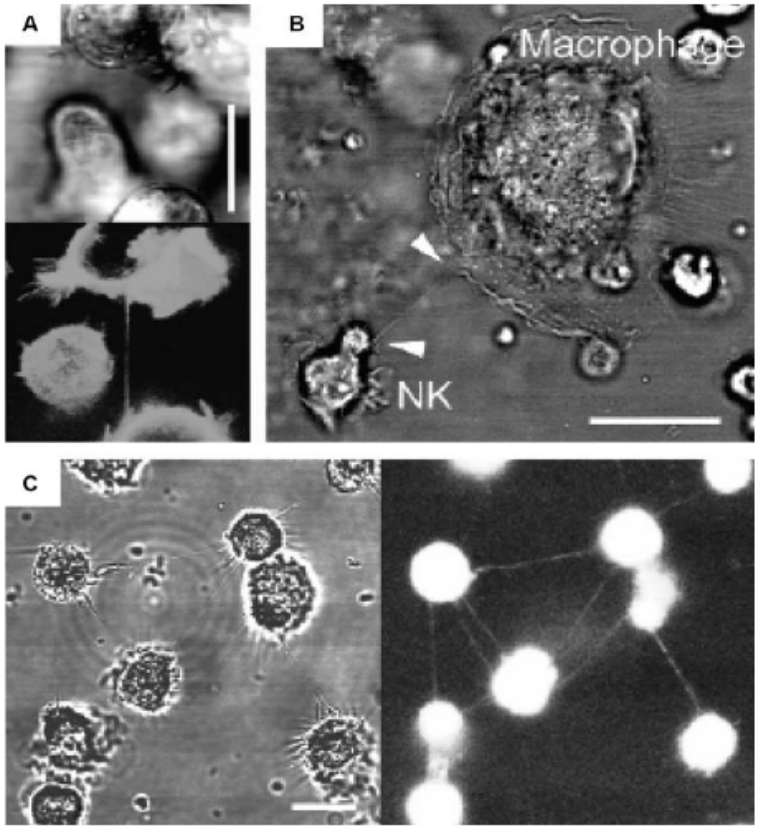
2. Quantum dots display a size dependent localization to different cellular compartments, the smaller targeting nuclear histones (Conroy et al., 2008)

3. CNTs mimic and interfere with microtubules, disrupting the mitotic spndle apparatus (Pampaloni and Florin, 2008)

4. Interactions of engineered NMs with living systems… learning from biological nanorganisms (viruses) and their interactions with the host.

Detailed study of nanomachines requires complementary single molecule imaging techniques

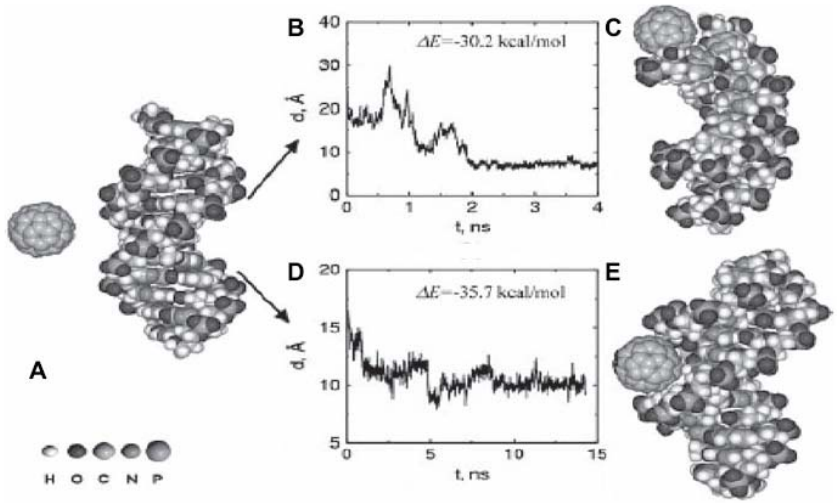
- AFM
- TEM
- Single-molecule fliorescence microscopy



Human & Experimental Toxicology (2009) 28: 393–400
www.het.sagepub.com

A nanobiological approach to nanotoxicology

JF Nyland[1] and EK Silbergeld[2]



Examples of nanobiological thinking

Intra and intercellular communication (cytoskeleton, cell membrane a complex patch-work of nanoscale structures

Gene function (DNA and nuclear proteins that regulate gene function are nanoscale structure)

Immune function (distortions in protein shape after interaction with NMs)

Development (chromosomal rearrangement of fertilized egg and epigenetic events of early embryogenesis involve interactions of nanostructures

Chemical Research in Toxicology

SEPTEMBER 2009
VOLUME 22, NUMBER 9

Editorial

Nanotoxicology—A New Frontier

The fabrication and characterization of nanoparticles for a range of biomedical uses has generated tremendous activity and excitement. All sorts of potential uses of these novel materials are being explored from molecular imaging to drug delivery. An emerging concern is that nanoparticles for biotechnology applications may exhibit toxicities that will limit their application. *Chemical Research in Toxicology* has received an increasing number of submissions on the topic of nanotoxicology and has published a number of articles that describe the toxicological properties of nanoparticles toward intact cells. Our recently published Thematic Compilation (http://pubs.acs.org/page/crtoec/thematic/nanotoxicology.html) highlights some of the most recent articles that focus on the chemical properties of particles leading to toxicity or on the mechanisms by which cells are killed.

Given the growing importance of nanotoxicology, the Editors of *CRT* anticipate that submissions of manuscripts in this field will continue to increase. Therefore, we feel it useful to outline some features that potential authors should consider to ensure that their manuscripts are in keeping with the scope of *CRT*:

1. The chemical and physical characteristics of the particles should be well-defined.
2. The study should contain novel chemical information that explores previously undefined linkages between nanoparticle structure and toxicity AND/OR
3. The study should directly explore the chemical/biochemical mechanism of nanoparticle toxicity.
4. Studies that simply demonstrate toxicity of particles to cells are discouraged.
5. The demonstration of superficial mechanisms, such as the generation of reactive oxygen species and/or the induction of apoptosis, may not be considered an adequate investigation of mechanism.

Fields evolve rapidly so these guidelines may change in the future. Furthermore, they are just guidelines, and every article will be evaluated individually. As a leader in the publication of research on the mechanisms of toxicity, *CRT* provides an excellent forum for articles that explore the chemical and biochemical basis of nanotoxicology. We look forward to your submissions.

Lawrence J. Marnett

Acknowledgements

•This overview was experienced in the Applied Cell Biology group of the POLARIS research Center, directed by Prof. Marina Camatini

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Daniele Gallinotti

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Paola Palestini

Francesca Farina

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