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Review Article

Health risks of Engineered Nanoparticles

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A B S T R A C T

Engineered nanoparticles (ENPs) thought to have the greatest promise for commercial applications. The current advances in nanotechnology present new challenges that manufactured ENPs become dangerous pollutants because of their anticipated widespread production and use could lead to new environmental problems. As we know that nanoparticulate matters are a collection of particles with at least one dimension smaller than 1 micron yet larger than atoms and molecules, in addition to the nanometer size, the production of nanomaterials involves chemicals, elements and combination of elements, which could either directly impact living cells or undergo transformations that would produce secondary toxic derivatives. Although there exists much enthusiasm for the potential societal benefits of engineered nanomaterials, concerns have also been raised about whether our knowledge of possible health risks of these engineered nanomaterials is keeping pace with products going to market. Infact the literature on nanoscience is quite abundant with studies dealing with both manufacturing and use of nanomaterials, but the potential impacts of this new technology on both the environment and living organisms have received less attention. Therefore, besides the abundant research on creating new means of detecting pollutants, cleaning polluted waste streams, recovering materials before they become wastes and expanding the available resources, there is presently a growing need for data assessment of the potential impacts of this new technology on the environment and living organisms. In this review, we try to access the toxicity of ENPs and were found that these materials enter in the body via dermal, gastrointestinal or inhalation routes and two another routes become important when nanotechnology-based medical devices and drugs releases in the body. To determine the risk of ENPs information is needed at each step of the processes. Exposure to some ENPs is associated to the occurrence of autoimmune diseases; diseases associated with inhaled nanoparticles are asthma, bronchitis, emphysema, lung cancer, and neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases. Some studies have been done, but more are needed to make blue print regarding the safety measures for an individual and workers from ENPs.

K e y w o r d s

Engineered nanoparticles, health risks, dermal, gastrointestinal and inhalation.

Introduction

Nanotechnology is an enabling technology that has the potential to bring benefits to multiple areas of research and application and to enrich our lives in many ways. Rapidly increasing investment from governments and businesses around the

world shows that it is a promising technology for future. Nanotechnology is defined by the National Nanotechnology Initiative as "the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomenon enable novel applications" (NNI, 2009) In theory, these materials can be engineered from nearly any chemical substance; semiconductor nanocrystals, organic dendrimers, carbon nanotubes, carbon fullerenes, nanowires, quantum dots, super paramagnetic nanoparticles and small molecules (polymers, dendrimers, and micelles) are a few of the many examples. Nanoscale materials are a broadly defined set of substances that have at least one critical dimension i.e. one billionth of a meter or 10^{-9} m and thus possess unique optical, magnetic, or electrical properties. Unique properties of engineered nanomaterials make them an appealing option for commercial applications. Nanomaterials have a much larger specific surface or interface area, i.e. a larger area to mass ratio, than coarser materials. Furthermore, there are intrinsic nanoscale properties that result from the confinement of atoms and electrons within boundaries of a few nanometers. These effects are dominant at sizes below a few tens of nanometers and they can change fundamental physical material characteristics such as the optical, electrical and magnetic properties of the nanomaterial. As the particle size shrinks, the proportion of molecules or atoms on the surface increases, leaving lesser proportions located within the inner volume of nanomaterials and enhancing and altering surface reactivity, modulated by the surface curvature and structure. As particle size decreases towards the molecular level, their behaviour is more like that of a vapour (ICRP, 1994). Also, the kinetic behaviour of nanoparticles follows basic laws of gaseous diffusion. It can be calculated that a 5 nm particle will undergo 8.2 collisions per nanosecond or 8.2×10^9 collisions per second (Preining, 1998). As well as inter-particle interactions, some collisions will occur between the nanoparticles and other airborne molecules, such as water or pollutants, given the high collision rate, these gas molecules will spend a relatively long time, i.e. longer than the time between collisions, adsorbed on the surface. This means that there is a significant likelihood of a reaction between the adsorbed molecule and the nanoparticle. That's why such great interest has been aroused in this particular field is that a substance can have completely different properties and combinations of properties than the same substance at larger scale. The principal reasons for the changed properties are an increased surface area per unit of mass when size decreases, and the fact that the quantum effects play a greater role the smaller a particle becomes. Another view about their altered behaviour is the principals of quantum mechanics, as it states that the energy levels of an atom can assume certain discrete values and when the atoms change energy state energy in a particular quantity is released or absorbed (known as quanta). Quantum mechanics also states that matter at the very smallest dimensions can behave as waves (particle-wave dualism) and due to this relatively few atoms are combined into a particle that is smaller than approximately 10 nm, the electrical, optical, chemical or magnetic properties may differ markedly from those of equivalent larger particles (SCA Report, 2008). Influence of "quantum mechanics" at the nanoscale and also the much greater relative surface area that nanomaterials have compared with larger particles, because of this

nanomaterials have increased chemical reactivity, making them attractive option (Nel et al, 2006).

Currently, relevant industrial sectors include those associated with, information technologies, imaging, electronics, energy generation and storage, material sciences, bio-physico-chemical processing and catalysis, food and feed refinement, environmental remediation, security, transport and space, diagnostic and therapeutic applications in medicine (Hu et al, 1999; Smalley, 2001 and West et al, 2003). Carbon nanotubes, nanowires and quantum dots include a few of the nanomaterials that have recently received a great deal of attention due to their superior electronic, optical, mechanical, chemical and even biological properties (Dresselhaus and Dresselhaus, 2001., Williams, 2002). Other engineered nanomaterials that have been investigated for their use in biology and medicine include super paramagnetic, polymeric, colloidal gold, metallic and composite nanoparticles as well as semiconductor nanocrystals, nanoshells, and nanoeggs (De Villiers and Lvov, 2007; Rieger et al, 2007). There are now more than 700 products that contain nanomaterials on the global market (Shand and Wetter, 2006). These include sunscreens and cosmetics, odour and wrinkle-repellent clothing, long-lasting paints, electronic and sports equipment, fuel catalysts, building equipment, medicines, and food products. Nanoparticles come from many different sources; they exist naturally in the environment (forest fires, viruses, and volcanoes) are produced as byproducts of industrial or combustion processes (engines, power plants, and incinerators) and engineered corresponds also to 'synthetic', 'man-made' or 'manufactured' or intentionally made for various industrial or consumer product applications. Ultra fine particulate matter is a well-known example of nanoscale particles found in the environment and produced unintentionally, produced during combustion, or in natural processes. On a sunny day new formation of organic nanoparticles takes place through photo-oxidation of organic substances that are emitted from forests. Other natural processes that lead to the new formation of nanoparticles are volcanic eruptions. Minerals also occur naturally at nanoscale, formed both through breakdown processes (weathering) and through building-up (e.g. redox chemical) processes. Macromolecular breakdown products such as humus substances are present in very large quantities on earth and also occur at nanoscale. They also interact with nanominerals. In addition, all living organisms are made up of biological macromolecules of which, like many viruses, can be regarded as a natural form of advanced nanoparticles (SCA Report, 2008).

As a transformative technology, nanotechnology has the potential to stimulate scientific innovation while greatly benefiting society. However, the enthusiasm with which the scientific and technical communities are embracing the technology is being tempered by concerns over possible downsides, including risks to human health. (Maynard, 2006). The unique and diverse physicochemical properties of nanoscale materials suggest that toxicological properties may differ from materials of similar composition but different size. Exposure to ENPs by using products that contain nanomaterials on skin, for example cosmetics, sunscreens, clothing, or through ingestion of products that contain nano-ingredients, like foods, beverages, nutritional supplements or

lipstick. Occupational exposure of ENPs to workers may be much higher during the production, manufacturing, packaging or transport of products and as the industry expands the exposure to nanomaterials is likely to increase. Waste containing nanomaterials will be released into the environment from households and industry, and products containing nanomaterials will disposed of in landfill. Nanomaterials may also be released into the environment intentionally, for example for agriculture, military are on large scale. The potential nanoparticles represent an incredible range of materials with respect to chemical and molecular form (e.g., metal alloy versus oxide, carbon particle versus nanotube), surface area (e.g., single versus agglomerate), solubility (e.g., manganese oxide versus soluble salts), charge, and bio persistence. Many of these properties appear to have some influence on biological effects. Hundreds of tons of nanoparticles are released through emissions into the environment annually, little is known of their interactions with biological systems. Exposure to nanomaterials can occur via dermal, gastrointestinal, or inhalation routes. While exposure will depend on a number of factors, such as how well nanomaterials are contained during manufacture, how widespread their use becomes, and if they are biodegradable or recoverable, the extent of absorption into the biological system depends on the chemical and physical properties of the nanomaterial. Once exposure occurs, the biological fate of nanomaterials depends on the balance of four processes: absorption, distribution, metabolism, and excretion. Biocompatibility and toxicity of engineered nanomaterials have only recently received attention from the scientific community. To appropriately evaluate the potential health effects of any airborne material, including nanoparticles, it is necessary to understand the (a) conditions under which the materials will become aerosolized, (b) characteristics which most influence particle uptake, distribution, and retention in the body and (c) dose metrics that best correlate with observed health effects from particle exposure. To address the potential influence of nanomaterials on the living organisms, assessment of their physiochemical properties will be needed to determine their fate, mobility, degradation, persistence, and bioavailability. The biological effects and the detection of nanomaterials in nature and in any environmentally exposed species, including humans, are also essential elements to consider. Nanomaterial risk assessment must evaluate the following: the toxicity of particular nanomaterials, the extent of their dispersion in the environment, environmental fate and transport, tranformations and modifications in the environment that may affect bioavailability, absorption, and toxicity upon exposure to biological systems, biological and ecological relevance of exposure, acute versus low level chronic exposure and the ability to determine and measure exposure to the environment and to biological systems. In humans, the extent of exposure in several settings will need to be considered. The include exposure from occupational, commercial, and environmental sources. For safety assessment it is important to take into account, as for any other chemical, potentially important other properties that may include surface charge, penetration ability, adhesion, solubility, immunogenicity, aggregation, shape, hardness, degradability, biopersistence, reactivity and other specific toxicities. Complexity of surface, multifunctionality

of nanomaterials and covalent or adsorbed surface coatings all play a role in the determination of risk (EASAC-JRC Report, 2011).

Engineered Nanoparticles (ENPS) and their associated risks

1. Carbon Nanotubes (CNTS)

Carbon nanotubes are tubes of rolled graphene sheets made of one atom thick carbons arranged in a honeycomb crystal lattice. CNTs are typically long and thin, may either consist of a single wall (SWCNT) or be multi-walled (MWCNT). Their unusual length-to-diameter ratio gives them unusual physio-chemical properties including high tensile strength and hardness (harder than diamonds). They are also flexible, lightweight, heat-resistant and have high electrical conductivity. Their unusual hollow one nanometer structure makes them useful for biological applications, such as drug delivery and medical imaging (Hussain, 2009). Untreated CNTs are biopersistent and lipophilic. Depending on how they are manufactured and treated their behaviours in terms of water solubility, transport behaviour and specific toxicity may change. There are 20 different structural types of single-walled carbon nanotubes alone, with an average length from 5 to 300 nm. Four different processes exist for their manufacture, five for their purification and ten surface coatings are typically applied hence there are up to 50,000 potential combinations of single-walled CNTs and each version may have different chemical, physical, and biological properties that determine their overall hazard (Hansen, 2009). CNTs are used in bicycle components, tennis rackets, golf clubs, display technology, solar cells, computer hardware, electronics, computers, plastics, catalysts, batteries, conductive coatings, supercapacitors, water purification systems, orthopedic implants, aircraft, sporting goods, car parts, concrete, ceramics, solar cells, textiles and these materials show their medical applications including substrates for neuronal cell growth (Hu et al, 2004), supports for liposaccharides to mimic cell membranes (Chen et al, 2004), ion channel blockers (Park et al, 2003) and drug delivery systems (Bianco, 2005).

The coating of a nanoparticle can be of special importance, as uncoated particles may be more or less toxic, have a different charge or have different mobility. Recent research efforts on the health effects of engineered nanoparticles have primarily focused on carbon nanotubes (Muller et al. 2005 and Warheit et al, 2004). The majority of these studies were conducted using in vitro methods, while only a few studies have evaluated health effects in vivo. SWCNTs appear to have greater toxic effects on cultured human fibroblasts than MWCNT active carbon, carbon black, and graphite carbon. Acid treatment of SWCNT (a method of carbon nanotube refinement and removal of residual metal catalysts) produced more toxicity. The addition of carbonyl, carboxyl, or hydroxyl groups on the surface of carbon nanotubes induces cell death in lung tumor cells (Magrez, 2006). CNTs cytotoxicity has been observed for a number of different organs and organ-specific cell lines; including human epidermal cells, human dermal fibroblasts, human embryo kidney cells and human bronchial cells (Shvedova, 2005 and Sayes 2006). Functionalization of SWCNTs with water-soluble functional groups appears to influence cellular-specific uptake and tolerance by primary immune cells; on the

other hand nonfunctionalized carbon nanotubes induce oxidative stress and apoptosis in a variety of cell systems. In vivo studies report inflammation, progressive fibrosis and granulomas in rodents exposed to carbon nanotubes via pharyngeal aspiration. Carbon nanotubes also produce pulmonary function deficits, impairment of bacterial clearance, aortic plaques, and atherosclerotic lesions because of their various formulations (Li, 2005).

A study shows that these effects can be accelerated by feeding animals a vitamin E-deficient diet, and thereby reducing the anti-oxidant capacity of the lungs while enhancing acute inflammation and fibrotic responses (Shvedova et al, 2007). As stated already, there is increasing evidence that some CNTs behave like asbestos fibers. When mice were exposed to 50mg of four different MWCNTs of various chemical composition, length, shape and diameters for up to 7 days, it was found that the exposure "produced length dependent inflammation that were qualitatively and quantitatively similar to the foreign body inflammatory response caused by long asbestos" (Poland et al, 2008). A study showed that mice that already suffer from asthma and inhale MWCNTs have a greater tendency to contract airway fibrosis, indicating that "individuals with pre-existing allergic history may be susceptible to the same effects" (Ryman-Rasmussen et al, 2009). First inhalation study conducted with carbon nanotubes showed changes in immuno suppression markers (e.g., T-cell antibody and proliferative response) and cytokine gene expression in the spleen, whereas no changes in oxidant stress markers were seen in the lungs (Mitchell et al, 2007). The biological significance and human health implications of these findings will need to be further investigated.

2.Carbonfullerenes (BUCKYBALLS)

Buckyball, short for "buckminsterfullerene", which in turn is the name for the C60 molecule. It is the spherical form of fullerenes that was discovered first. The C60 form is approximately 1 nm in diameter and consists of 60 carbon atoms arranged as hexagons and pentagons which together look like a football. It is the spherical form of fullerenes that was discovered first. Several areas of use can be predicted for fullerenes: as carriers for other molecules, to lubricate surfaces, for drug delivery in the body and in electronic and optical equipment. Buckyballs are used as removal of organ metallic compounds, cancer treatment, magnetic resonance imaging, X-ray contrasting agent, anti-viral therapy. Carbon fullerenes currently used in some facecreams and moisturisers. Inorganic nanotubes and inorganic C60-fullerene-like materials based on layers and these possess excellent lubricant properties, high capacity to store hydrogen and lithium are resistant to pressure waves and are catalytically reactive. These properties make them usable in several different areas (Bhatt and Tripathi, 2011).

Carbon fullerenes have been found to cause brain damage in fish (Oberdorster, 2004). A study which attracted considerable attention showed that C60 fullerenes caused measurable oxidative stress (a sign of inflammation) on the brain of juvenile carp at a concentration of 0.5 ppm and results indicated that the route of uptake to the brain may be through nerve cells (Oberdorster, 2004). C60 fullerenes have also been found in laboratory studies to have antimicrobial activity and to

inhibit bacterial growth at low concentrations (0.04 ppm, Fortner et al, 2005). The underlying mechanism of this effect may be that the C60 fullerenes dissolve in the cell membrane and cause oxidative stress (Fang et al, 2007).

It is known that spherical fullerenes cause oxidative stress in biological systems and the bacteria in this study showed signs of defence against oxidative processes in the cell membrane. Studies have found that even low levels of exposure to water soluble fullerenes are toxic to human liver cells, carcinoma cells and skin connective tissue (Sayes, 2004). Plants have also recently been shown to react adversely to fullerenes. Rice plants exposed to carbon fullerenes transmitted nanomaterials to the next generation. Exposure to both carbon fullerenes and carbon nanotubes also delayed the onset of rice flowering by at least one month and reduced the seed set. Given that over half the world's population relies on rice as a staple crop, the food security implications of the above results could potentially be devastating (Lin et al, 2009).

3. Titanium Dioxide (TIO_2)

Titanium dioxide in its bulk form is the most widely used white pigment because of its brightness and high reflectivity. Depending on its crystalline structure, TiO_2 can have significantly different physical and chemical properties. Cosmetics, sunscreens, food packaging, paints, wall coatings, dirt-repellent coatings for windows, car coatings skin care products, solar cells, food colorant, clothing, sporting goods, cement, electronic coatings and as a catalyst for the decomposition of organic contaminants present in water and waste water are where TiO_2 is used. It was commonly used in sunscreens, because it gave the skin a white or milky appearance. In nanoform TiO_2 loses its opaqueness, a property now widely preferred for clear sunscreens. (O'Brien and Cummins, 2008).

Crystalline structure, shape and exposure route as well as surface area and coating of the particles all influence TiO_2 toxicity. Certain forms of nano titanium dioxide are also highly photo catalytic, which means that they are capable of absorbing light and using it to change their rate of chemical reaction and reflect ultraviolet rays but are still transparent to visible light: the resulting sunscreen becomes both more appealing to the consumer and is claimed to be more effective. Ultraviolet light also appears to increase the cytotoxicity of titanium dioxide. Several studies observed increased cell death after UV light exposure, especially if the TiO_2 was the crystalline form that is more re-active to light (Hansen, 2009).These findings are important in determining which form of nano TiO_2 should be used in sunscreen.

Titanium dioxide is a known photo catalyst, even in the absence of UV light and at low doses, in a test tube experiment 20nm nanoparticles of titanium dioxide caused complete destruction of supercoiled DNA (Donaldson et a, 1996). In the absence of UV, titanium dioxide produced reactive oxygen species in brain immune cells and caused death of brain immune cells after 24 hours exposure (Long et al, 2006). The potential for nanomaterials in sunscreens and cosmetics to result in harm is made greater as production of reactive oxygen species and free radicals increases with exposure to UV light and cause oxidative damage to DNA in cultured human fibroblasts (Dunford et al, 1997). The crystalline structure of the fine and ultra fine TiO_2

particles differed, suggesting that the differential effects observed between the particle types might be more complicated, and may not be due to particle size alone (Warheit et al, 2007). These particles can physically exist in a single particle form or as agglomerates, morphologically occur as spheres, rods, and dots, chemically coated with alumina and amorphous silica, and arrange in different crystalline forms (rutile or anatase). Study of nanosized TiO_2 particles suggest that particle surface area is an important parameter for predicting inflammatory effects in the lungs (Renwick, 2001 and Tran et al, 2000), other studies have shown that surface area alone may not dictate toxicity (Warheit al, 2005 and Warheit et al, 2007).

More specifically, in vitro culture of human epithelial cells and intratracheal instillation studies of nanosized TiO_2 particles showed consistently greater cytotoxic effects with anatase compared to rutile TiO_2 particles (Sayes et al, 2006, Warheit et al, 2005 and Warheit et al, 2007). Anatase and rutile TiO_2 particles, delivered at similar surface area doses, increased release of lactate dehydrogenase, interleukin-8, and reactive oxygen species, as well as depressed mitochondrial activity in dissimilar patterns in cultured human epithelial cells (Sayes et al, 2006). Based on these biologic parameters, researchers concluded that anatase TiO_2 is 100 times more cytotoxic than rutile TiO_2 particles at a similar particle size and surface area. Some studies have suggested that chronic inhalation of TiO_2 nanoparticles is harmful.

Exposure to nanosized TiO_2 has been associated with a variety of pulmonary effects in rats, including inflammation, pulmonary damage, fibrosis, and lung tumours (Aitken et al, 2009). In vitro experiments show that nano TiO_2 can damage DNA, disrupt the function of cells and interfere with the defence activities of immune cells. It can also provoke inflammation by absorbing fragments of bacteria and 'smuggling' them across the gastro-intestinal tract (Ashwood et al, 2007). Studies of nanosized TiO_2 particles suggest that particle surface area is an important parameter for predicting inflammatory effects in the lungs (Cullen et al, 2002). Due to their small size, large surface area and strong electrostatic attraction, TiO_2 nanoparticles can absorb other metallic particles. For example, cadmium, which is extremely toxic and can bioaccumulate in organisms and eco-systems, has been shown to be strongly absorbed within nano TiO_2 and then transported into and accumulated in carp. This process raises the issue of nano TiO_2 acting as a magnifier for cadmium pollution (Takeda et al, 2009). Release of nanosized titanium dioxide into water could have detrimental effects on overall ecosystem health, especially given that the concentration is large enough to have some detrimental effect on organisms and that it readily accumulates in drinking water (Aitken et al, 2009).

4. Zinc Oxide (ZnO)

Nano size, zinc oxide is widely used as a pigment for paints and cosmetics, as well as a semiconductor. It also exhibit antibacterial properties. It is found in cosmetics, sunscreens, food packaging, food additives, paints, wall coatings, bottle coatings, gas purification and contaminant sensors. (Bhatt and Tripathi, 2011 and Hansen et al,2008)

Zinc oxide is considered relatively safe in its bulk form but in nanosized zinc oxide is toxic to human and rat cells even at very low concentrations. Test mice showed

severe symptoms of lethargy, vomiting and diarrhoea. A study in mice showed severe responses, ranging from death to heavy kidney damage, anaemia and liver damage (Wang, et al., 2006). Like other metal oxides, nano zinc oxide tends to aggregate and settle so most of the material can be found in sediments. A study presented evidence that nano zinc oxide aggregates cause toxicity to zebra fish embryos and larvae, including malformation in the cardiovascular system, blocked hatching and mortality in embryos. Zinc oxide is also toxic to some roundworms and can inhibit their growth and reproductive capabilities (Wanga, 2009). It can also inhibit seed germination and root growth in plants (Lin and Xing, 2007).

5. Nanoparticulate Silver

An increasing amount of silver in consumer and industrial products is now in nano form. Nanoscale silver or "nanosilver" has become one of the most commonly used nanomaterials in consumer products, predominately as a bactericide. Textiles (e.g., socks, shirts, pants), deodorants, laundry soaps, air filters, baby products (milk bottles, teethers), cosmetics, medical instruments, hardware (computer, mobile phones), food storage containers, cooking utensils, food additive/supplements, appliances (hair dryers, vacuum cleaners, washing machines, refrigerators), food contact materials (such as cups, bowls and cutting boards), cosmetics and personal care products, clothing, childrens' toys, health supplements, medical devices coatings/paints are the industries which are using nanosilver particles. Nanoparticles of silver are now used in toothpastes, soaps and face creams, food packaging, clothing, household appliances, disinfectants and wound dressings. Silver nanoparticles have a potent ability to kill bacteria (Salata, 2004). However there are concerns that silver nanoparticles may also kill beneficial bacteria.

The United States Environmental Protection Agency has announced plans to regulate as pesticides products that contain silver nanoparticles (Weiss, 2006). The toxicity of silver nanoparticles may exceed the toxicity of the most toxic silver compound in its standard form (Pal, 2007) and may have greater antimicrobial properties because they are able to kill bacteria for longer periods of time than normal silver. Indeed, silver has been shown to be comparatively more toxic than other heavy metals when in nanoparticle form (Zeng, 2007). In addition, different sized and shaped silver nanoparticles have different toxicities. Nanoparticles of silver less than 10 nanometers can penetrate the cell wall (Braydich-Stolle, 2005). The most common nanosilver toxicity studies focus on bacteria and to a lesser extent on complex animal species such as fish, rats, mice and quails. In addition to being an effective bactericide, silver nanoparticles are also toxic to mammalian cell cultures, such as rat liver cells (Berger, 2007). There is increasing evidence that silver nanoparticles at low concentrations will harm aquatic invertebrates and fish. Silver nanoparticles administered in vivo to zebra fish embryo increased deformation rates and ultimately led to death. Individual silver nanoparticles were found inside embryos at each developmental stage (Landsdown, 2007). Silver, widely used as an antibacterial agent, proves to be toxic to humans or animal cells when in nanoparticle form, its cytotoxicity being higher than that of asbestos (Soto et al, 2005) Inhalation of silver nanoparticles

leads to their migration to the olfactory bulb, where they locate in mitochondria (Oberdorster et al, 2005) as well as translocation to circulatory system, liver, kidneys, and heart (Takenaka et al, 2001). This is one of the few available in vivo studies to observe passive diffusion of nanoparticles and points to the severe consequences that the release of large amounts of silver nanoparticles may have, if the nanoparticles remain unchanged when reaching aquatic environments. As early studies suggest that microorganisms and plants may be able to modify and concentrate nanoparticles that can then bioaccumulate (or even biomagnify) along the food chain (Wang et al, 2009)

6. Quantum Dots

Semiconductor nanocrystals (Quantum dots) consist of a metalloid crystalline core (e.g., ZnS, CdSe, CdTe, InAs, and GaAs) and covered by a shell (e.g., proteins, peptides, nucleic acids, carbohydrates polymers, and small molecules). Quantum dots are used in many medical imaging, targeted therapeutics, solar cells, photovoltaic cells, security links, and telecommunications devices. They have also been explored for delivering bioactive molecules such as antibodies and receptor ligands to specific sites including neoplastic cells, peroxisomes, DNA and cell membrane receptors (Hardman, 2006 and Wu et al, 2003). Their toxicity is due to their metalloid crystalline core. Deterioration of the CdSe core can ultimately influence the cellular toxicity and biocompatibility of quantum dots (Derfus et al, 2004). Quantum dots accumulate in the liver and spleen regardless of the peptide used for quantum dot conjugation (Akerman et al, 2002). Administration of quantum dots coated with different molecular weights of polyethelene glycol (PEG) indicates that differential tissue and organ deposition in mice are time and molecular weight dependent, with larger molecular weight PEG-coated quantum dots clearing more slowly and accumulating more in lymph nodes, liver, and bone marrow than those coated with low molecular weight PEG (Ballou et al, 2004). Quantum dots have been administered to the respiratory tract of rodents to understand how different functional groups and surface coatings influence the deposition, transport, and retention of ultra fine particles in pulmonary and extra pulmonary tissues delivered via the respiratory tract. Preliminary findings demonstrate that nanosized quantum dots can translocate from olfactory epithelium of the nasal cavity to the olfactory bulb region of the brain (Hopkins and Pinkerton, 2007). Studies with mice and pigs show that quantum dots that have been injected into the skin find their way to the local lymph nodes (Kim et al, 2004). The likely transport mechanisms are through macrophages and Langerhans cells in the skin (Ohl et al, 2004). Future research efforts will need to explore and understand the similarities and discrepancies of biological responses towards different functionalized nanomaterials are which are being developed and will be developed.

As an individual or worker entries of nanoparticles into the body are likely to be of primary significance– inhalation, ingestion, and dermal penetration are the three routes of entry into the body, two additional routes become important when considering nanotechnology-based medical devices and drugs – injection and release from implants.Widespread inhalation of nanomaterials may also occur if nanomaterials become airborne and enter the atmosphere. Due to their small size, nanomaterials can form light dusts

that are easily distributed in the air, inhaled, and deposited in the lung. The size (single or aggregate) and shape of a nanomaterial help determine where it deposits within the lung, because of the difficulty in conducting uniform, controlled inhalation experiments, Particle size and air concentration, for example, are obvious factors that will influence inhalation exposure. Other factors include the composition and stability, pathway of exposure (i.e., direct versus incidental), rigor and method of manipulation, use of dust control measures (i.e., engineering controls and personal protective equipment) and the dispersion and fate of particles within a given environment. Larger diameter particles (i.e. >2–3 mmdiameter) act primarily by inertial mechanisms and will preferentially deposit in the upper respiratory tract whereas smaller particles (i.e., <100 nm diameter) act by diffusion, and will deposit both in the nasopharyngeal and tracheobronchial regions and to a greater extent, in the alveolar or gas exchange region of the lungs. Once particles are deposited within the respiratory tract, the mechanism by which they are cleared from the lungs depends not only on the site of deposition, but also on the size of the particle itself. Solid particles are cleared from the lungs through a variety of mechanisms: (a) sneezing, coughing, and removing mucus from the nasopharyngeal region, (b) direct or macrophage-mediated transport along the mucociliary escalator and subsequent elimination by the gastrointestinal tract, (c) direct or macrophage mediated transport across the bronchiolar or alveolar epithelium and subsequent clearance by the systemic circulation or interstitial lymphatics and (d) physicochemical processes, including dissolution, leaching, and physical breakdown of particles. Nanosized particles lack the rapid phase clearance typically observed in the first 24 hrs. of exposure and corresponding to tracheobronchial deposition of larger sized particles (Roth, 1993 and Roth, 1997). Nanosized particles have a potentially high efficiency for deposition target both the upper and lower regions of the respiratory tract, are retained in the lungs for a long period of time, induce more oxidative stress and cause greater inflammatory effects than their fine sized equivalents all suggest a need to better understand the true impact of these particles on the body.

There are a number of methods available to assess the different characteristics of airborne particles and several comprehensive reviews describe the advantages and limitations of these available analytical methods (Brouwer et al, 2004; Ku and Maynard 2006 and Powers, 2006).A good understanding of the underlying mechanisms for this characteristic pulmonary response in rats has been developed. Critical to the expression of pulmonary toxicity is the ability of the lung defence mechanisms to actively clear deposited particles. The pattern of inflammation and lung toxicity develops in situations where these normal lung clearance mechanisms are exhausted and refers to the loss of mobility of alveolar macrophages when their capacity to phagocytose and remove particles is exceeded (Morrow, 1988). Under these conditions and sustained inflammation, a process of hyperplasia, metaplasia and ultimately tumour formation can develop (Driscoll, 1996 and Faux et al, 2003).

Nanomaterials are incorporated into many consumer products that are meant to be applied to the skin. Whether a nanomaterial enters the body through the skin can depend upon whether the skin is injured, to what degree the skin is flexed

and to what degree the nanomaterial is lipid soluble. The latter may depend upon the surface coating or carrier of the nanomaterial. Gastrointestinal tract exposure may occur from the use of nanomaterial containing cosmetics or drugs or as a result of the mucociliary escalator clearing nanomaterials from the respiratory tract. Nanoparticles in the gastro-intestinal tract have been linked to cancer. Nanoparticles that enter the circulatory system are related to occurrence of arteriosclerosis, and blood clots, arrhythmia, heart diseases, and ultimately cardiac death. Translocation to other organs, such as liver, spleen, etc, may lead to diseases of these organs as well. Experimental evidence suggests that the initiation and promotion of neurodegenerative diseases are associated with oxidative stress caused by nanoparticle in brain regions associated with function loss and cell damage (Liu et al, 2006).

The study regarding the concern health risks of ENPs is still so immature that a clear pattern regarding which physicochemical characteristics are likely to expect cellular toxicity has yet to come out. Some key parameters, however, such as particle antigenicity, size, persistence, solubility, charge, reactivity, crystalline form do seem to come forward as important factors taken in account to investigate how surface properties of nanosized particles may influence the disposition, fate and transport and biological responses in living organisms. A realistic move toward the unwell effects of ENPs despite the lack of current nanoparticle exposure limits, or even an standard assessment strategy to estimate their levels in a workplace, the accrued knowledge of sound industrial hygiene practice, monitoring equipments should be at the forefront of any efforts to protect nanoparticle workers while investigation continues to detail and reveal specific approaches to best assurance for the health and safety measures.

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