What are the Potential Health and Environmental impacts of Nanotechnology?

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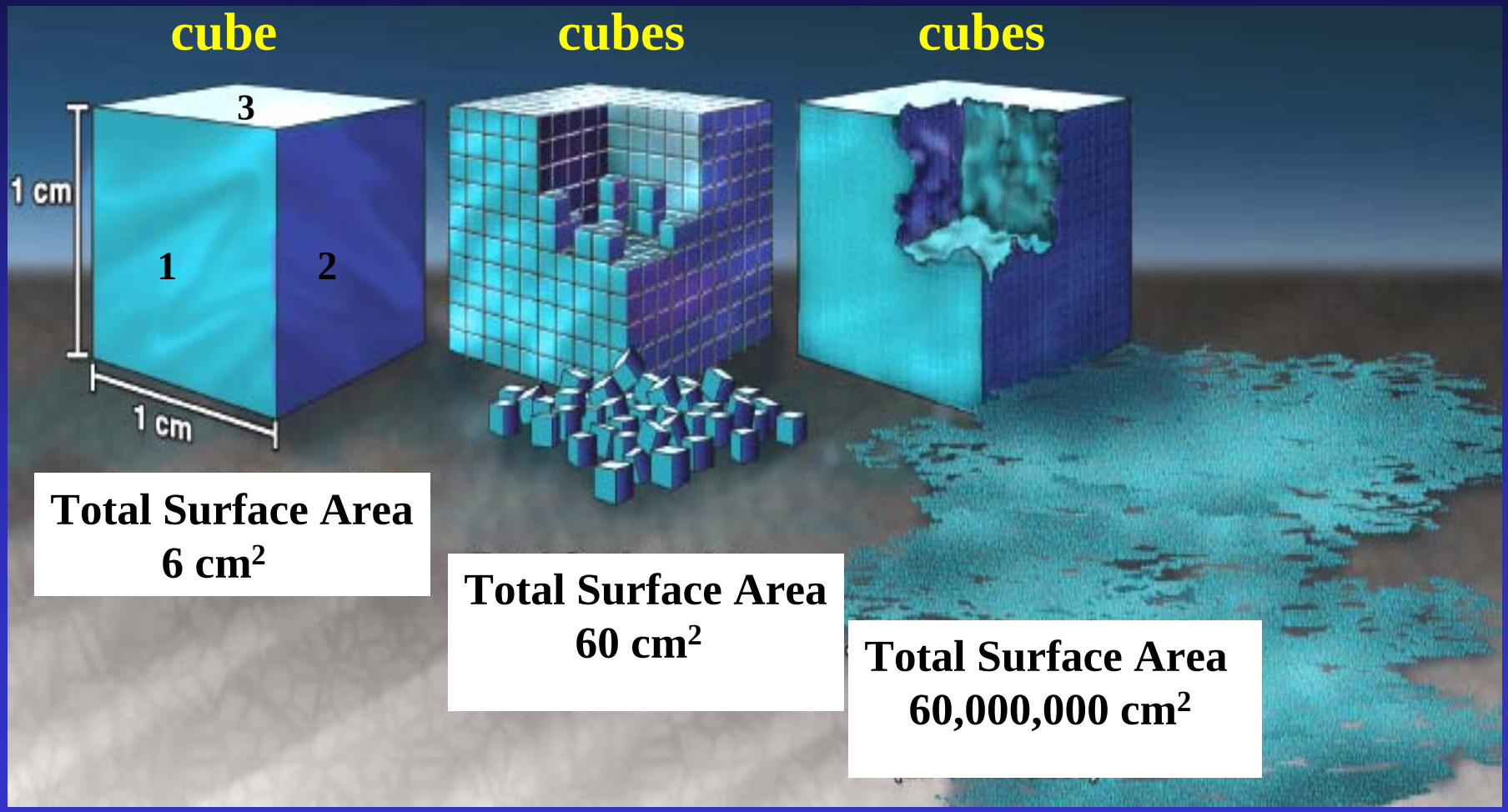
NANOTECHNOLOGY and CALIFORNIA

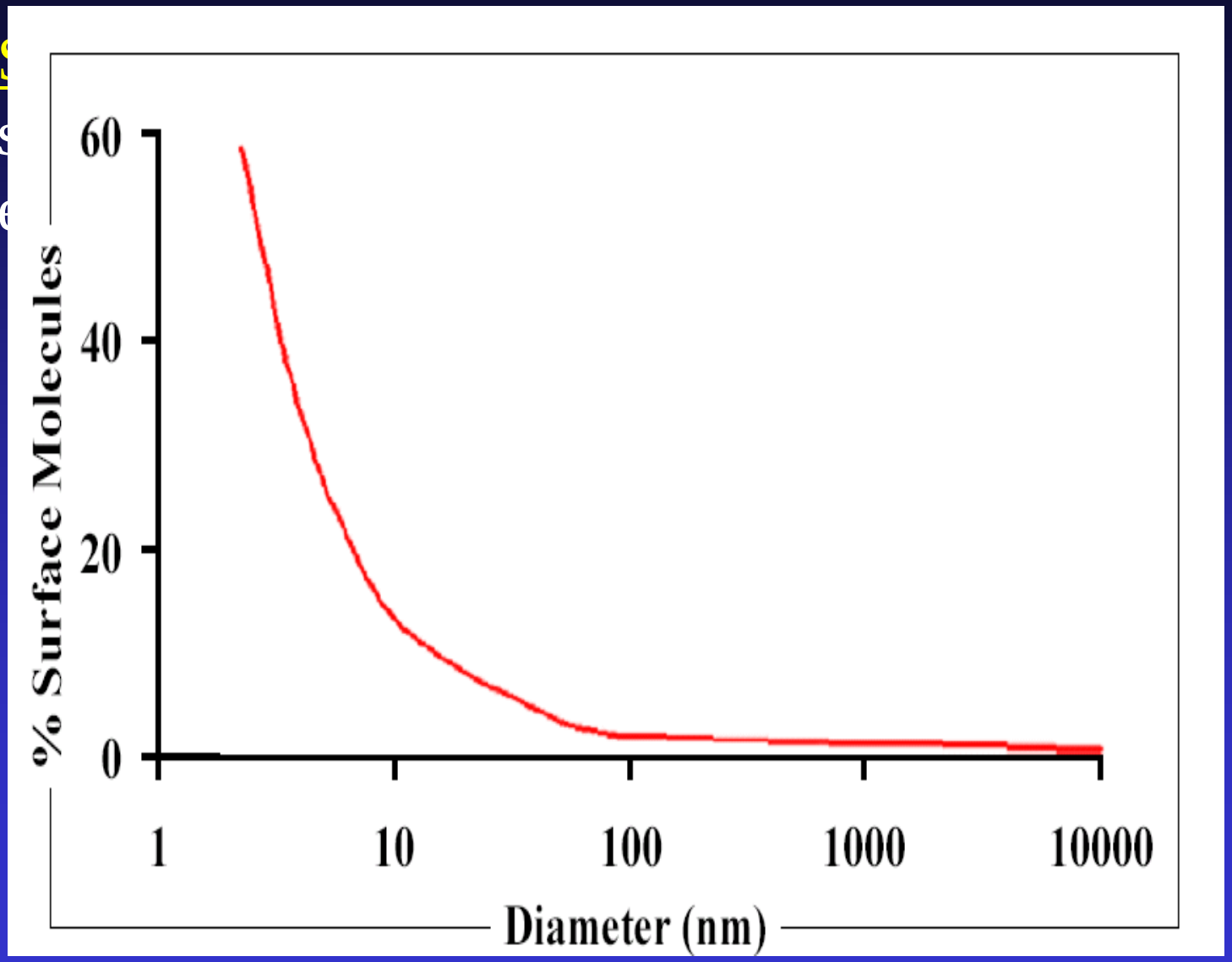
- New enabling technology
- Amazing new atomic building blocks & feats of chemistry, physics, optical properties, catalysis, conductivity
- Tremendous industrial potential/economic benefits
- Proviso: New physicochemical properties could → unexpected new interactions with biological substrates → potential for harm to humans and the environment

Why are Nanomaterials Potentially Dangerous ?
Large Surface area

1 centimeter cube → 1 millimeter cubes → 1 nanometer cubes



Why are Nanomaterials Potentially Dangerous ?



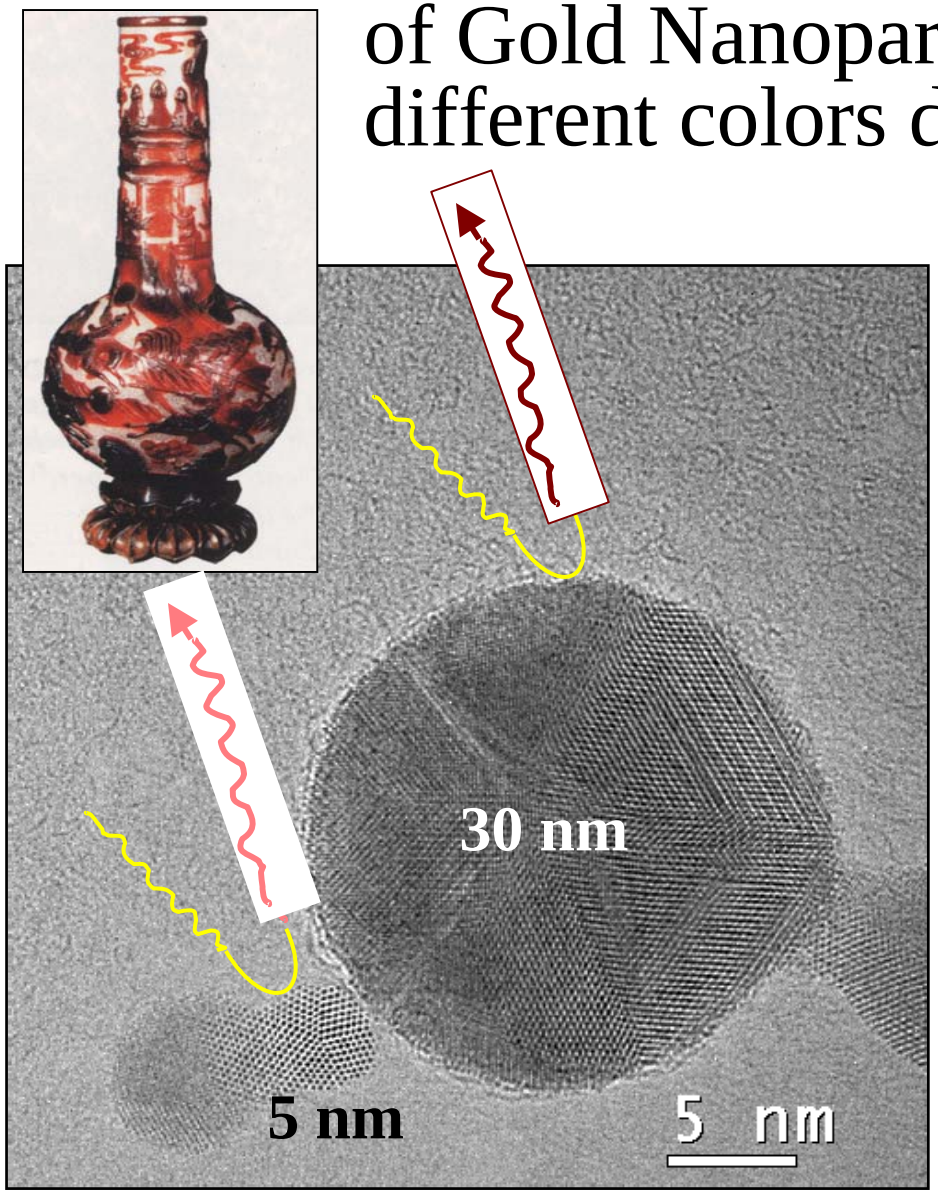
Why are Nanomaterials potentially dangerous?

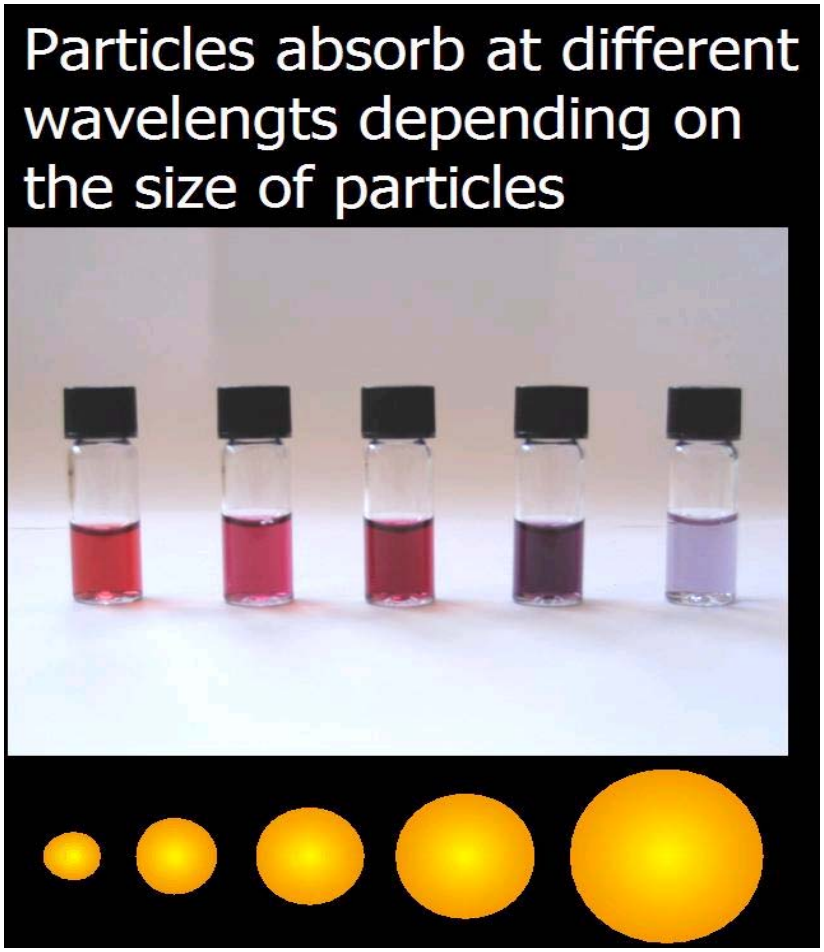
- More molecules on the surface
- ↑ surface area

} → ↑ reactivity

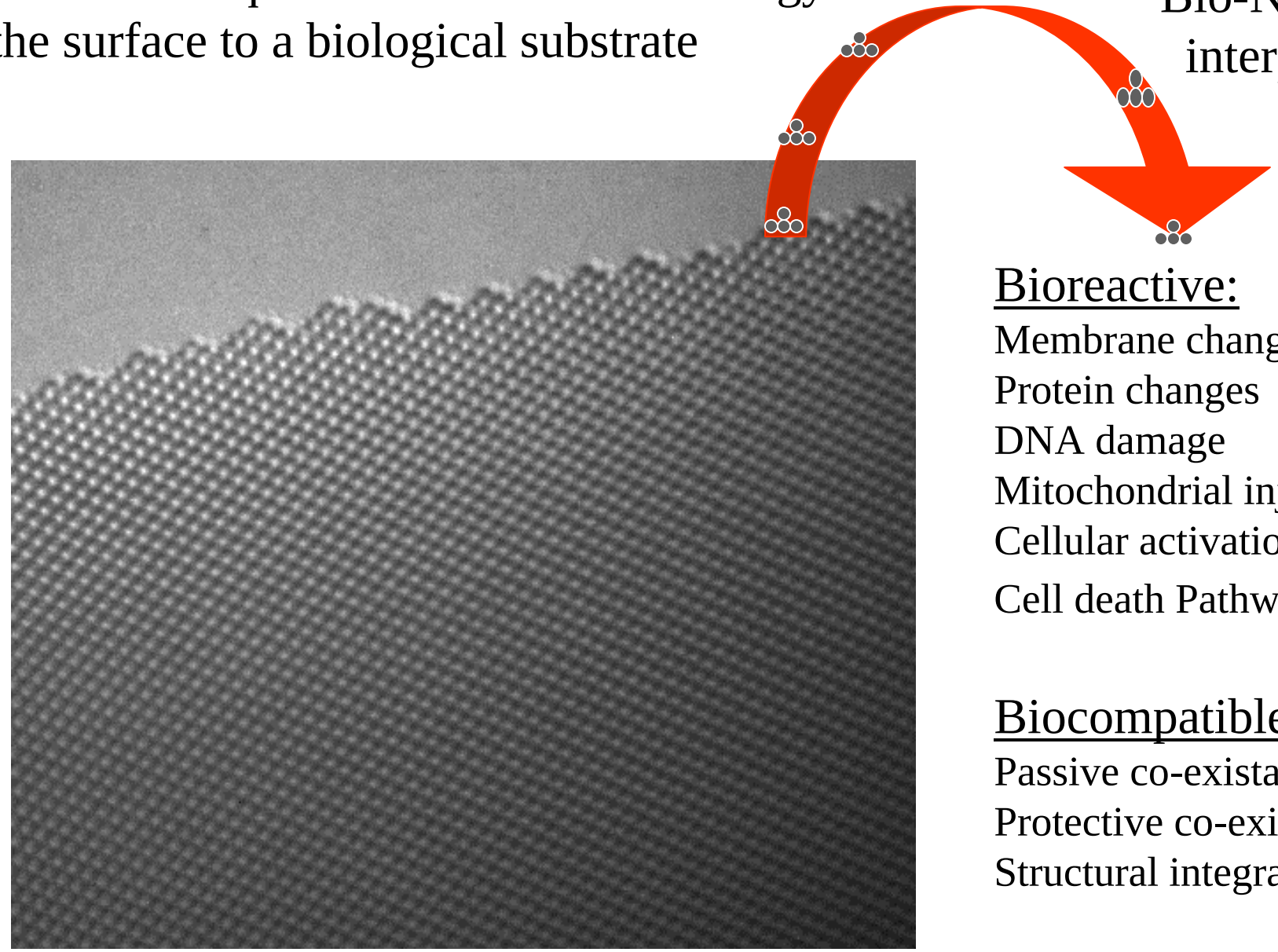
- Dominance of quantum effects:
  - electronic
  - optic
  - magnetic
  - mechanical

Example of an optical quantum effect of Gold Nanoparticles that generate different colors depending on particle size





Now imagine that the Nanoparticle transfers its quantum-mechanical “energy” on the surface to a biological substrate



Bio-Nano interphase

Bioreactive:

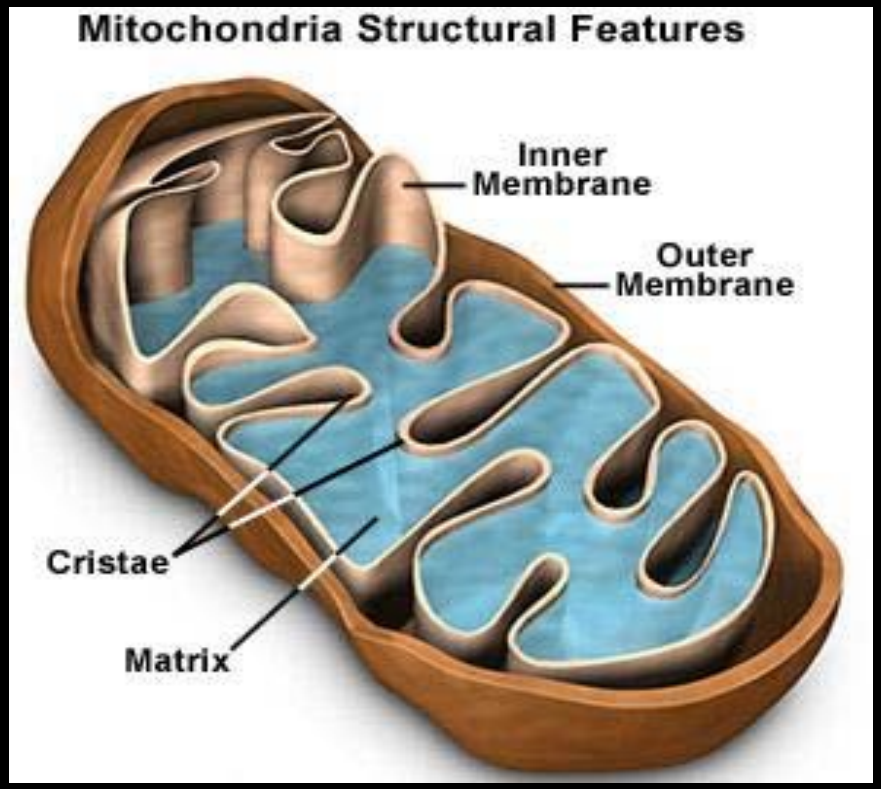
Membrane changes
Protein changes
DNA damage
Mitochondrial injury
Cellular activation
Cell death Pathways

Biocompatible:

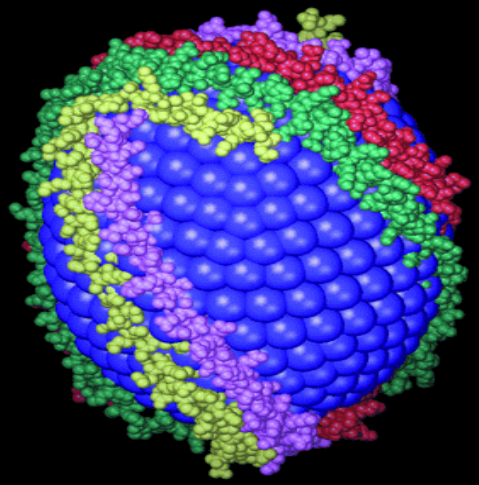
Passive co-existance
Protective co-existance
Structural integration

Many Biological Processes take place at nanoscale level……..

1. Many proteins function at nanoscale length
2. Some subcellular organelles are nanoscale assemblies, e.g. energy producing mitochondria

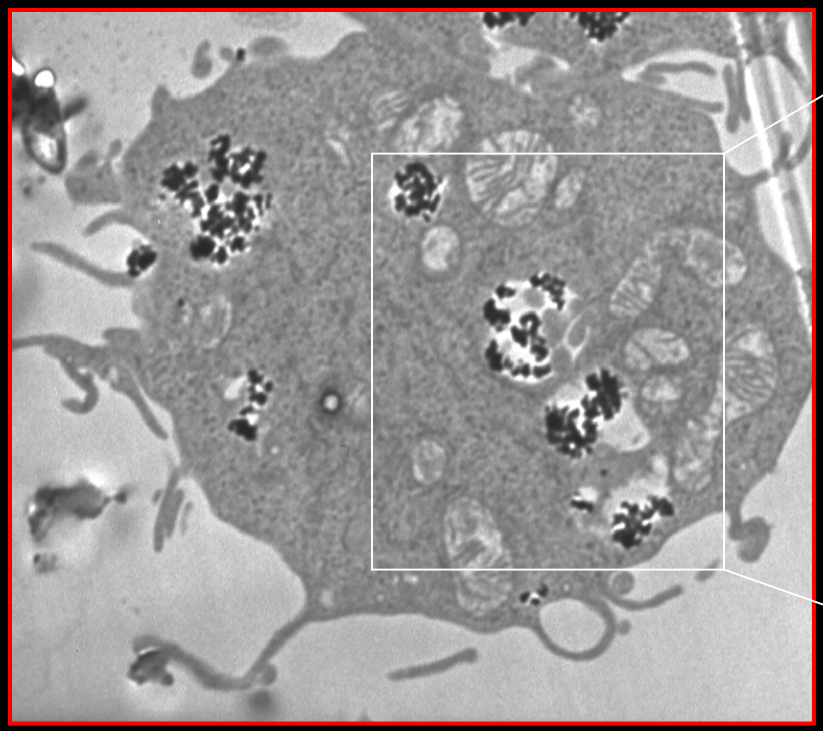


3. Cholesterol carrying particles in the blood resemble self-assembled nanoparticles



HDL particle

Cellular uptake and protection against a potentially toxic metal oxide nanoparticle



Titanium dioxide taken up

Encapsulation and toxicity dampened…….. cell survives

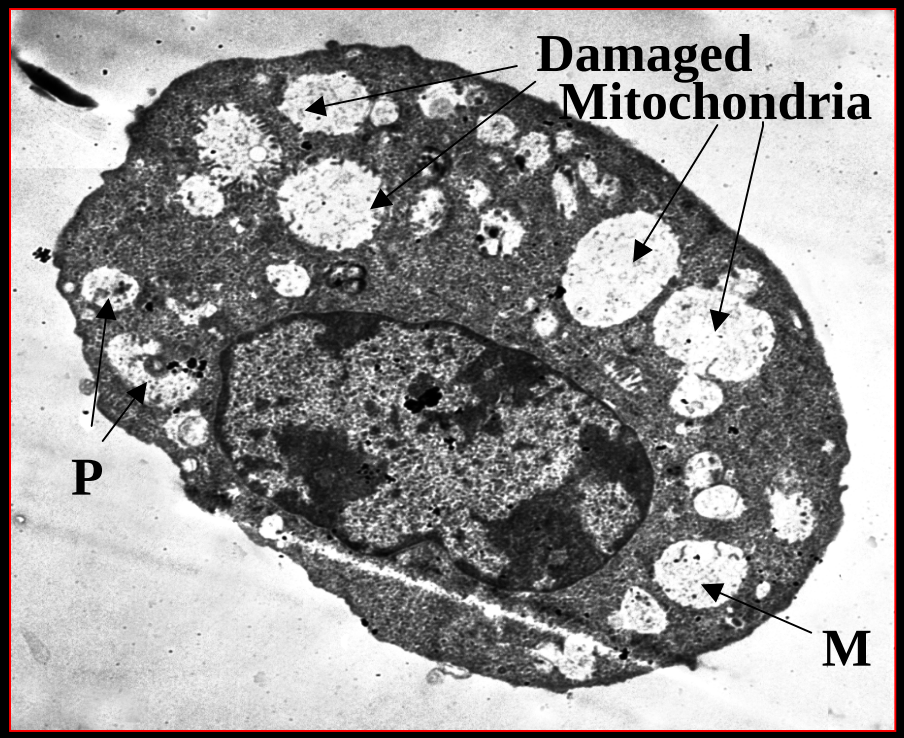
Nel et al. Nano Letters. 2006

Cellular uptake and damage by a highly charged Nanoparticle that targets mitochondria

Untreated healthy cell

Nel et al. Nano Letters. 2006

Cell treated with toxic nanoparticle



Mitochondrial injury and cell death

How should we consider the Safety of Engineered Nanomaterials?

What is the relevant analogy?

- Genetically modified foods?
- Nuclear power
- The introduction of plastics? *

** Note how profoundly the mundane introduction of plastics has transformed our world – without notice by ethicists and social scientists!*

Genetically Modified Foods was a public relations disaster that Nanotechnology should avoid

The discoverer of an art is not the best judge of the good or harm which will accrue to those who practice it.

Plato, *Phaedrus*

The First Industrial Revolution

1. Fossil Fuel combustion and Anthropomorphic activity
   - Human activity releases combustion and mineral dust particles with harmful effects on the Respiratory and cardiovascular system (first cases around 1820)
   - Air Pollution and Occupational Health effects

2. CO_2 emissions and global warming (seeing full impact last few decades)

The Second Industrial Revolution

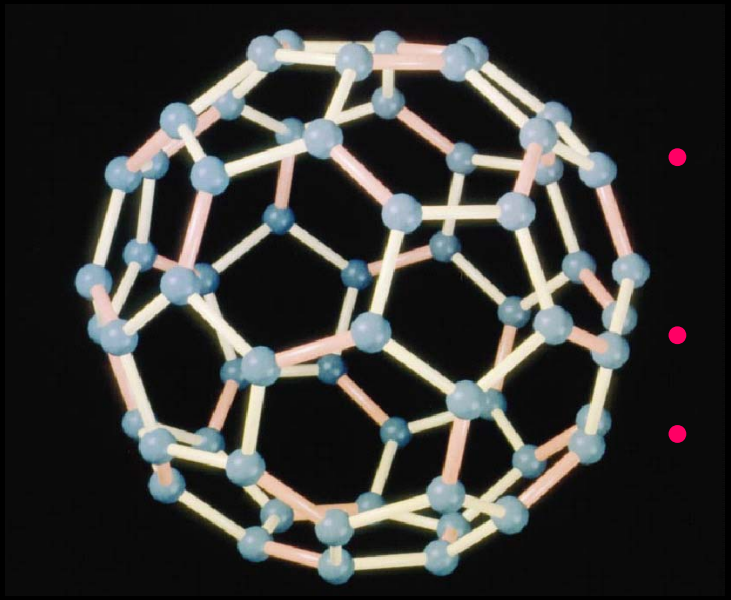
???????

Limited Experimental Toxicity of Manufactured Nanomaterials reported to date

- Fullerenes
- Carbon nanotubes
- Metal oxide nanoparticles

No Clinical Toxicity reported to date

Carboxyfullerenes (buckyballs)

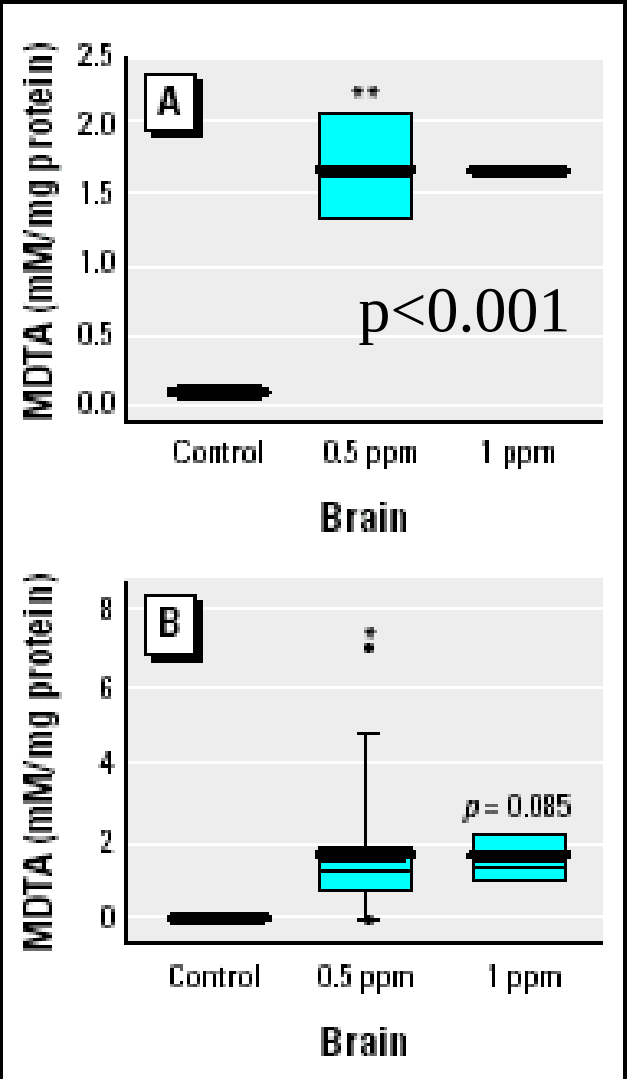


- R Buckminster Fuller
- Perfect spheres containing 60 C atoms
- Hydrophobic → cross cell membranes
- Unique free radical chemistry
- Only carbon nanostructure with suggested environmental toxicity
- Mass production for commerce

Oxidant injury to the Brain of Largemouth Bass after 48 hr exposure to manufactured Nanomaterial (fullerene C60)

Aquarium averages

Individual Fish

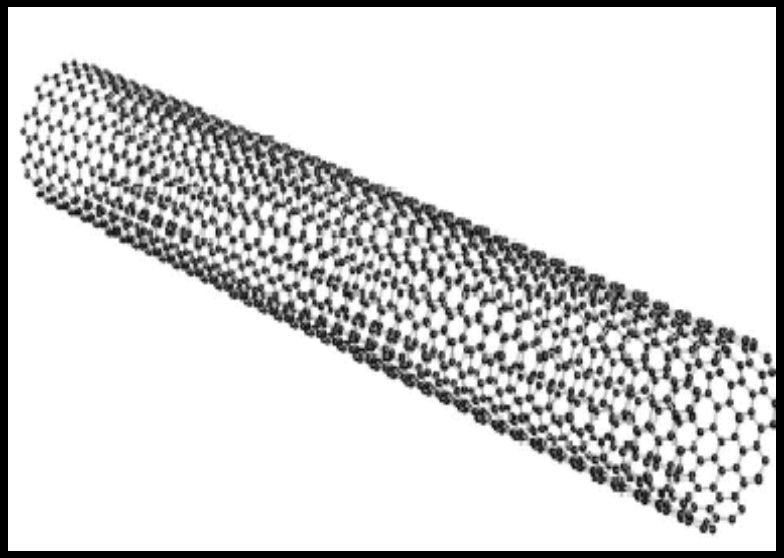


Still a lot of questions about the validity of this finding……

some fullerenes have the opposite effects, i.e., are protective

Oberdorster et al. 2004. EHP

Carbon Nanotubes

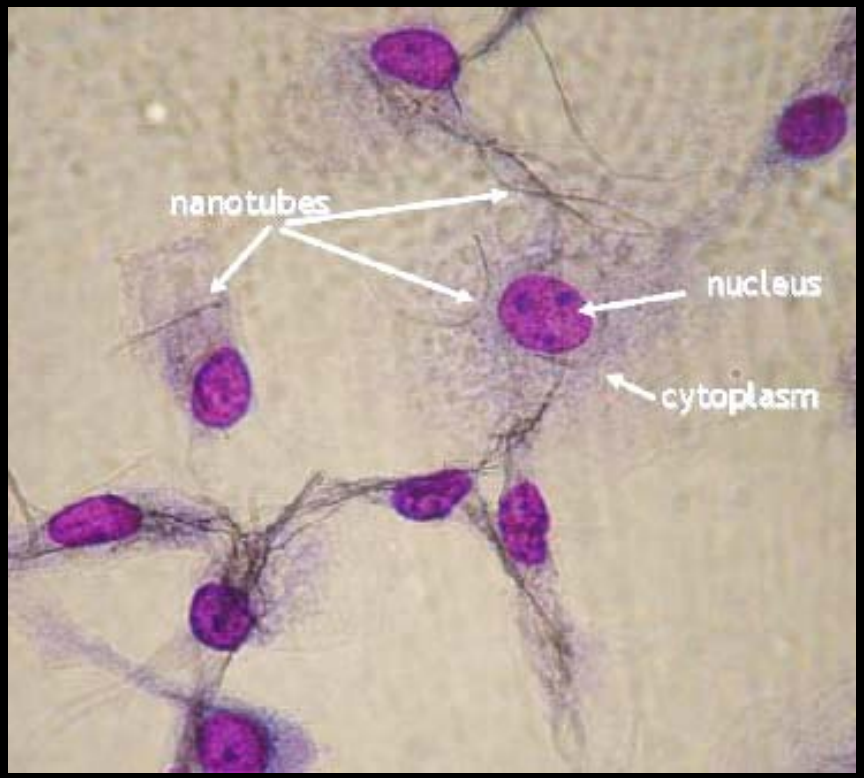


- Long, thin carbon-based tubes
- Single walled, multiwalled
- Lam *et al*: dose-dependent epitheloid granuloma and interstitial lung inflammation upon tracheal instil.
- Warheit *et al:* lung granulomas
- Shvedova *et al:* adverse responses in keratinocytes:

  → ROS generation, antioxidant depletion, peroxidation, loss of cell viability

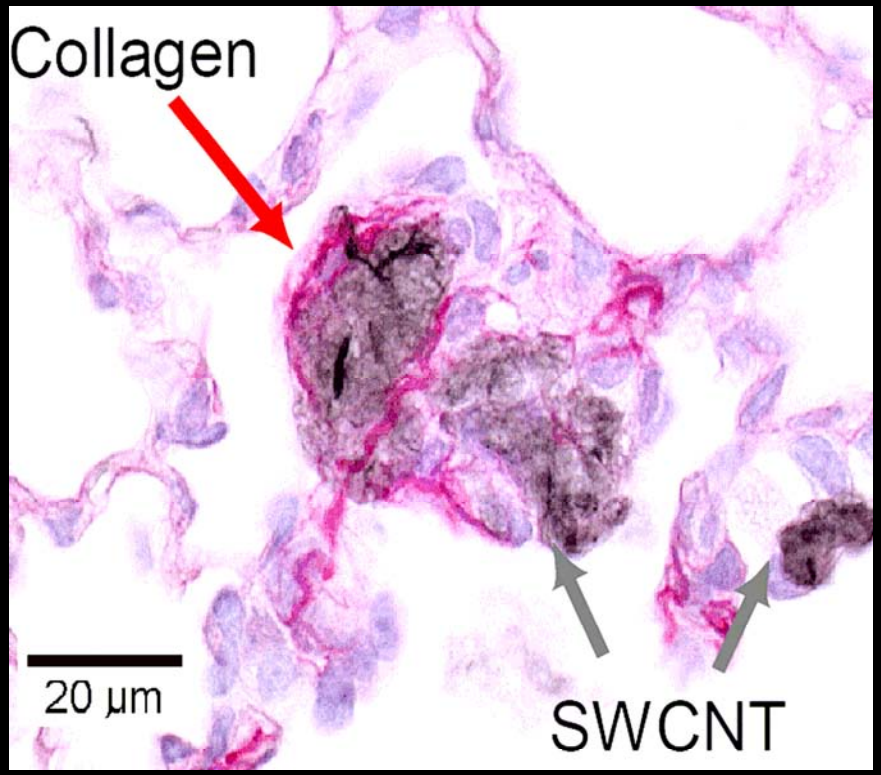
Nanotubes In Lung Cells eliciting an Interstitial Fibrotic Response

Cell



Dr David Brown and Dr Vicki Stone, UK

Lung



Dr Vincent Castranova et al, NIOSH

No clinical evidence, however, that this leads to toxicity or adverse health effects in humans

In the absence of Clinical Evidence of Manufactured Nanomaterial Toxicity, are there other Toxicological Paradigms that can be used to understand Nanomaterial Safety?

First Industrial Revolution: Air pollution particles

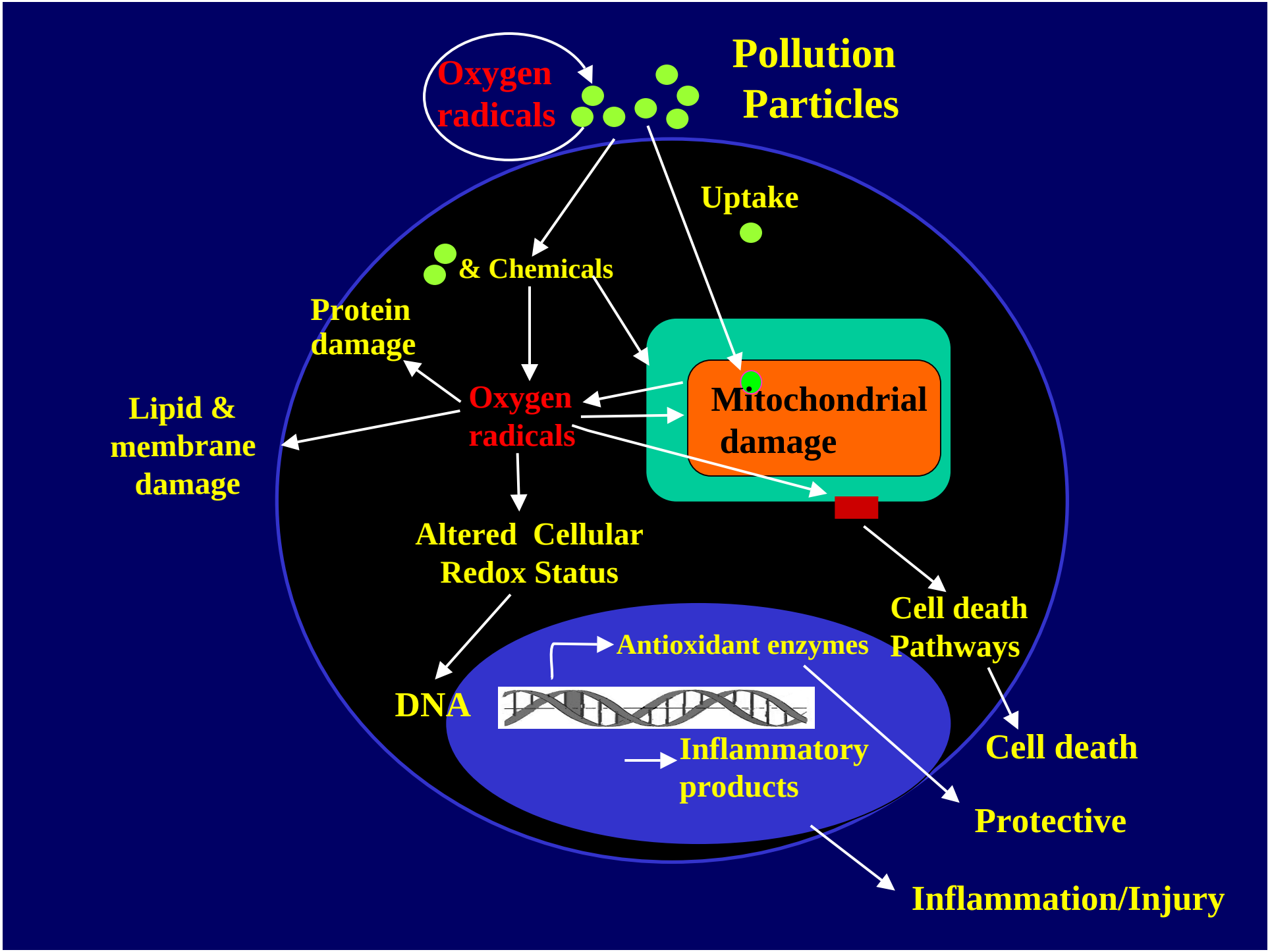
1. Characterization of harmful inhaled particles:
   Small size, large reactive surface area, oxygen radicals

2. Epidemiology linking PM → adverse health effects

3. Screening tests for Particle Toxicity

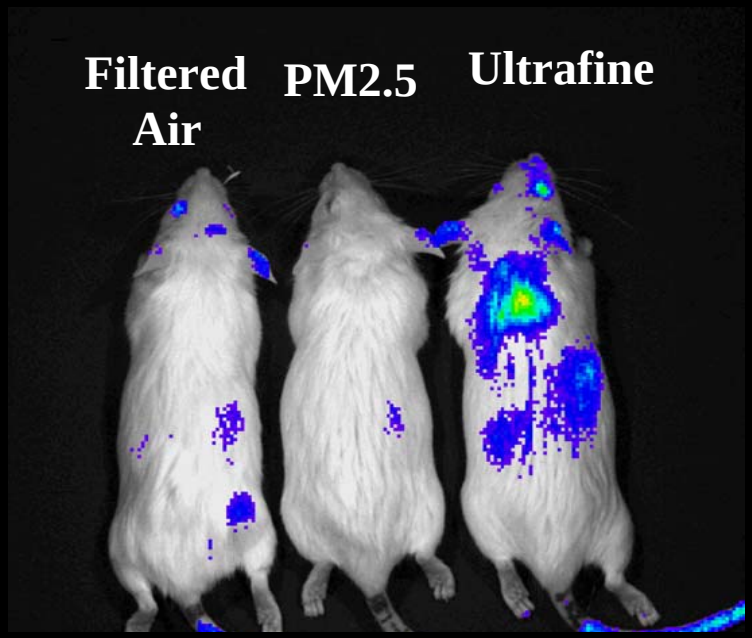
4. Systems biology approach to PM toxicity → Biomarkers for particle toxicity

5. Prevention and regulation


Oxygen radicals
Pollution Particles
Uptake
& Chemicals
Protein damage
Lipid & membrane damage
Oxygen radicals
Mitochondrial damage
Altered Cellular Redox Status
Cell death Pathways
Antioxidant enzymes
DNA
Inflammatory products
Cell death
Protective
Inflammation/Injury

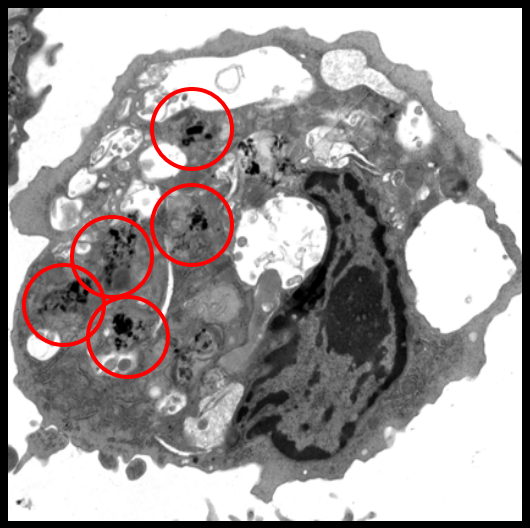
Small Ultrafine Particles (nano-range) is potentially more hazardous than other pollutant particles because they……

1



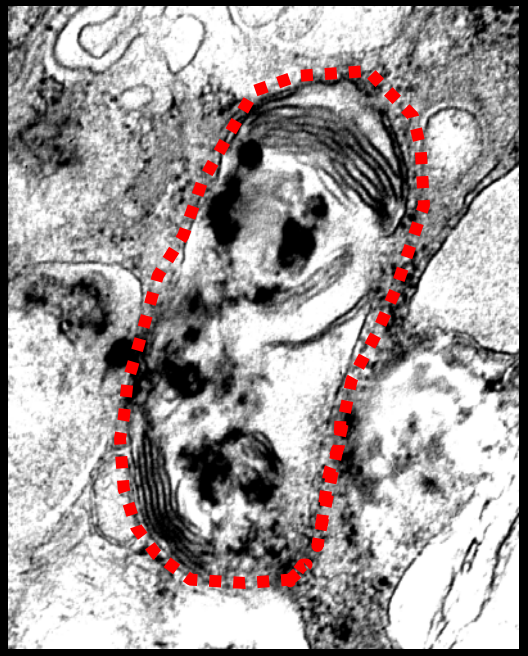
Generate Oxidant Injury in the Lung and Cardiovascular system (the lung signal is from an oxidative stress gene that is turned in a live animal exposed on an LA freeway)

2



Target subcellular sites in cells such as pulmonary alveolar macrophages

3



Lodge in and damage mitochondria, which leads to more oxygen radical generation and oxidant injury

Nanotoxicology Paradigms:

1. Catalyze ROS production → oxidative stress
2. Antioxidant defense → Protection
3. Inflammation
4. Cytoxicity
5. Mitochondrial dysfunction

Oxidative Stress Screening Paradigm

Other Biological Paradigms

1. Biocompatibility
2. Altered antigenicity/autoimmunity
3. Protein denaturation/disrupt enzyme function
4. Disrupt membrane function
5. Neurotoxicity
6. Mutagenicity/carcinogenicity, e.g. asbestosis

For Engineered Nanomaterials, we need to consider the following exposure sites:

1. Lung- inhalation exposure
2. Skin - direct contact (creams, sunscreens)
3. Gastrointestinal - food and water
4. Systemic spread with involvement of distal target sites such as the liver, brain, vasculature

NanoToxicology Risk calculation:

Hazard: Is the material potentially dangerous?

↓

Can it spread via Water, Food, Air, Skin contact?

↓

Is there exposure (ingestion, inhalation, skin contact etc) ?

↓

Does the exposure exceed the toxic dose in the target tissue?

↓

Injury, Pathology, Disease

How to test for Nanomaterial Toxicology: Some Sobering Thoughts in dealing with Industrial Chemical Compounds

80,000 chemicals registered for commercial use in the US

Only 530 have undergone long-term and 70 short-term testing by the National Toxicology Program

The resource-intensive nature of traditional tox studies puts the cost of each study at $2 to $4 million and takes > 3 years to complete (major cost factor animal studies)

Prefered Approach by the UC Lead Campus Program for Nanotoxicology Research and Training

Use of a predictive scientific model that focuses on mechanisms and tissue/cellular targets to predict toxic potential and then to take that to in vivo testing

Mechanism of toxicity

↓

Cellular/tissue damage

↓

Pathological Potential

↓

Potential Disease

UC Lead Campus Program for Nanotoxicology Research and Training

Anderson School of Business
Sociology
Bren School Enviroment (UCSB)

Nanomaterial Science Chemistry

CNSI (UCLA & UCSB)
Nanomaterials
Engineering
Chemistry

Public Policy
Societal implications
Economic forecasts

Nominated Standard Reference Materials

Exposure and Risk Assessment
Environmental Tox

Sch Public Health
Southern Cal Particle Center
Bren School of the Envir

Nanobiology
Nanotoxicology
High Throughput screening

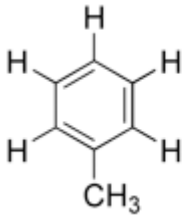
David Geffen Sch of Medicine
Biological Sciences
Bio-imaging
Jonsson Cancer Center
Howard Hughes Institute

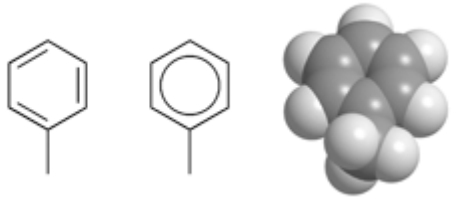
Scientific Director

Andre Nel

Potential pollutants

well-characterized

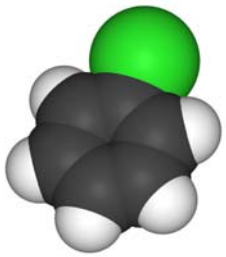




$C_{16}H_{34}$

hexadecane

toluene



Cr(VI)

chromium

chlorobenzene

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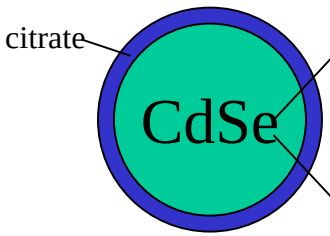
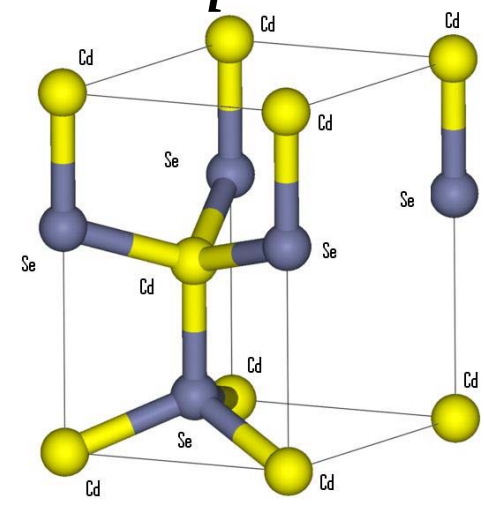
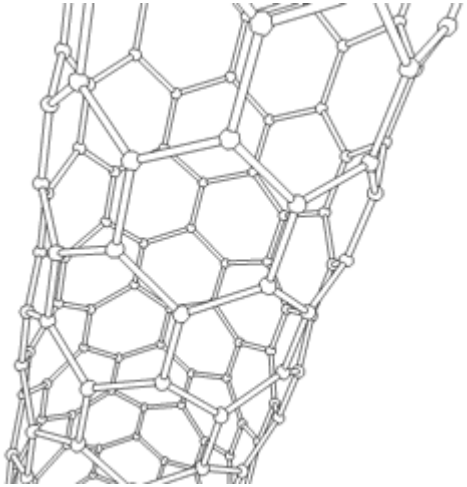
relatively uncharacterized

CdSe quantum dot







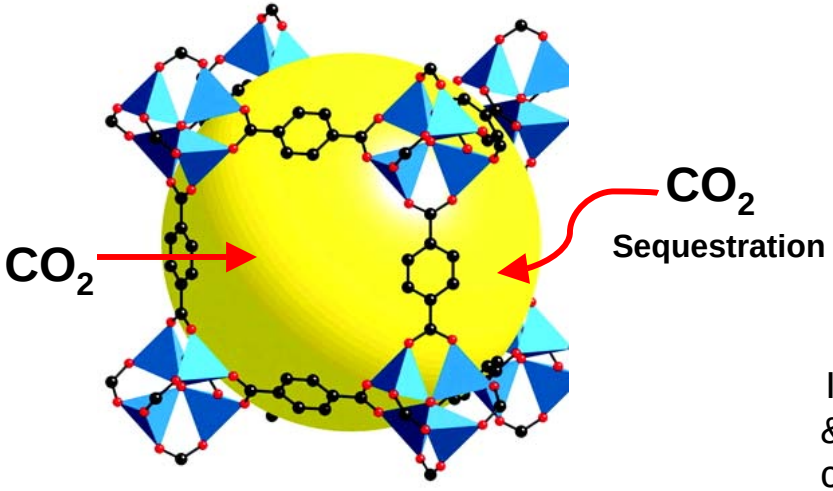
carbon nanotube

Information Status for conventional pollutants vs Engineered Nanoparticles

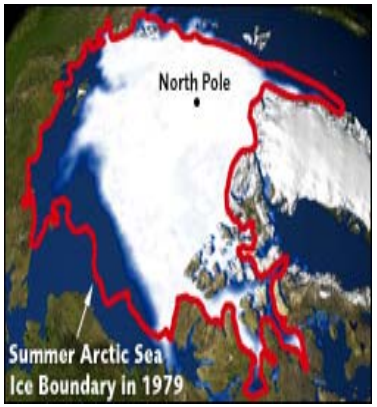
Useful Information	Conventional pollutants	Engineered nanoparticles
Structure and composition, including primary and functional groups	Well-defined databases available	Many are **proprietary** Objectives **ill-defined** **Impurities**
Physicochemical properties (e.g., aqueous solubility, vapor pressure, charge/oxidation state)	Compendia available. Relevant to environmental conditions.	Mostly **unknown** for environmental purposes. **Novel characteristics** (surface area, charge, chemistry) may apply.
Mass transfer characteristics (diffusivity in water, air, sorption)	Well-defined principles. Measurements and correlations available.	Mostly **unknown** for environmental purposes.
Environmental fates (speciation / complexation, reactivity, toxicity, biodegradability)	Characterized for many conditions. Pathways established. Models available.	**Unknown** for the most part.

Use of Nano to tackle a Major Challenge Facing Planet Earth: Carbon Dioxide Emissions and Global Warmimg

Metal Organic Frameworks (MOF)

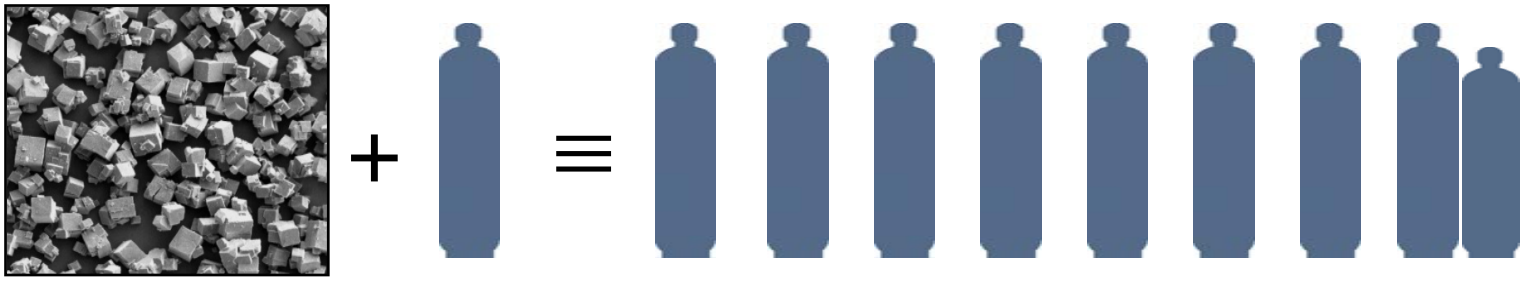


Increased acidity of oceans & destruction of shell and coral life



20% less ice cap, NASA

THE MOF SOLUTION AND EVIDENCE OF SUCCESS: CAPTURE CO_2 FROM POWER PLANTS AND AUTOMOBILES AND COMPACT IT IN POROUS MOF STRUCTURES BEFORE REACHING THE ATMPOSPHERE



MOF-177

One MOF container can hold the same amount of CO_2 as in nine ordinary containers

Inventor: Dr. O. M. Yaghi, UCLA Professor of Chemistry and Director of Center for Reticular Chemistry at CNSI