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REVIEW ARTICLE

Nanotechnology to Nanotoxicology: A Review Article

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ABSTRACT

A nanometer is one-billionth of a meter, or about 1/50,000th the width of a strand of hair. Sub-microscopically small, nanoparticles exhibit unique properties that are different from even slightly larger sized particles. They express quantum mechanical phenomena and can go places that other particles cannot—some research suggests they are small enough to pass through your skin and even through the tight mesh of cells that comprise the blood-brain barrier. The unique properties of Nanomaterials are being exploited by commercial, government, and academic laboratories to add value to existing products and enable new product development. These technical advances must be balanced with the potential human health and environmental adverse effects.

Keywords: Nanomaterial, Nanotube, Cytotoxicity, Hazard, Particle, Toxicity.

INTRODUCTION

Nanotoxicology is the study of the toxicity of nanomaterials. Because of quantum size effects and large surface area to volume ratio, nanomaterials have unique properties compared with their larger counterparts.[1] Nano-toxicology grew from studies of ultrafine particles. It might be useful, now, to define ultrafine and nano-particles. The term 'ultrafine' is used by many air pollution scientists to denote particle of less than 100 mm diameter. The term 'nano-particle' has rather overtaken the term 'ultrafine particle' and is now used to describe material presented in a form such that at least one dimension of the unit material is of less than 100 nm. Thus nano-dots, nano-spheres, nano-plates, nanotubes, nano-wires are all nano-materials or nano-particles. Nanotubes have attracted much attention. These graphene structures may be single or multi-walled and may carry contaminating metals (derived from the production process) on their surfaces.[2] Novel engineered nano materials are potentially hazardous and may have adverse

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effects on biological systems. Therefore it is important to develop methods to assess the degree of safety and toxicology hazards of nano particles. Nano-toxicology grew from studies of ultrafine particles. It might be useful, now, to define ultrafine and nano-particles. The term 'ultrafine' is used by many air pollution scientists to denote particle of less than 100 mm diameter. The term 'nano-particle' has rather overtaken the term 'ultrafine particle' and is now used to describe material presented in a form such that at least one dimension of the unit material is of less than 100 nm. Thus nano-dots, nano-spheres, nano-plates, nano-tubes, nano-wires are all nano-materials or nano-particles.Nanotechnology can be defined as the manipulation, precision placement, measurement, modeling, or manufacture of sub-100 nanometer scale matter. Nano particles are increasingly used in a range of industries, including engineering, environmental technology, information technology, food, health, chemicals and agrochemicals and pharmaceuticals. With increased use, there is recognition that nano particles can display unexpected toxicology and require testing on a case by case basis to address potential risk.[3]

1. History

Nano is not new various researchers are working on this emerging topic from years. Here we have highlighted some milestone research on nano:

(1985): Biological effects and toxicity assessment of titanium dioxides: anatase and rutile

(1992): Polymer degradation and ultrafine particles: potential inhalation hazards for astronauts.

(1992): Pulmonary retention of ultrafine and fine particles in rats.

(1992a): Role of the alveolar macrophage in lung injury: studies with ultrafine particles.

(1992b): Volumetric loading of alveolar macrophages (AM): a possible basis for diminished AM-mediated particle clearance.

2. Nanomaterial

Innovations in nanotechnology are generating a broad array of nanoparticles that are already incorporated into a wide variety of consumer products. Due to their rapid commercialization and corresponding exposure potential, there is concern over nanoparticle safety. Within the nanotoxicology community, there has been considerable debate about which nanomaterials are most relevant for determining hazard and risk. A major challenge in predicting the potential toxicity of nanoparticles is their complexity. The toxicity of each nanomaterial is dependent not only on the primary characteristics of the particles (e.g. Core chemistry, size, shape, crystallinity, surface and aggregation state), but also on secondary

characteristics which rely on the nanoparticle interaction with the target biological systems (e.g. Protein corona, dissolution rate, biodistribution). Discerning which properties are primary drivers of toxicity is complicated by the fact that the majority of commercially available nanomaterials is heterogeneous, unpurified, and are accompanied by little information concerning their manufacturing process. Toxicological profiles performed with these materials are difficult to interpret since the complexity of the starting material makes correlating physicochemical properties with the response of the endpoint unclear.[4] Different nanomaterial like Silver, Carbon nanotubes, Titanium, Silica, Gold, Zinc etc. are reported to have some unique features. They are discussed below:

Silver

It is the most prevalent nanomaterials used in consumer products in Food packaging, Wound dressings etc. Potential adverse effect of it is a bactericide. It causes development of antibiotic resistant bacteria. It is harmful to beneficial bacteria which form a symbiotic relationship to plants, animals and humans. It disrupts ecosystem function Silver Most people are exposed daily to very low level of silver mainly in food and drinking water, and less in air. Human skin penetration of silver nanoparticles through intact and damaged skin was reported by Larese et al., 2009.[5]

Figure No 1: Silver Nanomaterial

TiO2

Two arrangements are founded of this molecule: Anatase and Rutile. Anatase form is used for Photocatalytic air purification, Self cleansing surface, Solar cell, Paint and in Cancer therapy. Rutile form is used in Cosmetics, Sunscreen products and food additives. TiO2 reported to penetrate hair follicles. TiO2 nanoparticles in sunscreen product found to trap in the hair and oil pores in the skin.[5]

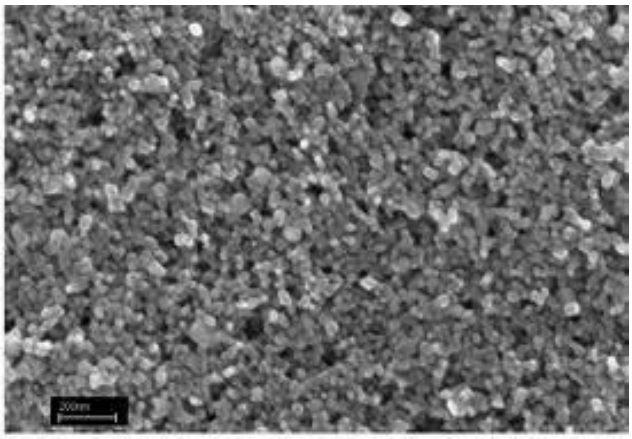

Figure No 2: Tio2 Nanomaterial

Zinc

Nanotoxicology is a nascent field of study concerned with the potential for nanotechnology to adversely impact human health or result in ecological damage. Nanomaterials can display unique physicochemical properties not present in the parent bulk material and it is these properties that may be a potential source of toxicity. There are a growing number of examples of nanomaterials functioning differently in Biosystems compared to the parent bulk material. With the rapid growth of nanotechnology and increasing exposure of people to novel nanomaterials there is an urgent need to evaluate the toxicity of nanomaterials. In this study the toxicities of silver and zinc oxide nanoparticles were assessed. The effects of size and surface coating on the cytotoxicity and immunogenicity of silver nanoparticles were investigated, with cytotoxicity found to be inversely proportional to nanoparticle size. The subcutaneous penetration of zinc oxide nanoparticles was assessed to determine whether this material can be safely used as a UV filter in sunscreens and cosmetics. No dermal penetration was detected using a porcine in vitro model. Zinc oxide nanoparticles were also used as a model material to investigate nano-specific toxicity by comparing cytotoxicity and changes to gene expression with bulk scale zinc oxide. In both cases cytotoxicity and changes in gene expression were greater for zinc oxide nanoparticles. Methods and techniques to test the toxicity of nanomaterials in vitro and the implication for in vivo toxicity are only beginning to be elucidated. The methods and techniques used in this study, particularly nanomaterial stabilization in biofluids and toxicity testing using blood cell cultures, may assist the establishment of standard in vitro testing protocols for nanomaterials.[6]

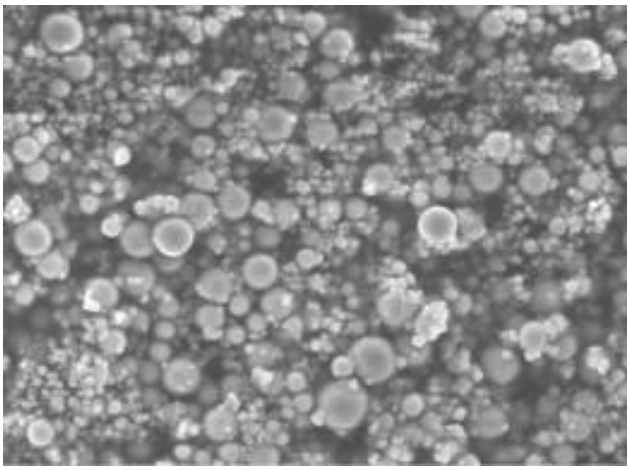

Figure No 3: Zinc Nanomaterial

Silica

Though, oxidative stress has been implicated in silica nanoparticles induced toxicity both in vitro and in vivo, but no similarities exist regarding dose–response relationship. This discrepancy may, partly, be due to associated impurities of trace metals that may present in varying amounts. Here, cytotoxicity and oxidative stress parameters of two sizes (10 nm and 80 nm) of pure silica nanoparticles was determined in human lung epithelial cells (A549 cells). Both sizes of silica nanoparticles induced dose-dependent cytotoxicity as measured by MTT [3-(4, 5-dimethyl thiazol-2-

yl) -2, 5-diphenyl tetrazolium bromide] and lactate dehydrogenase (LDH) assays. Silica nanoparticles were also found to induce oxidative stress in a dose-dependent manner indicated by induction of reactive oxygen species (ROS) generation, and membrane lipid peroxidation (LPO). However, both sizes of silica nanoparticles had little effect on intracellular glutathione (GSH) level and the activities of glutathione metabolizing enzymes; glutathione reductase (GR) and glutathione peroxidase (GPx). Buthionine-[S, R] -sulfoximine (BSO) plus silica nanoparticles did not result in significant GSH depletion than that caused by BSO alone nor N-acetyl cysteine (NAC) afforded significant protection from ROS and LPO induced by silica nanoparticles. The rather unaltered level of GSH is also supported by finding no appreciable alteration in the level of GR and GPx. Our data suggest that the silica nanoparticles exert toxicity in A549 cells through the oxidant generation (ROS and LPO) rather than the depletion of GSH.[8]

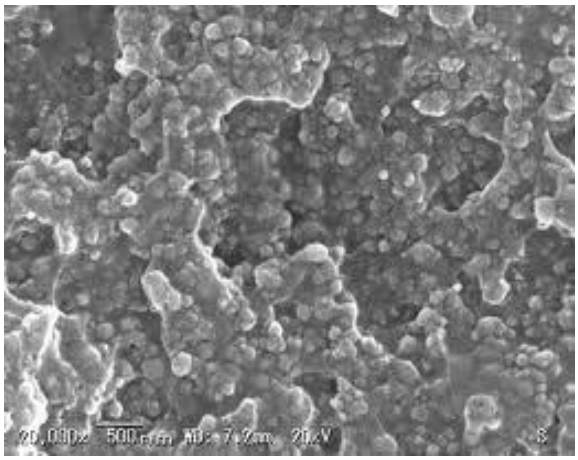

Figure No 4: Silica Nanomaterial

Carbon nanotubes

Toxicological investigations of carbon nanotubes have shown that they can induce pulmonary toxicity, and similarities with asbestos fibers have been suggested.we previously reported that Multiwall carbon nanotubes(MWCNT) induced lung inflammation, granulomas and fibric reactions. The same MWCNT also caused mutations in epithelial cells in vitro and in vivo.These inflammatory and genotoxic activities were related to the presence of defects in the structure of the nanotubes. In view of the strong links between inflammation, mutation and cancer, these observations promoted us to explore the carcinogenic potential of these MWCNT in the peritoneal cavity of rats. The incidence of mesothelioma and other tumors was recorded in three groups of 50 male wister rats injected intraperitoneally with a single dose of MWCNT with defects (2 or 20 mg/animal) and vehicle controls. After 24 months, although crocidolite induced a clear carcinogenic response (34.6% animals with mesothelioma vs.3.8% in vehicle controls) MWCNT with or without defects could not be verified in this bioassay. We discuss the possible reason for this absence of carcinogenic response, including the length of the MECNT tested (<1 mum on average), the absence of a sustained inflammatory reaction to MWCNT, and the capacity of these MWCNT to quench free radicals.[9]

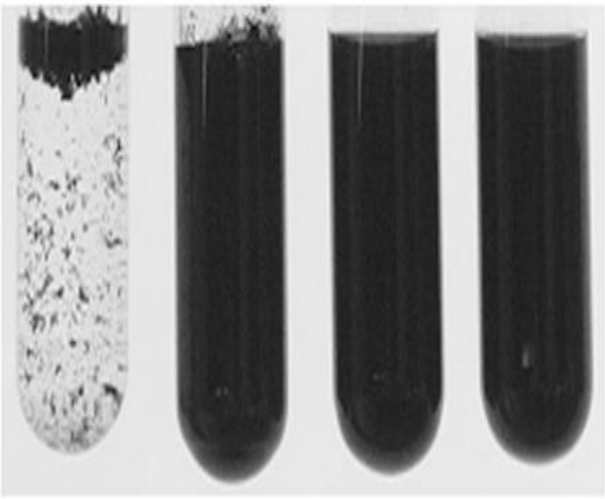

Figure No 5: Carbon Nanotube Nanomaterial Gold

Our gold nanomaterials are available in colloidal form, and we're happy to make custom formulations. Gold colloid has been used to color stained glass since ancient times, and has tremendous promise with current applications Cancer treatment, In vivo sensors, Bacteria identification, Enzyme identification, Heating, protective agents for optical imaging, Drug carriers, Contrast enhancers in computer tomography, X-ray absorbers in cancer therapy, Computer memory It disrupt ecosystem function gold Most people are exposed daily to very low level of gold mainly in food and drinking water, and less in air. Human skin penetration of gold nanoparticles through intact and damaged.[10]

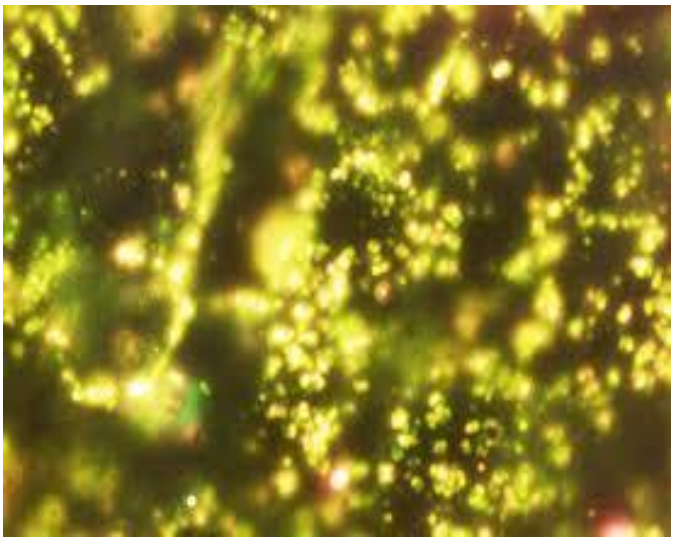

Figure No 6: Gold Nanomaterial

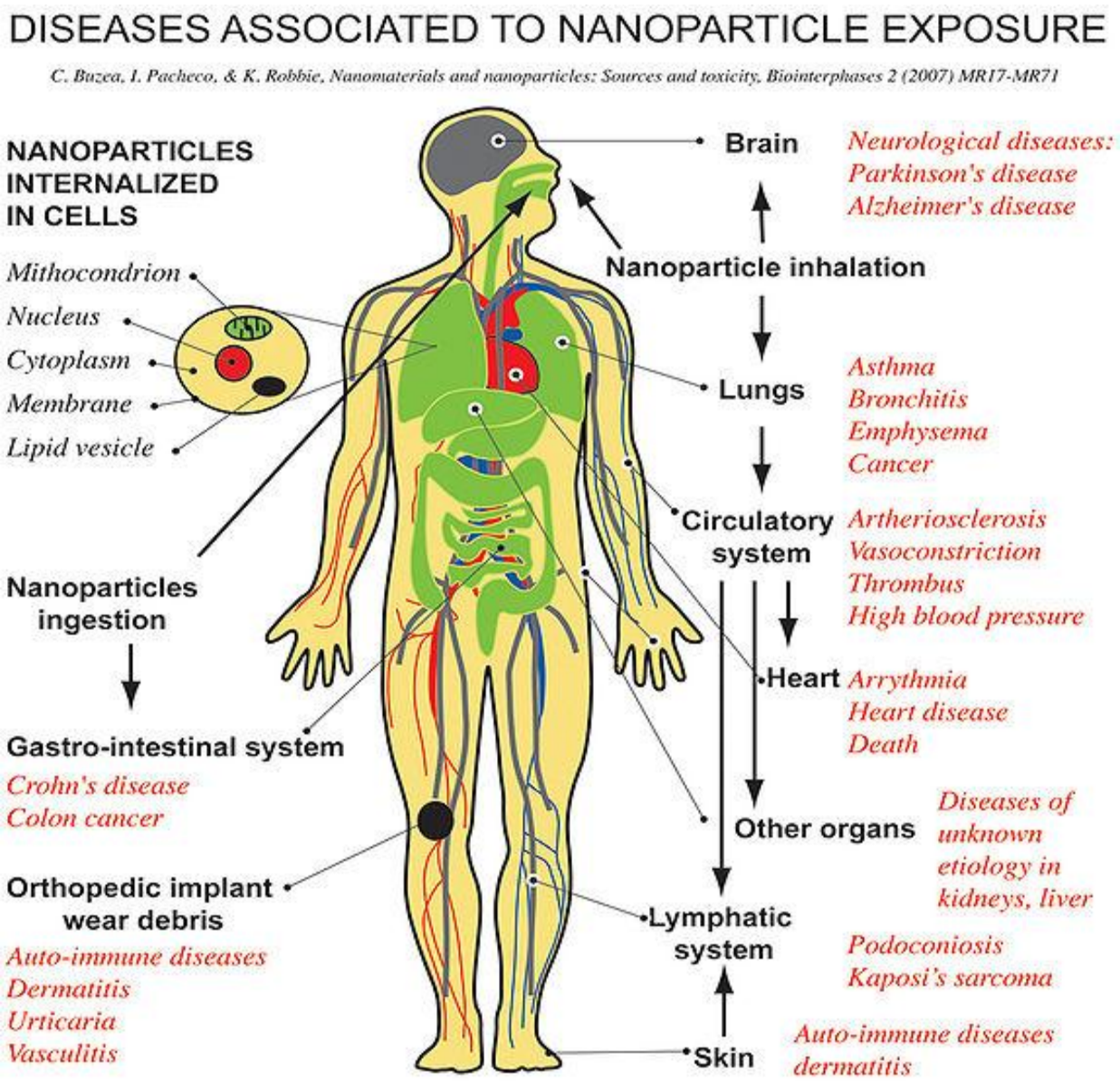

Figure No 7: Diseases Associated To Nanopartical Exposure

Table No 1: In Vitro Studies of Nanomaterial

Uptake and Intracellular fate	**Chemical Analysis**	**Cytotoxicity and Cell viability**	**Oxidative stress and Inflammation**	**Reactive Oxygen/Nitric Species**	**Genotoxicity and DNA Damage**
Laser scanning Microscopy	EELS	MTT assay/ WST assay	Reduction in Glutathion	DCFH-DA	Ames test
Fluorescenttrackers for cell Organelles	ICP-AES	Apoptosis	PCR analysis	PCR analysis	Comet assay
Electron Microscopy	EFTEM	LDH assay	Superoxide Anion	Greiss reaction Test	Micronucleus Assay
Light Microscopy	EDX analysis	BrdU assay	ELISA	Intracellular Calcium	PCR analysis
FACS analysis	Mass Spectrometry	TUNEL method	Western Blot Analysis	Antioxidant	Various kit Stimulation [3]

4. Characterization

1. Material Characterization

• Morphological assessments: size, surface area, shape

• Chemical nature: composition, reactivity, charge, solubility

2. Environmental Health and Safety

• In vitro toxicology: primary cells, carcinoma cells, co-cultures

• In vivo toxicology: hepatic, pulmonary, dermal, circulatory, gastrointestinal effects

3. Environmental Assessments

• Mobility, fate, transport

• Transformation over time

5. NanoToxicology

Particle toxicology has historically addressed the mechanisms of lung injury caused by environmentally generated nanoparticles. Following the rapid development of the nanotechnology industry, lung injury is now only one of the potential risks that may require toxicological assessment. Adverse effects can manifest via a range of actions (particularly oxidative stress) and in a number of organs, ranging from respiratory and cardiovascular (diesel exhaust or bulk manufacture) and gut (food additives) to systemic and hepatic systems (drug delivery/carrier

systems and novel imaging modalities). An appropriate battery of in vitro and in vivo testing is required to assess systemic toxicology as well as tissue specific adverse effects (e.g. Respiratory, cardiovascular, dermal and hepatic).[6] In 2007, a review of nanotoxicology peer-reviewed publications found that of 38 studies of carbon based and metallic nanoparticles, 24 indicated some negative biological impact such as cell death, DNA damage, oxidative stress, increased reactive oxygen species levels, pro-inflammatory response, and altered immune function.[10]

1. Nano-particles and the brain

Nano-particles have been shown to enter the sensory cells of the olfactory epithelium and to be transported via the olfactory nerves to the olfactory lobes of the brain . That they enter the nerve a terminal is surprising, that they are transported via the axons to the brain is not. Retrograde axonal transport is a well established process: it explains the movement of the polio virus from skin abrasions to the spinal cord. That nano-particles are transported onwards along the olfactory pathways of the brain is surprising. This implies that they can cross synaptic junctions: how they do this is unknown. It will be appreciated that such findings have the capacity to induce a high level of concern: are the nano-particles of the ambient aerosol, even now, penetrating to our brains.[11]

2. Translocation to lung to blood

One early study showing very rapid translocation was flawed due to the rapid dissolution of the particles, overestimating translocation Kreyling studied the transport of radioactive iridium particles through lung 80 nm--0.1% translocated through the lung and ended up in the liver. Only a small fraction of intratracheally instilled UFPs can pass rapidly into systemic circulation. This translocation is markedly increased following LPS pretreatment. Pulmonary inflammation seems to play a major role in enhancing the extrapulmonary translocation of particles. Relevant to epidemiology outcome which suggests that the elderly and people with pre-existing cardiorespiratory disease are at a higher risk of particles-induced injuries[9] Carbon nanotubes do penetrate the lungs of mice and migrate to the pleura, just like asbestos.[3]

3. Translocation from Nose to Brain

Known that polio virus particles can enter the brain via the olfactory nerves since 1941Studies in monkeys with intra nasally in stilled gold ultrafine particles (UFPs; < 100 NM) and in rats with inhaled carbon UFPs (36 mm) suggested that solid UFPs deposited in the nose travel along the olfactory nerve to the olfactory bulb Lung Dosed Nano TiO2 Interferes with systemic arterial function.[12]

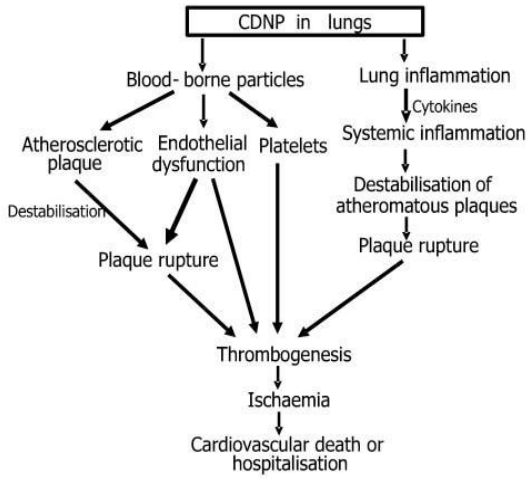

Figure No 8: Translocation from Nose to Brain Nanomaterial

4. Nanoparticle and eye

Nanoparticles are thought to improve the bioavailability in the retina and the permeability of therapeutic molecules across the barriers of the eye, such as the cornea, conjunctiva, and especially, blood-retinal barriers (BRBs). However, consisting of multiple neuronal cells, the retina can be the target of neuronal toxicity of nanoparticles, in common with the central and peripheral nervous system. Furthermore, the ability of nanoparticles to pass through the BRBs might increase the possibility of toxicity, simultaneously promoting distribution in the retinal layers. In this regard, we discussed nanotechnology and nanotoxicology in the treatment of retinopathy.

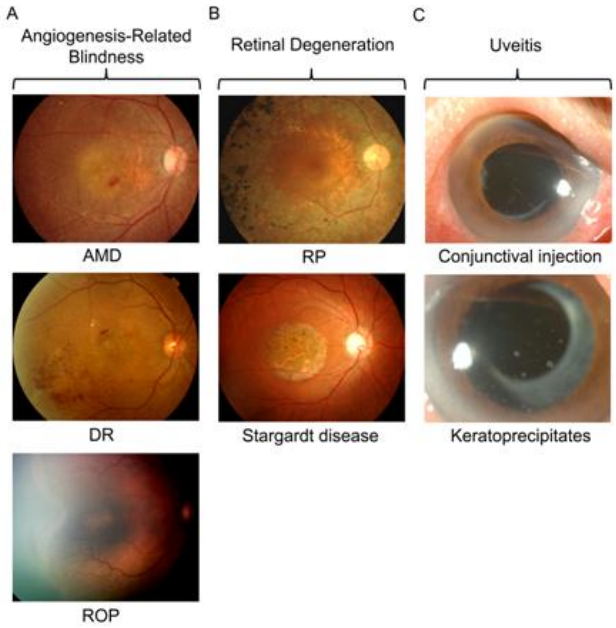

Figure No 9: Nanopartical in Eye

5. Nanoparticle and Environment

There are many potential benefits of nanomaterials including their use in medicine for drug delivery and imaging, electronics, new textiles, innovative building materials, water-treatment technology, remediation of contaminated land and much more. However, we are only just beginning to understand the effect of nanomaterials on organisms and the environment. The focus of our research is on understanding the Ecotoxicology and environmental chemistry of nanomaterials.

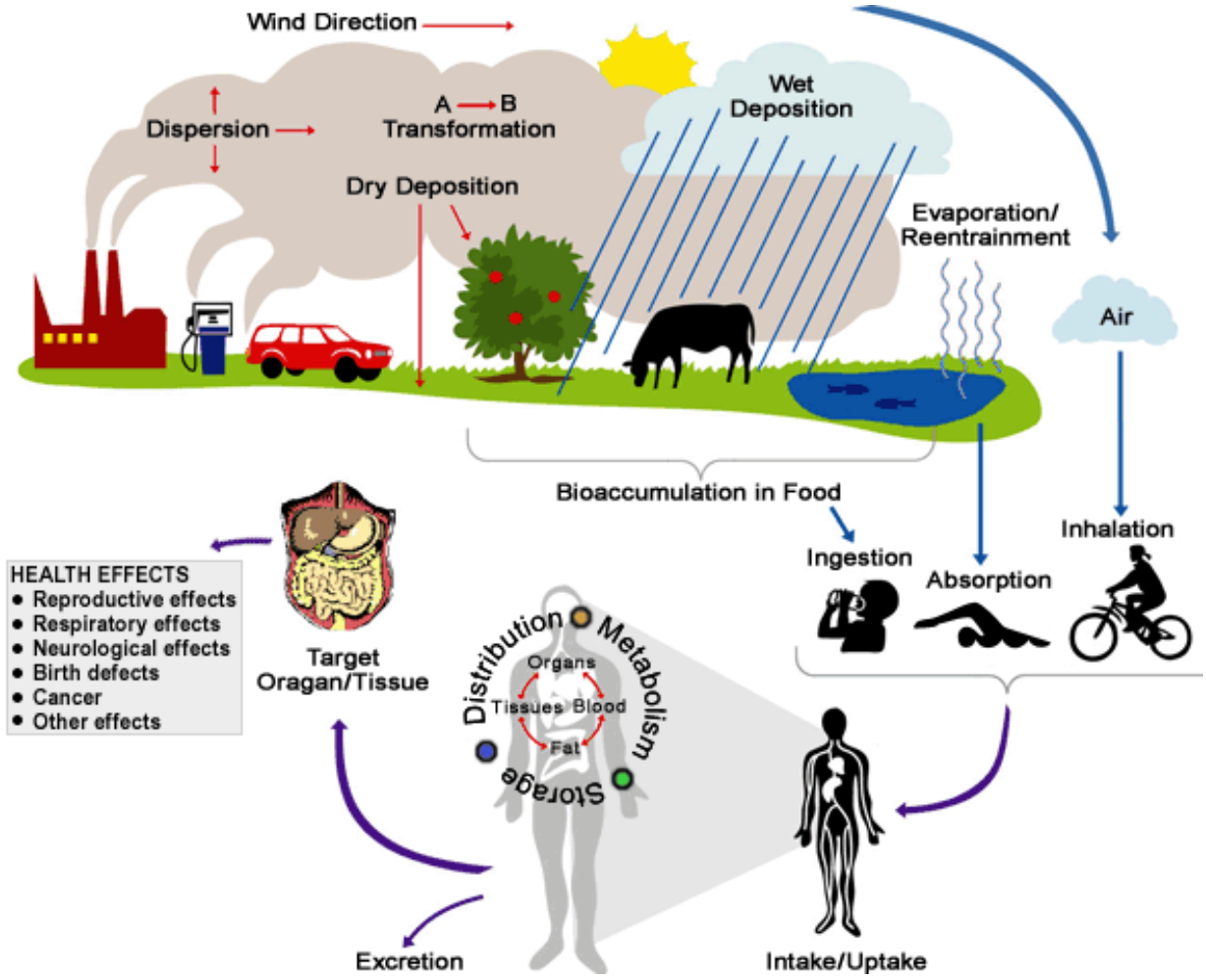

Figure No 10: Nanopartical and Environment

6. Hazards:

• The very young field of nanotoxicity has already linked some nanoparticles too:

• Damage to DNA5, 6

• Disruption of cellular function7 and production of reactive oxygen species

• Asbestos-like pathogencity

• Neurologic problems (such as seizures)

• Destruction of beneficial bacteria in wastewater treatment systems.

• Organ damage, including significant lesions in the liver and kidneys.

7. Regulatory Guidance

The situation for developers of nanomaterials is complicated by the evolving status of regulatory guidance. Until recently, there was very little specific guidance for nanoparticles, but this is

changing. For instance, recently there has been concern that the current registration threshold limit of 1 tonne under REACH may not be suitable for nanometers and there is the suggestion that nanoscale substances < 1 tonne per year should be registered. This is an approach which has now been adopted by the French whom in February 2012 published a decree that all companies producing, distributing or importing nanomaterials in France, irrespective of quantity, must register this by July 2013.This step, as well as the commissioning of research and reports to address the issue of readiness and suitability of current legislation to deal with nanomaterials (e.g. REACH implementation projects on Nanomaterial) demonstrates that this is a dynamic situation. As guidelines evolve, CXR has developed a broad platform of in vitro and in vivo models for designing and conducting early investigative and mechanistic safety assessment programs, which can both assist in the better design of formal safety studies, and assess the relevance to men of previous adverse findings.[13]

CONCLUSION

Consumer products containing nanotechnologies have been entering the commercial market at a rate of about20 a month for the last year, while the government is granting new patents for nanotechnology at a rate of about10 a week, trying to work its way through 3500 pending applications. Current financial revenue from nanotechnology, which was predicted to contribute to $166 billion worth of products in 2008, is dwarfed by predictions for2015, which foresee sales of one trillion dollars. 171 J. Clarence Davies, a senior advisor to the Project on Emerging Nanotechnologies and a senior fellow at Resources for the Future, has predicted that "twenty years from now, most of the products we use are likely to have some nanotechnology.

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