Review Article

TOXICITY OF NANO-MATERIALS TO ENVIRONMENT AND MANKIND: AN OVERVIEW

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ABSTRACT

We reviewed nanomaterials and nanotoxicology to investigate their implications on the environment and the human system. The advent of any new technologies have unexpected outcomes which can be both beneficial and harmful to the mankind and environment. Despite of beneficial outcomes of nanotechnology in different fields, nanomaterials have created a global concern due to toxicities related to them. Nanotoxicology involves study of the nature and mechanism of toxic effects of nanoscale materials and particles on living organisms and other biological systems. It quantitatively assesses the intensity and frequency of the nanotoxic effects. Mixed opinion exists regarding their advantages and disadvantages. However, due to their strange and new physico-chemical properties, they behave uniquely when inadvertently enter in environment and life forms. Their unique properties, like electrical conductivity, stability, reactivity, *etc*. could be alarming if they are at wrong place. In the living forms, they may enter through various portals and cause toxicity that has a lethal impact on the bio-systems, especially humans. It has deleterious effects on precisely on respiratory, gastrointestinal, neural, cutaneous, and cardiovascular systems. There are certain factors which affect nanotoxicology, for instance, size of nanomaterials, their surface area and chemistry, chemical components, dosage, and their free radical production. There are certain environmental concerns related to these materials, especially their non-biodegradable and bioaccumulation properties which make them lethal in both terrestrial and aquatic habitats.

Keywords: Nanotoxicology, nanotechnology, nanomaterials, carbon nanotube, fullerene

INTRODUCTION

'Nano' means extremely tiny and is connected to the materials which are measured in nanometres. The smallest life forms, like Mycoplasma and viruses along with macromolecules like DNA, proteins come in this form of dimension. The idea of manipulation of the matter at nano level gives the concept of nanotechnology [1]. Nanomaterials produced from nanotechnology have unique properties and characteristics, such as, altered electrical conductivity, melting point, magnetic permeability, fluorescence, and high chemical reactivity [2]. Adhesive quality of paint is improved by adding nanoparticles in it, while nanoscale titanium dioxide in glass prevents streaks and thereafter it needs no washing forever. Carbon nanotubes are very strong and strengthen tennis rackets and other related sports equipments. Nano-coated fabrics are free from getting stain or dust. Numerous improved cosmetics are engineered using nanotechnology. Nanoscale silver is antibacterial and is used in washing clothes and utensils, machine drums, kitchen tableware, etc. More than sixty nations have started national nanotechnology programs worldwide [3]. Both government and corporate sector at global level are largely investing to develop nanotechnologies in different fields. This recent revolution of nanotechnology in spite of benefiting mankind has imposed certain serious concerns related to the toxicity of nanomaterials [4]. They have increased surface area and on entering a living system, they increase their reactivity resulting in adverse biological effects [5]. Nanotoxicology undergoes quantitative assessment of the intensity and frequency of the nanotoxic effects. There is a mixed opinion regarding advantage and disadvantages of nano materials. However, as nano materials have strange and new physico-chemical properties, they behave differently when unintentionally enter in environment and life forms. New features of nano materials could be alarming and disturbing if they are in wrong place and have properties, like electrical conductivity, stability, reactivity, etc. For instance, carbon in the form of graphite is soft and malleable, although at a nano-sized scale. If it is spread with increased surface area and is shaped in the form of a nanocarbon tube, it becomes even tougher than steel. Similarly, one gram of catalyst having a diameter of 10 nm is about hundred times more reactive than a similar particle with a diameter of 1 μm. Nanotoxicological effects of certain nanomaterials have catered much attention and had become a centre of serious concern nowadays [6-8]. Hence, we reviewed literature pertaining to nano-materials and nanotoxicology with an objective to present an overview of the types of nanomaterials, their deleterious effects on the environment and the

human systems, factors affecting nanotoxicology and their environmental concerns.

CERTAIN NANO MATERIALS/ PARTICLES AND THEIR TOXICITY

(i) Carbon Nanotubes (CNT) are hollow nanotubes created by rolling graphene sheets. These are nowadays widely used in electronic and semiconductor industries. They contain a seamless graphite cylinder having single or numerous walls [9]. Certain nanoparticles may be compressed, but nanotubes such as nanoropes, which are special forms of nanotubes, can rotate around each other and make larger fibres. These can cause severe adverse effects on human health as they could be highly toxic to mammalian cells. Certain CNT can twist in the form of a rope and can cause severe adverse effects to vital organs, especially lungs. They may give a series of multiple lesions in lung tissues in a time and dose dependent manner. For instance, pulmonary or lung toxicity will occur at high doses of single or multiple-wall carbons, however even low doses may cause inflammation in lungs [10]. This suggests that potential occupational hazard for the users who are handling them. Even the raw materials and polymers used in the synthesis of these nanotubes may be hazardous to humans. Furthermore, certain carbon nanotubes may have fibrogenic effects, such as, big granulomas, especially tested positive in rodents.

(ii) Bucky Ball or Fullerene has revolved around a 60 C- atom spherical closed cage. Korto discovered it in 1985 and stated that it has 20 dimensions in various situations and is composed of apexes and twenty faces [11]. Its molecular makeup has been modified to suit different applications and surface chemistry has been altered to provide versatility to its structure. It was first used in making optics and conductors, and later on used to produce various creams and sanitary products. It also entraps other small molecules in its cage, which can provide different types of utilities in nanomedicine and other related applications. They can be used in drug delivery system. Their physicochemical properties and biological mechanisms can create various kinds of nanotoxicities like genotoxic, oxidative and cytotoxic responses at cellular level [12]. Their anti-oxidative property can inhibit lipid oxidation and radicalization and super oxidation [13]. They even influence the cellular membrane due to the induced peroxyl free radicals.

(iii) Metal Nanoparticles: Certain nanoparticles are made of noble and some transition metals, e.g. titanium, gold, silver, copper, aluminium, and iron, which are useful in pharmaceutical and medical industries. However, these metallic nanoparticles impose serious health effects. Aluminium oxide nanoparticles in antiperspirant and deodorants have severe toxic effects, including Alzheimer's disease. Copper nanoparticles in lipsticks are used to reduce ill-effects of lipstick ingestion but they themselves enter in multiple organs and induce hepato and nephrotoxicity. Excess of copper nanoparticles may cause copper ion overload leading to metabolic alkalosis. Gold nanoparticles induce relentless sickness response in mice and also induce weight less, loss of appetite and change of fur colour. Iron nanoparticles are used in biomedical devices, such as biomimetic systems due to their magnetism. However, their intracellular delivery may induce deleterious effects on structure and function of the cell. Silver nanoparticles are effective in burn injury treatment. However, these are highly toxic and may cause inflammation. Titanium nanoparticles, especially titanium dioxide (TiO_2), may cause cytotoxicity and erythrocytic toxicity.

NANOTOXICITY IN THE LIVING SYSTEM

In the living forms, these nanomaterials may enter through various portals and cause toxicity. Some of the toxicological relevant portals of entry of nanotoxicants into the life forms and their related toxicity are mentioned below.

(i) Respiratory System Nanotoxicity: It is more likely that small sized metal particles may cause more inflammation than the larger ones [14]. Cohignac et al. [15] in 2014 reviewed in detailed about the possible toxicity of nanomaterials to the respiratory system and their role of autophagy. Respiratory system may be divided into naso-branchial, trachea-branchial and alveolar regions. Although these regions have effective defense mechanism to protect foreign infections, the nano-materials pass through the defense systems with lots of ease. On inhalation, they can easily be deposited, cleared and translocated. Because of the diffusion motion, the inhaled nano-particles in air may get deposited through the respiratory tract, including, trachea, bronchi and alveoli [16]. These are cleared from respiratory tracts by both chemical and physical methods. The chemical clearance is mainly done for the biosoluble nano-materials in intracellular and extracellular fluids. From there, these nano-materials are absorbed and diffused in other sub-cellular structures or binding to proteins, which later on be deposited into blood or lymphatic circulation. Only, insoluble or partially soluble nanomaterials are cleared by physical translocation. The efficiency of this kind of clearance is largely dependent on the size of nanomaterial and on the site of deposition. Inhaled particulate matter causes pulmonary toxicity, like increased mortality or undesirable effects, such as, emphysema, asthma and chronic bronchitis. If inhaled particles have nanoparticles then the conditions will be worsened. Furthermore, the weaker capacity of alveolar macrophages to recognize these particles may cause pulmonary inflammation and fibrosis. For instance, intratracheally instilled ferric oxide nanoparticles can cause follicular hyperplasia, protein effusion, and alveolar lipoproteinosis in lung. Inhaled SiO_2 nano-particles may also cause intense pulmonary

inflammation in the older rats. Long and stiff fibres of nanomaterials are persistent in the respiratory tracts and cannot be removed easily through the action of mucociliary clearance mechanism. Especially, the fibres having length > 20 μm and diameters of < 3 μm having biopersistent properties, like asbestos fibres, which cannot be phagocytized and cleared by the macrophages and are likely to cause inflammation, fibrosis, and even cancer in the lung. Similarly, single-walled carbon nanotube (SWNT) and multi-walled carbon nanotube (MWNT) are used increasingly in different materials science applications. The intratracheal instillation of these nanotubes may cause pulmonary granuloma formation and interstitial inflammation. Injection of carbon nanotubes in the abdominal cavities of mice showed tissue modifications similar to those caused by asbestos.

(ii) Gastrointestinal Nanotoxicity: Modern food industries adopt nanotechnology to develop new packaging concepts and new food additives. Nanopreparations of titanium oxide or silica are approved food additives used as brighteners or flow-regulating agents. Packaging films are engineered with silicate finishes to prevent oxidation, or with silver nanoparticles to retain the freshness of food. Such nano-particles enter the gastrointestinal (GI) tract by ingesting food, water, drugs, etc. which makes G.I. tract as a nano-material reservoir. Copper nano-toxicity may induce symptoms, like diarrhoea, nausea, vomiting and appetite loss apart from negatively affecting kidney, liver and spleen. Zinc oxide (ZnO) nanoparticles may damage vital organs due to inflammation of gastric lamina propria, serosa or submucal layers of stomach, fatty degeneration of hepatocytes and cardio-vascular cells, and enlargement of splenic corpuscles. Similar high doses of TiO_2 and SiO_2 can cause acute cytotoxicity and genotoxicity.

(iii) Neuro Nanotoxicity: Certain nanoparticles can cross the blood brain barrier and are largely responsible for brain toxicity [17]. The inhaled ultrafine particles get deposited into the olfactory mucosa and later on translocated to the CNS. Carbon nanotubes and manganese oxide nanoparticles reach CNS via olfactory neuronal pathway. Ultrafine carbon black nanoparticles may cause inflammation in the brain olfactory bulb. This inflammation depends highly on the size of nanoparticles, as the smaller ones are more toxic than the bigger ones. Similarly, TiO_2 nanoparticles adversely affect the olfactory bulb and hippocampus after entering into the brain.

(iv) Cutaneous Nanotoxicity: Some cosmetics, especially sunscreens are engineered for the protection of skin against solar and UV radiations. This is achieved through addition of coated TiO_2 or ZnO nanoparticles. Other nanomaterials, such as carbon nanotubes, silver nanoparticles, quantum dots, nor lipophilic C60 fullerenes or aluminium are also capable of penetrating the corneal layer of the stratum corneum [18]. In fact, few evidences support that some nanoparticles may directly enter into living body through epidermal or dermal exposure [19]. Meagre studies indicate that lipophilic or instable (soluble) particles are more likely to penetrate the stressed skin or skin that is affected by solvents is more permeable [20-21]. TiO_2 nanoparticles enter human body when applied as an oil-in-water emulsion. The penetration inside the skin was even more profound if the skin has hairs on it, which also suggested that these nanoparticles may enter through hair follicles or pores. These nanoparticles may cause dermaetoxicity after entering a living body. Beryllium nanoparticles can easily penetrate the stratum corneum and develop hapten specific cell mediated immune responses. High doses of TiO_2 (sized 3–10 nm) nanoparticles significantly reduce the cell function. Both SWNT and MWNT after entering in a cell can trigger cytotoxic reactions, for instance oxidative stress in keratinocytes, induce production of inflammatory factors, or even lead to cell death (apoptosis or necrosis). Very small TiO_2 or ZnO nanoparticles may cause photocatalytic effects and production of DNA-damaging free radicals in the epidermal layers of skin. Single-walled carbon nanotube (SWNT) also shows a dose response reduction in the cell viability and oxidative stress biomarkers.

(v) Cardio-vascular Nanotoxicity: Ultrafine particles in air may cause cardio-vascular diseases and the single intrapharyngeal instillation of SWNT may activate heme oxygenase-1, which is a marker of oxidative insults in heart and lung [22]. In addition, prolonged exposure to carbon nanotubes can cause pathophysiological changes related to cardio-vascular diseases, like mitochondrial DNA damage, elevation of mitochondrial glutathione and protein carbonyl levels. The SiO_2 nanoparticles can cause severe myocardial ischemia, increase in blood viscosity and fibrinogen concentrations [23]. Furthermore, ageing persons are more vulnerable to this toxicity than the younger ones.

FACTORS AFFECTING NANOTOXICOLOGY

(i) Size: The size of a nanomaterial is crucial in inducing toxicity, as decrease in nanoparticle size increases the incidence of pulmonary toxicity. A decrease in size also increases the surface area of nanomaterials, which enables them to attach more number of molecules to them and thereby increasing their reactivity and making them toxic. These can easily be absorbed by the mucous and are translocated to the blood stream and then spread through the tissue. A recent study has revealed that 33% of 50 nm, 26% of 100 nm, and 10% of 500 nm particles were discovered in mucosal and lymphatic tissues of the intestine [24]. Bigger sized nanoparticles (300 nm) accumulate more in the lymphatic tissues than the smaller ones (100 nm), as latter can be readily absorbed by the intestinal cells

but not the former ones. Particles larger than 400nm cannot be absorbed by the intestinal cells and only those smaller than 500 nm can enter in the circulatory system.

(ii) Surface Area and Chemistry of the nanomaterials is directly related to their increased reactivity and toxicity. Increased surface area can attach more molecules present on the surface, which provides greater tendency to conjugate and energy sustainability. Nanoparticles that are small but have greater surface area are highly toxic, e.g. carbon nanotubes. Smaller nanoparticles have greater pathological and destructive power on the lungs than the larger ones [25-26]. Subtle modification in surface chemistry of quartz and silica affects their cytotoxicity, inflammogenicity, and fibrogenicity. The specific cytotoxicity of silica has a strong correlation with the appearance of surface radicals and reactive oxygen species (ROS), which is mainly responsible for the development of fibrosis and lung cancer. It is likely that the reactive groups on nanoparticles influence their interaction with the lungs. In some instances, it may be possible to predict the reactivity of the nanoparticle surface. The degree of hydrophobicity and hydrophilicity of a surface is the key factor in determining the toxicity. Hence, it appears that the surface area of nanoparticles is important in their absorption in intestinal mucosa. Nanoparticles produced by hydrophobic polymers are absorbed more than nanoparticles produced by hydrophilic polymers.

(iii) Chemical components: Chemical components of the nanoparticle surface have significant effects as they can react with metals. Nanoparticles also affect iron and promote the induction of ROS in a free cell system. Surface modification of nanoparticles can reduce toxicity. Studies on nanotoxicity have determined that the iron oxide nanoparticles toxicity decrease by coating them with pullulan, which is a naturally occurring fungal polysaccharide [27-28].

(iv) Dosage: Nanotoxicity could be greatly elevated with increase in dosage of nanoparticles in the biological system. High dose of small or big nanoparticles could be harmful to the health.

(v) Free radical production: Pathogenic nanoparticles can make free radicals that cause oxidative stress leading to inflammation, cell destruction, and genotoxicity.

ENVIRONMENTAL CONCERNS

Malik et al. [29] in 2014 expressed serious concerns about the biomedical nanotoxicology on the environment. Apart from having complicated interactions with soil and severe toxicants, most of the nanomaterials after turning into a waste become an environmental threat as they are non-biodegradable. This is largely due to the complicated chemical structure of these materials. However, fullerenes can be decomposed by certain wood decaying fungi [30]. Certain nanomaterials of transition metals have good catalytic properties and thus could be used for the wastewater treatment. However, in the treatment process they accumulate in the form of lumps and induce toxicity to the associated microorganisms, including bacteria and fungi [31]. Nanomaterials have the tendency to persist in nature, as they possess inimitable physicochemical properties. They can bio-accumulate and magnify in food chains [32]. Due to their small size, they lack tendency of settling or becoming inert and thus are free from gravitational control. Nanomaterials impose severe toxicity in general to the aquatic living forms. However, the threat can be reduced by covering them with natural organic matter [33]. Nanomaterials after entering in water bodies, especially river and sea get significantly altered in their composition and exhibit erratic behavior, which eventually threatens and imposes risks to biodiversity in the water apart from degrading the aquatic habitat. Invertebrates are the most susceptible to aquatic nanotoxicology, as they get most exposure environmental contaminants [34-35]. Silver nanoparticles may several deleterious effects to the aquatic fauna by inducing edema production, abnormalities in the spine, fins, heart, and eyes [36].

Conclusion

The worth of Nanotechnology can never be ignored; however, scrutiny related to their harmful effects should be done thoroughly before preparing them for the environment and mankind. Due to the very recent advent of nanoparticles, the toxicity related to them is novel and largely unexplored, which represents new challenges. However, bulk creation of these nanomaterials is imposing the threats of exposure to the environment and to the mankind. This is seemingly critical as we are still naive in the knowledge related to their toxicity. The implications of nanotoxicology seem to be more critical in the future from what we are surmising today.

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