Asian Journal of Biomedical and Pharmaceutical Sciences
ISSN : 2249 - 622X

REVIEW ARTICLE

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Received on: 01-04-2014
Accepted on: 22-05-2014
Published on: 15-06-2014

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Conflict of Interest: None Declared !

QR Code for Mobile users

DOI: 10.15272/ajbps.v4i32.480

Nanoparticle Induced Nanotoxicity: An Overview

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ABSTARCT
Nanotechnology investigation is generating extraordinary improvements for identifying, treating, and avoiding health problems. However, while nanoparticles can mainly to breakthrough applications, they may also root for dangerous side effects. It has been revealed that nanomaterials can enter the human body through a number of ports. Nanoparticle can modify the physiochemical properties of material as well as create the opportunity for increased the uptake and interaction with biological tissue through inhalation ingestion and injection. This combination effects generate adverse biological effects in living cell. Health effects of nanoparticles are attracting extensive and increasing concern of the public and government worldwide. So far, most of the nanotoxicity investigation concentrated on respiratory tract contacts for considering the health effects of nanoparticles. Other exposure routes, e.g., gastrointestinal tract also need to be considered as potential portals of entry. We review the recent accepting threat of NPs resulting from the novel science of nanotoxicology and the restricted exploration to date into human contact to these particles.

Keywords: - Nanoparticle, Nanotoxicity, Nanoparticle classification, Oxidative stress.

Cite this article as:
K. Janrao, M.V. Gadhave, S.K. Banerjee, D.D.Gaikwad. Nanoparticle Induced Nanotoxicity: An Overview. Asian Journal of Biomedical and Pharmaceutical Sciences; 04 (32); 2014; 1-7.

Introduction

The overview of all novel technologies will have unexpected consequences, both beneficial as well as harmful. Public awareness about nanotechnologies is currently increasing promptly, principally as a consequence of non-specifically delimited introduction of products comprising nanomaterial's into the marketplace. In addition, both governments and supervisory body endeavor the challenging assessment act concerning prompt rapid technological enlargement and business, even though at the same interval making assured that it is finished safely and changeable new technology efficiently. Numerous governing establishments, governments and international administrations such as the OECD, ISO and BSI have been taking initiative trying to understand nanotechnology and how best to assist its safe enlargement and use. The prefix "nano" is resulting from the Greek word "nanos" meaning "dwarf". Nanotechnology comprises the manipulation and application of engineered particles or systems that require at least one dimension less than 100 nanometers (nm) in length.[1] A particle which having one or more dimensions order of 100 nm or less.[2] "Nano" is at the present a prevalent marker for much of modern science, and numerous "nano" words have recently appeared in dictionaries, including: nanometer, nanoscale, Nano science, nanotechnology, nanostructure, nanotube, nanowire, and nanorobot. The exploration in nanoparticle is an existing area of scientific investigation due to extensive diversity of application in numerous field generally growing advances in biomedical and in therapeutic filed[3].Due to subsequent returns,

a) Reduction of dosing frequency as well as improved the drug bioavailability.
b) Nanomaterial's for imaging and drug delivery remain frequent purposefully coated with biomolecules such as DNA, proteins, and monoclonal antibodies to target precise cells.[4]
c) Materials in this dimension possibly will approach the length scale at which particular definite physical or chemical interactions through their environment can occur.[5]
d) Due to their enormously small size, nanomaterials possess exceptionally high surface area to volume ratio which renders them highly reactive.

History of Nano Hazards

The perception that nanoparticles possibly will ensure distinctive toxic properties is an existing one, though the rationale behind, it is resulting from traditional particle toxicology and epidemiology, principally from investigation of air pollution. The destructiveness of air pollution was supposed in the control of Charles II but its actual cost in lives lost come to be clear in the 1930s and 1940s with two episodes, one in the Meuse valley in Belgium and the further in Donora in Pennsylvania. in the 1990s two distinct lines of investigation come together: epidemiological investigation demonstrated associations among deaths and particulate air pollution even at unusually low mass concentrations[6, 7] and investigation of deposition of inhaled particles in the lungs of rats directed to the surveillance that particles in the nanosize range remained retained in the lungs and translocated to the interstitial tissues more readily than greater particles[8]. The toxicological examination, in the beginning carried out to understand why this chemically inactive mineral had such disturbing effects on the health of those inhaling it[9], turn into significant investigation of probable hazards from substitute fibrous minerals[10].

Nano Toxicological Classification

The classification application: NCS classes I to IV Constructed on the concerns about size classes and biodegradability, four classes of increasing hazard/toxicity can be done in this system low hazard particles are linked to green, medium hazard particles to yellow and high hazard particles to red traffic light. Consequently, it explains composite circumstances into vibrant information and enables the discrimination of nanoparticles, in green, yellow or red nanoparticles.

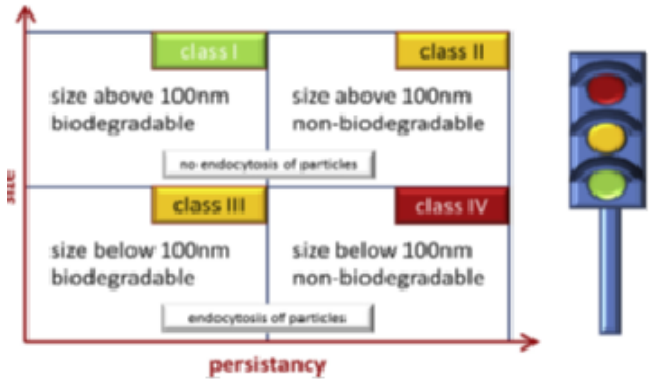

Fig.No.1.Nanotoxicological Classification System[11]

Class I comprises the particles of no or lowest risk, i.e. particles exceeding 100 nm to just inferior to 1000 nm being biodegradable. Illustrations for this class of ''green'' nanoparticles are nanoemulsions, liposomes, drug nanocrystals and lipid nanoparticles in the corresponding size range. These particles do not necessarily possess any risk an earlier. Several of them can retain a slight risk in case. They produce hazardous side effects throughout their presence, e.g. interaction with the immune system. From class I to II the persistency rise. Identical to class I nanoparticles, the class II nanoparticles are greater than 100 nm, but nonbiodegradable Class III nanoparticles are smaller than 100 nm, but biodegradable. From the above

revealed illustrations of class I nanoparticles are in class III. Class II and III retains moderate risk, i.e. yellow particles. The maximum toxicity risks retain nanoparticles of class IV. They are smaller than 100 nm and can consequently access all cells, on top they are no biodegradable. As a result, particles of this class are called ''red'' nanoparticles.[11]

Nanotoxicology

Nanotoxicology is developing as a significant subdiscipline of nanotechnology. Nanotoxicology mentions in the direction of investigation towards interactions of nanostructures with biological systems with a prominence on revealing the relationship among the physical and chemical properties such as the size, shape, surface chemistry, structure, composition and aggregation of nanostructures with induction of toxic biological response. Nanoparticle can transform physiochemical properties as well as construct the opportunity for better uptake and interaction with biological tissue. presently, a comprehensive understanding of the size, shape, structure composition and aggregation reliant interactions of nanoparticle with biological systems is lacking thus it is unpredictable whether the contact of humans, animals, insects and plants to engineered nanoparticle possibly will produce harmful biological responses[12]. Hence, a new subdiscipline of nanotechnology called nanotoxicology has developed[13, 14]. Nanotoxicology investigation because of the processing of nanoparticle in biological systems possibly will lead to unpredictable effects. Nanoparticle is having a capability to cross the biological membrane and access the cells tissue and organ inhalation and consumption. Human skin, lungs, and the gastro-intestinal tract remain in persistent contact with the environment. Whereas the skin is commonly an effective barrier to foreign substances, the lungs and gastrointestinal tract are more susceptible. These three behaviors are the most likely points of entry for natural oranthropogenic nanoparticles. Injections and implants are other conceivable routes of exposure, predominantly restricted to engineered materials. Due to their small size, nanoparticles can translocate from these entry portals into the circulatory and lymphatic systems, and eventually to body tissues and organs. Some nanoparticles, liable on their composition and size, can develop permanent destruction to cells by oxidative stress or organelle injury. The size of a cell and its organelles associated to nanoparticles of numerous sizes, making it easy to understand why nanoparticles remain capable to enter cells and interact with numerous cell constituents such as nucleus, mitochondria, etc. The toxicity of nanoparticles rest on different factors, together with: size, aggregation, composition, cystallinity, and surface functionalization with surrounding tissue.

Behavior of Nanoparticle with body

Nanoparticles have remained established to be distributed to various parts of the body and mainly in colon, lungs, bone, marrow, liver, spleen, lymph, brain. In what manner these nanoparticles behave inside the body is still a most important question that necessity to be resolved. Nanomaterials having an ability to cross biological membranes and access cells, tissues and organs[15].Nanomaterials can increase access to the blood stream through inhalation[16] or ingestion[17]. At least several nanomaterials can penetrate the skin; [18] even greater micro particles may penetrate skin when it is flexed.[19] Broken skin is an ineffective particle barrier[16] proposing that acne, eczema, shaving wounds or severe sunburn possibly will accelerate skin uptake of nanomaterials. Then, formerly in the blood stream, nanomaterials can be transported around the body and be taken up by organs and tissues, together with the brain, heart, liver, kidneys, spleen, bone marrow and nervous system.[16] Nanomaterials have confirmed toxic to human tissue and cell cultures, ensuing in increased oxidative stress Inflammatory cytokine productionand cell death.[20] Dissimilar larger particles, nanomaterials may be occupied by cell mitochondria[21] and the cell nucleus.[22,23]investigation reveal the prospective for nanomaterials to cause DNA mutation[23] and induce major structural damage to mitochondria, even succeeding in cell death.[21,24]

Mechanism of nanoparticle toxicity

As associated to the increasing viable attentiveness of nanomaterial, modest investigation work has remained devoted in assessing the prospective adverse effects of these engineered nanomaterials. The complete diversity of the physicochemical parameters of nanomaterial such as size, shape, structure, and elemental constituents makes the research of their toxic effects composite and exciting[25]certain of the prototypes for nanoparticle facilitated toxicity take account of oxidative stress, inflammation, genetic destruction, and the inhibition of cell division and cell death [26,27,28,29] Most advanced effort to date has recommended that ROS generation which can be moreover protecting or destructive throughout biological interactions and subsequent oxidative stress are persistently detected with nanoparticle toxicity[30].The physicochemical characterization of nanoparticle comprising particle size, surface charge, and chemical conformation is a key indicator for the subsequent ROS response and nanoparticle tempted injury since various of these nanoparticle distinctive properties can catalyze the generation[31]. The mechanism for ROS generation is diverse for each nanoparticle and to date the careful underlying cellular

mechanism for ROS production is to some extent understood and remains to be clarified. Mitochondrial destruction plays a key role in CNT-facilitated ROS production[32].For various forms of particles, having smaller particle size, greater their surface area to volume ratio and the higher their chemical reactivity and biological activity. Higher their chemical reactivity of nanomaterials resulting consequence in increased generation of reactive oxygen species (ROS), together with free radicals[33].ROS production has remained found in a numerous range of nanomaterials comprising carbon fullerenes, carbon nanotubes and nanoparticle metal oxides. ROS and free radical generation is one of the basic mechanisms of nanomaterial toxicity it may consequence in oxidative stress, inflammation, and subsequent destruction to proteins, membranes and DNA[33]. The enormously small size of nanomaterials also means that they much more readily gain entry in to the human body than larger sized particles. In what way these nanoparticles act inside the body is still a key question that wants to be determined. The activities of nanoparticles are a function of their size, shape and surface reactivity with the adjacent tissue. In acceptance, an enormous amount of particles might overload the body's phagocyte, cells that ingest and destroy foreign matter, in that way generating stress reactions that lead to inflammation and weaken the body's resistance against other pathogens. In addition to queries about what take place if non-degradable or slowly degradable nanoparticles accumulate in bodily organs, an additional concern is their potential interaction or intervention with biological progressions inside the body. Due to large surface area, nanoparticles will, on exposure to tissue and fluids, immediately adsorb onto their surface some of the macromolecules they encounter. This may, for instance, affect the regulatory mechanisms of enzymes and other proteins.

Properties of nanoparticle that induces toxicity

Nanotoxicology is a subspeciality of particle toxicity .It reports the toxicology of nanoparticle which seems to have toxicity effects that remain irregular and not too understood with larger particle. The smaller a particle the grater its surface area to volume ratio and higher its chemical reactivity and biological activity. Because of their large surface area, nanoparticle will, on exposure to tissue and fluids, immediately adsorb onto their surface some of the macromolecules they encounter this may for instance, affects the regulatory mechanism of enzymes and other protein the mediators of toxicity of particles

Physico-chemical characteristics -dependent toxicity

The extreme essential parameters in defining the adverse health effects of nanoparticles are dose, dimension, and durability. Correspondences between various physicochemical properties of nanoparticles and the linked health effects, raising some worries as to which are the most significant parameters in determining their toxicity: mass, number, size, bulk or surface chemistry, aggregation.

DOSE-DEPENDENT TOXICITY

Dose is defined as the quantity or measure of substance that will influence a biological system. The dose is directly related to exposure or the concentration of substance in the applicable medium such as air, food, water increased by the extent of contact. Health effects of inhaled TiO2 nanoparticles with different sizes, it is amazing that the low dose (10 mg/m3) exposure to 20 nm diameter particles give rise to lung tumor incidence than the high dose (250 mg/m3) exposure of 300 nm diameter particles[17].

Size-dependent toxicity

In the last decade, toxicological studies have demonstrated that small nanoparticles (<100 nm) cause adverse respiratory health effects, typically causing more inflammation than larger particles made from the same material [34, 35, 36]. Decrease in size to the nanoscale level consequences in an massive growth of surface to volume ratio, so relatively additional molecules of the chemical are present on the surface, consequently increasing the intrinsic toxicity. In the previous decade, toxicological studies have confirmed that small nanoparticles (<100 nm) cause adverse respiratory health effects, classically producing more inflammation than larger particles made from the same material. Rat inhalation[34] and instillation of titanium oxide particles with two sizes, 20 nm and 250 nm diameter, having the same crystalline structure show that smaller particles led to an insistently high inflammatory reaction in the lungs compared to larger size particles.

Surface area-dependent toxicity

Greater toxicity was originated from nanoparticles of identical mass with the identical chemical composition and crystalline structure. The inflammatory effect may be reliant on the surface area of nanoparticles; smaller nanoparticles have higher surface area and particle number per unit mass compared to larger particles. Larger surface area leads to enlarged reactivity[37]and is an enlarged source of reactive oxygen species[38].The higher surface area of nanoparticles causes a dose dependent increase in oxidation[39]and DNA destruction[38], much higher than larger particles with the same mass dose[39].

Particle chemistry and crystalline structure dependent toxicity

Particle chemistry may be additional significant than chemical composition in determining nanoparticles toxicity[38].Particle chemistry is critical in defining

nanoparticles toxicity from the point of view of cell molecular chemistry and oxidative stress. Depending on their chemistry, nanoparticles can show dissimilar cellular uptake, subcellular localization, and ability to catalyze the production of reactive oxygen species[40].

Surface coating and functionalization

Particle surface show a key role in toxicity as it makes contact with cells and biological material. Surfactants can extremely change the physicochemical properties of nanoparticles, such as magnetic, electric, optical properties and chemical reactivity[41, 42], affecting their cytotoxicity. Surface coatings can render noxious particles non-toxic even though less harmful particles can be made highly toxic. The existence of oxygen, ozone[38], oxygen radicals[43], and transition metals[39]on nanoparticle surfaces leads to the formation of reactive oxygen species and the induction of inflammation For example; specific cytotoxicity of silica is strongly related with the occurrence of surface radicals and reactive oxygen species[17].

Nanoparticle exposure

The resulting discussion of nanoparticles exposure things to see the limited exposure investigation that have been conducted, as well as studies on the ability of the external surfaces of the body to limit systemic exposure and mechanisms of nanoparticles translocation[44].

Inhalation exposure

Inhalation is supposed to be an important route of nanoparticle exposure, subsequently nanoparticles can transportable great distances in air by Brownian diffusion and are respirable, leaving within the alveolar regions of the lung

Neuronal translocation

Neuronal uptake of inhaled nanoparticles may take place via the olfactory nerves and blood-brain-barrier. More current studies approve the uptake of inhaled nanoparticles from olfactory mucosa via the olfactory nerves in the olfactory bulb. For example, rat inhalation studies with 30 nm magnesium oxide[45] and 20-30 nm carbon[46]nanoparticles indicate that nanoparticles translocate to the olfactory bulb[45].

Lymphatic systems

Translocation of nanoparticles to lymph nodes is a topic of intense study today for drug delivery and tumor imaging.[47] Progression of many cancers (lung, esophageal, mesothelioma, etc.) is seen in the spread of tumor cells to local lymph nodes[47]. Numerous investigations show that interstitially injected particles permit especially through the lymphatic system and after incoming the lymphatic system, they localize in the lymph nodes[47].Oxidative stress produced by certain kinds of nanoparticles could lead to destruction of lymphocytes lymph nodes, spleen.

Circulatory system

Inhalation or instillation investigations in healthy animals demonstrate that metallic nanoparticles with size smaller than 30 nm permit rapidly into the circulatory system[44], Subjects suffering from respiratory and circulatory diseases have higher capillary permeability, permitting fast translocation of metallic or non-metallic nanoparticle into circulation.

GI exposure

Current investigations have addressed that the absorption of nanoparticles into GI through subsequent oral exposure. Like occupational and environmental route, resulting from absorption of contaminated .Food and water, the swallowing of inhaled particles, or hand-to mouth transfer of particles.

Dermal exposure

The interaction of nanoparticles with skin has normal substantial concern in current periods for the reason that the increasing use of nanoscale particles in stain-resistant clothing, cosmetics, and sunscreens. The dermal route of contact is also crucial for the attraction of agglomerated airborne nanoparticles to settle down on surfaces and the difficulties in preventing dermal contact with these settled particles. Several research have been carried out in reviewing the ability of nanoscale TiO2, used as a ultraviolet (UV)-absorbing component in sunscreens, to penetrate the epidermis in human volunteers, and animal and in vitro models The skin is generally self-possessed of three layers - epidermis, dermis and subcutaneous .The external portion of the epidermis, called stratum corneum - is a 10 μm thick keratinized layer of dead cells and is challenging to pass for ionic compounds and water soluble molecules[17]. As with many subjects concerning nanoparticles, dermal diffusion is still debated[48]. Numerous investigation show that nanoparticles are capable to penetrate the stratum corneum[49, 50]. Nanoparticle penetration through the skin naturally occurs at hair follicles[50], and flexed and broken skin. Spherical particles with diameter between 750 nm and 6 microns principally penetrate the skin at hair follicles with a maximum penetration depth of more than 2400 microns (2.4 mm) [50]. Damaged skin assists the entry of an extensive range of larger particles (500 nm - 7 μm). While stationary undamaged skin has remained to be impermeable to penetration, nanoparticles have remained observed to penetrate when the skin is flexed.

Regulatory guideline for nanoparticle toxicology

In spite of the extensive assortment of probable exposure circumstances and therefore potential risks, definite regulation has been deliberate to emerge. One of the issues here is that because of the extensiveness of applications, from paints to cosmetics to medicines, many dissimilar regulatory frameworks apply. For example, in Europe, this would include regulations on

worker safety, chemicals, general products, cosmetics, food, pollution, biocides, water, waste and labeling. However, appraisals of regulations ,for example the BRASS report have constantly informed that, however the regulatory framework is capable of dealing with nano issues, the regulations are not well attuned to dealing with the specifics of nano-sized materials Currently, there is no regulation and guideline in nanomaterial toxicology at all provincial, national level. In early this year, US-EPA published "Nanotechnology White Paper" in that EPA registered problems or restriction & some necessities in environmental health for enlargement of nanotechnology. However, it is far way to form a regulations or guidelines is of efficiency toxicological techniques that can powerfully identify factual toxicological factors for assessing nanomaterial toxicity since too many untouched factors. To launch such regulations or guidelines in nanomaterial toxicology is depend on the development.

Examples of Toxicities of Nanoparticle

Investigators in the University of Texas in the United States establish that carbon nanotubes squirted into the trachea of mice produced severe inflammation of the lungs and granulomas. In a comparable experiment carried out at the National Institute of Occupational Safety and Health in Morgantown, West Virginia, in the Unites States, investigators not only found granulomas in the lungs, but also damage to mitochondrial DNA in the heart and the aortic artery, and considerable oxidative damage, both foreshadowing atherosclerosis. Inflammation and oxidative stress can be mediated by several primary pathways: Hypothetical cellular interaction of NSPs and epidermal growth factor receptor

Conclusion

Nanotechnology is developing at an exponential rate and will incontrovertibly have both beneficial and toxicological, dangerous influence and concerns on health and environment. Possible undesirable results of these capabilities are destructive interactions with biological systems with the potential to produce toxicity. Moreover, toxicity investigations are dangerous to establish the full in vivo potential of nanomedicine. Accepting the physiochemical, molecular, and physiological processes of nanoparticles is important for nanomedicine to become a reliable and sustainable treatment modality.

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