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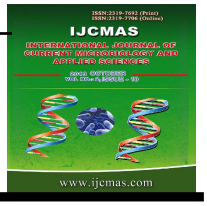

Review Article

Nanoparticles and its Toxic Effects: A Review

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A B S T R A C T

Nanotechnology research is producing remarkable advances for detecting, treating, and preventing health problems. However, while nanoparticles can lead to breakthrough applications, they may also cause hazardous side effects. It has been shown that nanomaterials can enter the human body through several ports. Nanoparticles such as TiO_2, copper nanoparticles, silver nanoparticles etc are found to exert deleterious effects on human beings, acquatic organisms as well as plant life. Health effects of nanoparticles are attracting considerable and increasing concern of the public and government worldwide. So far, most of the nanotoxicity research focused on respiratory tract exposures for assessing the health effects of nanoparticles. Other exposure routes, e.g., gastrointestinal tract also need to be considered as potential portals of entry. Most nano-sized spherical solid materials are found to enter the lungs easily via inhalation and reach the alveoli. In general the intestinal uptake of particles is better understood and studied in more detail than pulmonary and skin uptake. However, the body distribution of particles is strongly dependent on their surface characteristics.

Keywords

Nanoparticles;
Toxic effects;
Vital organ;
Nanotoxicity;
Nanomaterials.

Introduction

Nanomaterials are defined by the U.S. National Nanotechnology Initiative as materials that have at least one dimension in the 1 to 100 nm range. Due to their unique physical and chemical characteristics, nanoparticles have been interact with objective cells in certain ways to induce and maximize desired physiological responses (Silva, 2008). There are important applications of nanoscience in biology and biotechnology, and nanotechnology offers new tools to

biologists (Whitesides, 2003). The increasing and widespread application of nanomaterials in the fields of medicine and high technology is projected to result in a $1.5 trillion industry by 2015 (Nel *et al.,* 2006). A recent trend in nanotechnology has been to investigate the interactions of nanomaterials with biological systems, known as nano-bio interactions. These nanoparticles are exposed to plants, animals, cells, or tissues, and a biological outcome, such as toxicity, is measured. While benefits of nanotechnology are widely publicized, the discussion of the potential effects of their widespread use in the consumer and industrial products are just beginning to emerge (Luther 2004). Accidental or involuntary contact during production or use is most likely to happen via the lungs from where a rapid translocation through the blood stream is possible to other vital organs (Nemmar *et al.,* 2001). On the cellular level an ability to act as a gene vector has been demonstrated for nanoparticles. Carbon black nanoparticles have been implicated in interfering with cell signaling Brown *et al.,* (2004). The development of nanotechnologies has introduced important amounts of manufactured nanoparticles into the environment, including those in the ambient air and water.

Importance of nanotoxicology

Nanoparticles have attracted a lot of attention because of our increasing ability to synthesize and manipulate such materials. The forecasted huge increase in the manufacture and use of nanoparticles makes it likely that increasing human and environmental exposure to nanoparticles will occur. As a result nanoparticles are beginning to come under scrutiny and the discussion about the potential adverse effects of nanoparticles has increased steadily in recent years; in fact it has become a top priority in governments, the private sector and the public all over the world (Roco, 2005; Helland *et al.,* 2006; Siegrist *et al.,* 2007).

A selection of findings on nanoparticle toxicity on a host of living systems can be illustrated to elucidate these points, and also advocate the need to understand these interactions in greater detail. For example, some studies on rats have shown that 15 per cent of the sample population died within 24 h due to blockage of the airways as a result of carbon nanotubes being injected into their lungs (Lecoanet *et al.,*2004; Warheit *et al.,*2004). More of a concern is the effect observed from micro- and/or nanoscaled debris of artificial hip replacements as there is a growing demand for such biomaterials (e.g. implantable devices). These loose particulates arise as a result of friction, and travel into the blood stream and eventually lead to the formation of a thrombus (De Jong and Borm 2008). There is also evidence to suggest migration of particles into organs (liver and the spleen) from similar prostheses (Gatti *et al.,* 2004). Moving away from implantable devices, there is a risk posed from inhalation. Research has demonstrated that radio-labelled nanoparticles can reach the blood stream within 60 s via inhalation; and the liver within 60 min (Chunfu *et al.,*2004).

Toxic effects of nanoparticles

Health effects of nanoparticles are attracting considerable and increasing concern of the public and government worldwide. So far, most of the nanotoxicity research focused on respiratory tract exposures for assessing the health effects of nanoparticles. Other

exposure routes, e.g., gastrointestinal tract also need to be considered as potential portals of entry. For instance, nanoparticles cleared from the respiratory tract via the mucociliary escalator can subsequently be ingested into the gastrointestinal tract; nanomaterials can be ingested directly via water, food, cosmetics, drugs, drug delivery devices, etc. (Peter *et al.*, 2004; Oberd¨orster *et al.*, 2005). Uptake of particles of different size via the gastrointestinal tract can also lead to different toxicological effects (Jani *et al.*,1994).

Effects on Lungs

It has been reported recently that nanotubes show a sign of toxicity, confirmed in two independent publications by (Warheit *et al.*, 2004 and Lam *et al.*, 2003), which demonstrated the pulmonary effects of single walled cabon nanotubes in vivo after intratracheal instillation, in both rats and mice. Both groups reported granuloma formation, and some interstitial inflammation and the results indicated that if carbon nanotubes reach the lungs, they are much more toxic than carbon black and can be more toxic than quartz.

A sub-chronic 3 months inhalation exposure of rats to ultrafine (~20 nm) and fine (~200 nm) titanium dioxide (TiO2) particles demonstrated that the ultrafine particles cleared significantly slower, showed more translocation to interstitial sites and to regional lymph nodes when compared to the fine TiO2 particles Oberdorster *et al.*, (1994). Comparing the health effects of chronically inhaled TiO2 particles with distinctly different sizes, it is remarkable that the low exposure (10 mg/m^3) study Heinrich *et al.*, (1989) resulted in a greater lung tumour incidence than the high exposure (250 mg/m^3) study (Lee *et al.*, 1986).

Effects on Intestines

The intestinal tract is a more complex barrier – exchange side, it is the most important portal for macromolecules to enter the body. The kinetics of particle translocation in the intestine depends on diffusion and accessibility through mucus, initial contact with enterocyte or M-cell, cellular trafficking, and post-translocation events. Charged particles, such as carboxylated polystyrene nanoparticles (Jani *et al.*, 1989) or those composed of positively charged polymers exhibit poor oral bioavailability through electrostatic repulsion and mucus entrapment. In a double-blind randomised study, it has been shown that a particle low diet (low in calcium and exogenous microparticles) alleviates the symptoms of Crohn's disease (Lomer *et al.*, 2002). Diseases other than of gut origin also have marked effects on the ability of GIT to translocate particles. The absorption of 2-micron polystyrene particles from the PP of rats with experimentally induced diabetes is increased up to 100-fold (10% of the administered dose) compared to normal rats (McMinn *et al.*, 1996). However, the diabetic rat displayed a 30% decrease in the systemic distribution of the particles. One possible explanation for this discrepancy is the increased density of the basal lamina underlying the GI mucosa of diabetic rats that may impede particle translocation into deeper villous regions.

Effects on Skin

It has been reported by Lademann *et al.*, (1982) that micrometer-sized particles of TiO2 get through the human stratum corneum and even into some hair follicles – including their deeper parts. Emzaloid™ particles, a type of submicron emulsion particle such as liposomes and nonionic surfactant vesicles (niosomes), with a

diameter of 50 nm to 1 micron, were detected in the epidermis in association with the cell membranes after application to human skin (Verma *et al.,* 2003). The authors suggested that single molecules, which make up the particles, may penetrate the intercellular spaces and, at certain regions in the stratum corneum, are able to accumulate and reform into micro spheres.

Body distribution and systemic effects of nanoparticles

The body distribution of particles is strongly dependent on their surface characteristics. For example, coating poly (methyl methacrylate) nanoparticles with different types and concentrations of surfactants significantly changes their body distribution (Araujo *et al.,* 1999). Coating these nanoparticles with ≥ 0.1 % poloxamine 908 reduces their liver concentration significantly (from 75 to 13 % of total amount of particles administrated) 30 min after intravenous injection. Another surfactant, polysorbate 80, was effective above 0.5%.

Nanoparticles and Thrombosis

Epidemiological studies have reported a close association between particulate air pollution and cardiovascular adverse effects such as myocardial infarction (Peters *et al.,* 2001). Nemmar *et al.,* (2002) studied the possible effects of particles on haemostasis, focusing on thrombus formation as a relevant endpoint. Polystyrene particles of 60 nm diameter (surface modifications: neutral, negative or positive charged) have a direct effect on haemostasis by the intravenous injection. Positively charged amine-particles led to a marked increase in prothrombotic tendency, resulting from platelet activation. A similar effect could be obtained after the intratracheal administration of these positively charged polystyrene particles, which also caused lung inflammation (Nemmar *et al.,* 2003).

Nanoparticles and Central Nervous System

In vitro systems to study the effects of particles on the nervous system have included neuron and nanoparticle cultures to determine the effects on neuronal functions (Oberdorster *et al.,*2005). Research has been carried out using metal nanoparticles such as Ag, Cu and Mn on P12 brain cells to investigate potential neurotoxicity (Wang *et al.,* 2009). Small-sized particles have better mobility and it is expected that the transportation of nanoparticles across the BBB is possible either by passive diffusion or by carrier-mediated endocytosis (Hoet *et al.,* 2004). In addition, nanoparticles may be taken up directly into the brain by trans-synaptic transport (Oberdorster, 2004). For example, Ag nanoparticles can enter via the BBB (Panyala *et al.,* 2008) and accumulate in different regions of the brain (Rungby and Danscher, 1983), and this may be beneficial for drug delivery, but may also pose a risk to the patient (Sarin *et al.,* 2008).

One of the promising alleys of nanotechnology is organor cell- specific drug delivery mediated by nanoparticles (Alayudtin *et al.,* 2001).

Nanoparticles and Vital organs

The copper-fluoropolymer nano-composite is employed as bioactive coatings that are capable of inhibiting the growth of target microorganisms such as *Saccharomyces cerevisiae, Escherichia*

coli, *Staphylococcus aureus*, and *Listeria* (Cioffi *et al.*, 2005). Accordingly, nano-copper particles, similar to any of other nanomaterials, are likely to enter the environment and human body via different paths such as effluent, spillage during shipping and handling, consumer products and disposal, etc. In human body, copper is maintained in homeostasis (Jesse and Mary, 2004). Specifically, for nano-copper particles, compared with the micro-copper, their primary alteration in biochemical property is the higher reactivity originated from a larger specific surface area. Chen *et al.*, (2006) studied the effect of copper nanoparticles in vivo and found that spleen is one of the target organs for nanoscale copper particles.

Nanoparticles represent a new challenge to those involved with toxicology and biocompatibility since evidence suggests that they behave differently from particles of larger size. Relatively little is known of the biological consequences of exposure to nanoparticles. The increasing availability of sophisticated methods of evaluating biological phenomena, including molecular biology especially as it is applied in immunology and genetics, present opportunities for unfolding knowledge in this exciting and important area. A critical size might exist beyond which the movement of the nanoparticles in parts of the body is restricted. The pharmaco-kinetic behaviour of different types of nanoparticles requires detailed investigation and a database of health risks associated with different nanoparticles (e.g. target organs, tissue or cells) should be created. Whereas it is already obvious that particle size plays an important role with respect to toxicity, much less is known how size affects the behavior and reactivity of NP. It is also important to realize that many engineered NP are functionalized and this significantly affects their behavior. Changes in functionalization by environmental factors or the coating of the surface by natural compounds is clearly an important process in the environment which has, however, been studied only marginally so far. Nanotoxicity research can be applied to a number of applications, such as determining composition levels in coatings for medical devices, medical-grade sheet moulding compounds for hospital equipment, aircraft filter fabrics, printing-coat films/inks and compositions for high-performance aviation gas turbine lubricants. Exposure scenarios with functionalized engineered nanoparticles that are primarily used in technical applications rather than pristine engineered nanoparticles should be investigated and could be relevant for assessing impacts on the environment.

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