J. Environ. Nanotechnol.
Volume 4, No.3 (2015) pp. 55-72
ISSN (Print): 2279-0748
ISSN (Online): 2319-5541
doi:10.13074/jent.2015.09.153165

Nanotoxicology - Health and Environmental Impacts: A Review

Samreen Heena Khan[1], M. H. Fulekar[2], Bhawana Pathak[3*]

[1]*Center for Nano Sciences, Central of Gujarat, Gandhinagar, Gujarat, India.*
[2,3*]*School of Environment* and *Sustainable development, Central of Gujarat, Gandhinagar, Gujarat, India.*

Received: 11.08.2015 Accepted:15.08.2015 Published: 30-09-2015

Abstract

Nanotechnology is the new field of technological innovation that transformed the industrial development. This revolution emphasized the large scale production of nano-based materials. The novel behaviour of nanoparticle is dominated by quantum mechanics, materials confinement in small structures, large surface to volume ratio and other unique properties, phenomena and processes. The consumption of products containing nanomaterial is increasing and represents a risk to health and the environment. Understanding the toxicity of engineered nanomaterial and nano-based products is important for human environmental health and safety.Nanotoxicology, is intended to define the toxicological activities of potential nanomaterial and their products to determine whether and to what extent these materials pose threat to environment and human health. In this context the fate of nanoparticles in environment with reference to air, water, soil has been studied. Health aspects of nanomaterials have also been cited including nanomaterials effect on different organ systems. The main objective of present review is to focus on the effect of nano materials on health and environment and to discuss the sources, fate, distribution, deposition, bioavailability and toxicity of engineered nanomaterial.

Keywords : *Health hazards; Nanomaterial; Nanotechnology; Nanotoxicology; Risk assessment.*

1. INTRODUCTION

Nanotechnology has attracted a great interest in recent years because of its expected impact on areas such as energy, medicine, agriculture, electronics, textiles, and space industries (Linkov, 2008; Besley, 2010). Since the beginning, nanotechnology has been considered as the branch of sciences that will even cross the limit of miniaturisation in technology, as described by the Moore's law, but this miniaturisation has its own limitation in terms of nano. Nano scale is not just another step toward miniaturisation, but a qualitatively new scale (Joachim, 2005). Nanotechnology has become a buzz word for the science and technology refers to the visualization, manipulation and control of materials at the nanometer scale. Nanotechnology is a field of applied science concerned with the control of matter at dimensions of 1-100 nanometres (Handy and Shaw, 2007). Nano scale materials have different molecular organizations and properties than the same material in a bulk. Nanotechnology defines as- the design, synthesis and application of materials and devices whose size and shape have been engineered at the nano scale and at least one dimension in the nano range (Donaldson *et al.* 2001; Roco, 2003). The various applications of engineered nanomaterial in various sectors are presented in table 1.

Nano materials are materials that have structural components smaller than 1 micrometre in at least one dimension (Donaldson *et al.* 2001). Nanomaterials with a significant effect on biological activity are: surface area-to-volume ratio and physico-chemical properties (Dawson *et al.* 2008). The fundamental properties of nanomaterial, such as melting point, colour, and electrical conductivity vary with size and shape of the material within the 1–100 nm range (Hubert and Birgit, 2012). The potential benefits of nanomaterials to the environment and human health is remarkable, and that include sensors for environmental monitoring, nano-remediation, nano-drug-delivery systems, bio-robotics, nano-arrays, and nanoscale implants in medicine (Maxine, 2011).

These nano products are new to environment and have certain adverse effects that give rise to particle toxicity when release to the environment in/or certain extent or through the exposure of the nano based products. All nano based products have some or less toxicological impacts depends on parameters that lead to the toxicity caused by nanoparticles. Nano

** Bhawana Pathak Tel. No.: +918980095357*
E-mail : bhawanasp@hotmail.com

toxicology addresses the adverse environmental and health effects caused by nanoparticles and explores the effects of exposures to nanomaterial (Oberdorster *et al.* 2005). Generation of nanoparticles are not restricted only in laboratory experiments and highly sophisticated target oriented activities but there is also a significant degree of natural sources of nanomaterials *i.e.* pollen grains, ultrafine particles in smoke, aerosols, dust particles, air contaminants and many other natural exhaust mechanisms carry nanomaterials to a higher or lower extent (Colvin, 2008). For understanding the concept of nanotoxicology, two things are necessary to have an insight upon, (i) the interaction of the nanomaterial with the environmental components and (ii) the interaction of different nanomaterial with the living systems (Donaldson *et al.* 2004). Humans are already exposed to a wide range of natural and engineered nanoparticles in the air and exposure via the food chain, water supply and medical applications also likely. The size of nanoparticles and lack of metrological methods to detect them is a huge potential problem in context of identification and remediation, in terms of their fate in the human body and in the environment (Vicki and Ken, 2006).

1.1 Toxicological concerns

Nanotechnology research has stimulated new interest in the role of particle size in determining toxicity. Nanoparticles can be more toxic than larger particles of the same substance because of their larger surface area, high ratio of particle number to mass, enhanced chemical reactivity, high surface reactivity and potential for easier penetration of cells (Renata and Harald, 2008). Nanomaterial has been proposed for use in many biological applications, although little is known of their toxicity, potential mutagenic effects, or overall risk to human health. All nanoparticles are not toxic to the environment; it all depends on concentration, dosage and exposure (Martin, 2008).

Table 1. Engineered nanoparticle (ENP) and their applications

ENP	Applications	References
Carbon nanotubes and derivatives	Electronics, computers, plastics, catalysts, batteries, conductive coatings, super capacitors, water purification systems, orthopedic implants, aircraft, sporting goods, car parts, concrete, ceramics, solar cells, textiles	*Danail, 2012; Popov, 2004; Ajayan and Zhou, 2001.*
Fullerenes	Removal of organo-metallic compounds, cancer treatment, cosmetics, magnetic resonance imaging, X-ray contrasting agent, anti-viral therapy.	*Yadav and Kumar, 2008.*
Graphene	Ultrafiltration, Nanofiltration, Optoelectronics, Energy storage devices, Photovoltaic cells.	*Das and Prusty, 2013; Lonkar and Abdala 2014.*
Titanium Dioxide	Sunscreen lotions, cosmetics, skin care products, solar cells, food colorant, clothing, sporting goods, paints, cement, windows, electronic coatings, bioremediation, photocatalysts, packaging, etc.	*Ronald et al. 2010; Jonathan et al. 2012; Bermudez et al. 2004; Masanori et al. 2012; Isabella et al. 2012; Gupta and Tripathi, 2011; Senić et al. 2011.*
Zinc Oxide	Skin care products, bottle coatings, gas purification, contaminant sensors, photocatalysis.	*Kołodziejczak-Radzimska and Jesionowski, 2014.*
Cerium Oxide	Combustion catalyst in diesel fuels, solar cells, oxygen pumps, coatings, electronics, glass/ceramics, ophthalmic lenses	*Aleksandr et al. 2012; Wason and Zhao, 2013.*
Quantum dots	Medical imaging, targeted therapeutics, solar cells, photovoltaic cells, security links, telecommunications	*Jamiesona et al.2007; Sametband et al. 2007.*
Zero-valent iron	Remediation of water, sediments and soils to remove nitrates, detoxification of organo-chlorine pesticides and polychlorinated biphenyls	*Wan Yaacob et al. 2012; Muller et al. 2012.*

Several possible mechanisms of action for the toxicity of particles have been proposed, including injury of epithelial tissue, inflammation, oxidative stress response and allergy (Abdelhalim, 2011; Ruhung *et al.* 2012). At the cellular level oxidative stress is considered to be of extreme importance. Nanoparticles are found to induce oxidative stress responses in keratinocytes, macrophages and blood monocytes after in vitro exposure. The mechanism of toxicity of nanoparticles broadly depends on five D's: *Dose; Deposition; Dimension; Durability* and *Defense* (Danail *et al.* 2012). A key aspect of understanding the toxicity of materials is to know how much of a substance can cause harm to the human and environment. When bodies are introduced to materials at the wrong dose, or unintentionally, the exposure can result in toxicity, but with nano scale materials, the results of the studies are difficult to interpret (Bernd and Thomas, 2007). One of the complexities is that particles behave differently when they are in nano scale, because of increased surface area and high surface reactivity of the particle, so doses equivalent on the basis of mass are very different on the basis of the area (Mélanie *et al.* 2009).

1.2 Methods to assess toxicity of nanoparticle

Nanomaterials in the environment are tough to be analysed, because of their extremely small size and their uncertain physical and chemical interactions with other materials in the environment and the biological milieu (Renata and Harald, 2008). Toxicity assay include mammalian toxicity (acute and chronic tests, oral toxicity, dermal toxicity, skin irritation tests), tests for mutagenicity, and eco-toxicity tests to enable some assessment of the risk to the environment (Shan *et al.* 2009; Jin *et al.* 2012). A rational approach to nanomaterial toxicity begins with an assessment of the physico-chemical properties of the materials that allow them to interact with and possibly damage biological systems (Marina *et al.* 2009). Another set of tests involves *in vitro* cellular assays that reflect the response of many different cell types that can be targeted at the portal of entry or systemic sites after nanomaterial uptake and distribution. In general, the *in vitro* results at the cellular level are more useful for understanding the mechanism of bio-kinetics of ENMs. For example, the results obtained *in vitro* can be gathered to predict *in vivo* ADME/Toxicity (absorption, distribution, metabolism, excretion, and toxicity) of the ENMs through systematic information on (a) the effective cellular uptake and bioavailability at target sites, (b) cellular metabolism and organ toxicity and (c) cellular excretion and tissue accumulation and long-term risks (Marina *et al.* 2007; Zhu *et al.* 2013).

There are numerous microscopic and spectroscopic techniques presently available for detection of nanomaterials in the environment. The upper size limit for the toxicity of nanoparticles lies between 65 nm and 200 nm (Kevin, 2007). *In vitro* studies done on cell cultures have confirmed the increased ability of nanoparticles to produce free radicals that can cause cellular damage (Poonam and Sheefali, 2011). Generation of reactive oxygen species (ROS) upon exposure of cells to particulate matter is considered as a major contributor to nanoparticle toxicity **(**Unfried, 2007**;** Aleksandr *et al.* 2012). The cell membrane, mitochondria and cell nucleus are considered appropriate for possible nanoparticle induced toxicity. Finally, any test strategy should include appropriate use of animal models, potentially the most difficult assay to consider. Current research on nanomaterial has examined their influence on biochemical reactions in a cell up to the survivability of whole multi-cellular organisms. In order to make comparisons between chemicals and organisms for risk analysis, several standard measurements have been established. The most common is the LC50, or lethal concentration of chemical that kills 50% of an exposed population as compared to a control. Another common measurement is the EC50, or effective concentration of a chemical that elicits some response in 50% of the population. Tests of both the LC50 and EC50 must be carefully controlled and performed in a standardized manner to ensure comparability between experiments and laboratories. Daphnia LC50 test also used to test the toxicity of nanomaterial in aquatic environment (Oberdörster *et al.* 2005).

1.3 The mediators of the toxicity of particles

Several studies have confirmed that nanoparticle toxicity is extremely complex and multi-factorial, potentially being regulated by a variety of physico-chemical properties, size and shape, as well as surface properties like charge, area, and reactivity (Kevin *et al.* 2007). The important physical property of a nanomaterial in determining cellular uptake, transport and accumulation is its nano-scale size. Organisms have highly tuned and precise function of regulating the uptake and transportation of nanosized biological components and also exists within the cell, i.e. membrane bi-layers exhibit a thickness of 4-10 nm (Garnett and Kallinteri, 2006; Zhu *et al.* 2013). Information on physico-chemical properties, solubility, sorption, biodegradability, size distribution, agglomeration accumulation and all likely depending on the specific size and detailed composition of the nanoparticles, also makes the particle toxic at nano-scale (Jones *et al.* 2013). The mediators of toxicity of nanoparticles shown in fig. 1.

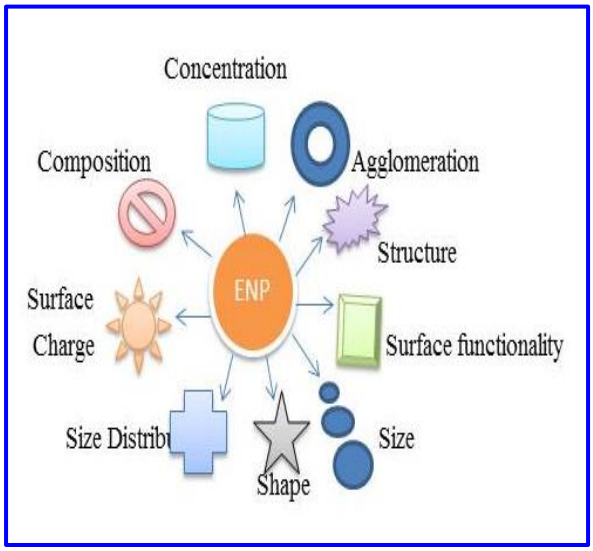

Fig. 1: Mediators of Toxicity of Nanoparticle

2. ENVIRONMENTAL AND HEALTH ISSUES ASSOCIATED WITH NANO MATERIALS

Despite the widespread use of nanomaterial, understanding of the toxicity and potential health risk and environmental risk associated with nanomaterial use is extremely limited (Linkov, 2008**;** Dietze and Herth, 2011). In fact, toxicity issues associated with nanomaterial used in nano medicines and other environmental remediation techniques are often ignored (Chidambaram and Krishnasamy, 2012). Many nanomaterial and nano-based products used in environmental remediation, health improvement and in biomedical applications now-a-days leading to the extensive exposure of these nanoparticles to human and releases to environmental bodies from the workplace is likely (Bernd and Thomas, 2007). There are several health and environmental issues related to the use and release of nanomaterials or nano based products responsible for the toxicological concerns of the nanomaterial (Powell, 2007).

2.1 Health risk

The extremely small size of nanomaterial means that they are much more rapidly taken up by the human body because of the low surface-to-volume ratio that increases the chemical reactivity and biological activity of the particle. The toxic action of nanoparticle interactions with biological systems can be divided into two categories:-

(i) the enhanced delivery of chemical agents known to be toxic and
(ii) the toxic effects of relatively benign materials derived from the size-related disruption of biological structures.

Nanoparticles enter the body by a variety of different routes and this makes the assessment of the risks in relation to any material even more difficult (Oberdorster, *et al.* 2004). As it is reported in various literature, particles enter the body by one route and then widely dispersed to various organs and tissues. The most significant method of exposure to nanoparticles is by inhalation, through ingestion with food, or application to the skin, either intentionally or unintentionally, are the other means of access to the body (Bakand *et al.* 2012). Potential human exposures to nanomaterial's, or mixtures of nanomaterial's, include workers exposed during the production and use of nanomaterial, general population exposure from releases to the environment during the production or use in the workplace, and direct general population exposure during the use of commercially available products containing nanomaterial (Oberdorster and Utell, 2002). The principal routes of occupational and environmental nanoparticle exposures are through the skin, gastrointestinal tract and respiratory tract (Amy and Kent, 2009). Conversely, many nanoparticles intended for medical imaging and therapeutics are still in an investigational stage and other forms of major exposure routes, importantly, nano-medical products expose to workers as well as patients (Garnett and Kallinteri, 2006; Hubbs *et al.* 2011). At present, techniques available for measuring airborne particulates were not developed to measure workplace exposures to particulates with-in nanoscale dimensions (Danail *et al.* 2012). The nanoparticle uptake in human body more rapidly occurs through different routes i.e. inhalation, dermal, oral and injection.

2.1.1 Inhalation

The presence of nanoparticles in the atmosphere poses a serious risk. The fact that nanoparticles are easily spread by wind increasing their exposure to people, to understand how inhaled nanoparticles affect humans, early studies of nanoparticle inhalation have focused on the path and deposition of the inhaled particles and their potential toxicity to the inhabited organs (Donaldson and Tran, 2002). Inhaled particulate matter can be deposited throughout the human respiratory system including pharyngeal, nasal, trachea-bronchial and alveolar regions, depending on particle size (Donaldson and Seaton, 2008). Respiratory tract is the major portal of entry for airborne nanoparticles; this exposure route can be used as an example to discuss some key concepts of nanotoxicology, including the significance of dose, dose rate, dose metrics and bio-kinetics (Oberdorster *et al.* 2004). Size and shape are important as particles over 5 µm in diameter are filtered out in the airways proximal to the small terminal bronchioles, while those between 0.5 and 5 µm are able to reach the more distal respiratory part of the lung, though some of them may be deposited higher up in the nose or large conducting airways (Jessica *et al.* 2009). After deposition in the respiratory tract,

translocation of nanoparticles may potentially occur to the lung interstitium, brain, liver, spleen and possibly to the foetus in pregnant females. It is emphasized that there is extremely limited data available on these pathways. Passage of inhaled nanoparticles into the bloodstream was demonstrated in one human study, but two other similar studies have failed to show such a translocation (Sharma *et al.* 2009; Bakand *et al.*, 2012).

On the other hand, inhalation is the major route of intake of airborne contaminants, the respiratory system serves as the portal of entry into the body for a large variety of airborne contaminants, such as gaseous, vapors and particulate matter. Exchange of gases between inhaled air and blood occurs in the alveoli (McKinney *et al.* 2012). The airways from the nasal cavity to the bronchioles are continuously wetted by a layer of mucous. The fate of inhaled nanoparticle depends upon their physical and chemical property (Nel, 2005). Gases and vapors are directly absorbed into the blood or dissolved in the mucous in airways, depending whether they are water or fat soluble, whereas case of nano-particulate matter, depending on their size, particles are trapped into the mucous layer or the alveoli. Also the pattern and depth of breathing and irritant effects of inhaled material may alter the deposition of nanoparticles (Oberdorster *et al.* 2004). There is need to study the biokinetics of inhaled biopersistent nano- and micrometer-sized particles to assess their toxicity and to understand their potential risks (Meike *et al.* 2008). When particles are inhaled, they do not necessarily remain at their sites of deposition in the respiratory tract. Instead they can undergo numerous transport processes within the various tissues of the lungs, including clearance from the lungs. The average half-life (t1/2) for nanoparticles in the respiratory tract is about 700 days in humans (Ronald *et al.* 2010)

Materials which are not very harmful could be toxic if they are inhaled in the form of nanoparticles (Zholdakova *et al.* 2008). Another potential route of inhaled nanoparticles within the body is the olfactory nerve; nanoparticles may cross the mucous membrane inside the nose and then reach the brain through the olfactory nerve (Chapman *et al.* 2007). Inhaled nanoparticles can traverse the alveolar endothelium and enter the capillaries, and particles can penetrate the skin and translocate to the lymph nodes. When nanoparticles enter the circulatory system, they are transported to the liver, spleen, lymph nodes and bone marrow. Additionally, nanomaterial can traverse cell membranes and accumulate in the mitochondria and often cross the blood-brain barrier (Gevdeep *et al.* 2009).

In vivo tests have been conducted using various methods of administration, dosage and measurement. Early experiments on nanoparticles impact on health have used carbon nanotubes of less than 10 nm in length, these tubes are thought to present a danger to people in a manner similar to asbestos, which chokes the lungs of individuals who breathe the microfibers, causing inflammation that can lead to respiratory problems and cancer (Buford *et al.* 2007). In a study, carbon nanotubes injected into mice to see what effect, if any, was observed. Some targeted mice were found to have internal swelling and cuts which are symptoms similar to those of asbestos damage (Meike *et al.* 2008).

2.1.2 Dermal

The skin acts as a barrier to many naturally occurring substances. However, penetration through the skin can occur in case of certain liquid and dissolved materials. Lipid solubility and molecular size are the most important factors, that means high lipid solubility and small molecular size enhance penetration through the skin (Tarl *et al.* 2012). Dermal exposure to nanomaterials has received much attention, perhaps due to concerns with occupational exposure and the introduction of nanomaterial's such as nano-sized titanium dioxide into cosmetic and drug products (Ronald *et al.* 2010). Nanomaterials have a greater risk of being absorbed through the skin than macro-sized particles because of ease of penetration to the epidermal layer (Khara *et al.* 2012). Dermal exposure to NPs also occurs with consumer products such as TiO_2 and ZnO NPs in sunscreens (Bermudez *et al.* 2004; Isabella and Flavia, 2012). There are some evidences suggest that nanoparticle can penetrate to epidermis, dermis and are able to penetrate the stratum corneum and can penetrate the skin by entering between or through epithelial cell or *via* the skin appendages, for an instance by the use of cosmetics containing nanoparticles (USEPA, 2003). Nanoparticle causes dermatoxicity was reported by both *in vitro* and *in vivo* experiment (Ronald *et al.* 2010). There are concerns about the toxicity of titanium dioxide (TiO_2); commonly used as a physical sunscreen since it reflects and scatters UVB (290-320 nm) and UVA (320-400 nm) light rays – the skin-damaging portion of the solar spectrum (Masanori *et al.* 2012). TiO_2 also absorbs a considerable amount of UV radiation, however, that in aqueous media leads to the production of reactive oxygen species, including superoxide anion radicals, hydrogen peroxide, free hydroxyl radicals and singlet oxygen. These reactive oxygen species can cause substantial damage to DNA (Dobrovolskaia and McNeil, 2007; Gevdeep *et al.* 2009). Titanium dioxide particles under UV light irradiation have been shown to suppress tumour growth in cultured human bladder cancer cells *via* reactive oxygen species. Sun-illuminated TiO_2 particles in sunscreen were observed to catalyse DNA damage both *in vitro* and *in vivo* (Tral *et al.* 2012; Gevdeep *et al.* 2012).

2.1.3 Injection

Injection is the administration of a fluid into the subcutaneous tissue, muscle, blood vessels or body cavities. Injection of nanoparticles has been studied in drug delivery and medicine based on nanotechnology *i.e.* Nano medicines (Garnett and Kallinteri, 2006). Nanoparticles injected intravenously retained longer in the body than ingested ones. For example, 90% of injected functionalized fullerenes are retained after one week of exposure. The adverse health effects of injected nanoparticles are a function of particle chemistry and charge. A common side effect of injecting nanoparticles intravenously is hypersensitivity, a reaction that occurs in many recipients and is probably because of complement activation (Shvedova *et al.* 2010). Nanoparticles have been found to be distributed to the colon, lungs, bone marrow, liver, spleen, and the lymphatics after intravenous injection. The translocation of nanoparticles after injection depends on the site of injection: intravenously injected nanoparticles rapidly spread throughout the circulatory system, with subsequent translocation to organs; intra-dermal injection leads to lymph nodes uptake; while intramuscular injection is followed by neuronal and lymphatic system uptake (DeJong and Borm, 2008).

2.1.4 Oral

Nanoparticles for instance in the workplace and oral nano medicines. The passage of nanoparticle to the nervous system is also possible via the blood-brain-barrier (BBB) through the oral uptake (Suh *et al.* 2009). After oral exposure, nanoparticles distribute to the kidneys, liver, spleen, lungs, brain, and the gastrointestinal (GI) tract. Some nanoparticles can pass through the GI tract and are rapidly eliminated in faeces and in urine, indicating that they can be absorbed across the GI barrier and into the systemic circulation (Jonathan *et al.* 2012). However, some nanoparticle systems can accumulate in the liver during the first-pass metabolism (Susan *et al.* 2011).

2.2 Toxicokinetic and Toxicodynamic study of nanomaterial

Toxicokinetics study is mainly intended to determine what the body does to the individual nanomaterial. The main questions scientists are currently facing are: what is the mechanism of toxic action of nanoparticles; how does the reactive surface of nanoparticles interact with the internal environment of the body; and what is the relative contribution of particle size versus particle composition in the overall toxicity of nanoparticles (Balbus *et al.* 2007). Nanomaterials are most likely to enter in a cell membrane by diffusion, through endocytosis as well as through adhesion. In general, data that describe the fate of nanomaterial from their absorption at a portal of entry in the body to their excretion are of paramount importance for understanding interactions with the organism (Flemming *et al.* 2011). Toxicokinetic studies mainly depend on Absorption, Distribution, Metabolism and Excretion (ADME) (DeJong and Borm, 2008). Nanoparticles may be absorbed in the body by various means like its rapid absorption to lung through inhalation, then passage and adsorbed by the gestro-intestinal tract, dermal, intra-venous and sub-cutaneous (Deguchi *et al.* 2007). Variable transport influenced by size, shape, surface chemistry of the particle. In Distribution, NP can be cleared, translocate from blood by secondary tissues such as liver, kidney and spleen. NP size and charge plays an important role in distribution to the other organ, dispersal by lymphatic system also for some NP (Marina *et al.* 2009). Distribution is followed by rapid clearance from the systemic circulation, predominantly by the action of liver and splenic macrophages. Metabolism of nanoparticle is likely minimal (Kagan *et al.* 2005). Some biodegradable and polymeric nanoparticles have the ability to metabolize to certain extent. Excretion of nanoparticle by the renal filtration system, size and charge is important factor for the clearance of nanoparticles from the body (glomerular pore diameter approx. 5 nm, favours positive particles to transport). Clearance by immune system by macrophages and reticulo-endothelial system is also reported (Hirose *et al.* 2009). Fig. 2 systematically depicts the toxicodynamic and toxicokinetics effect of nanomaterial.

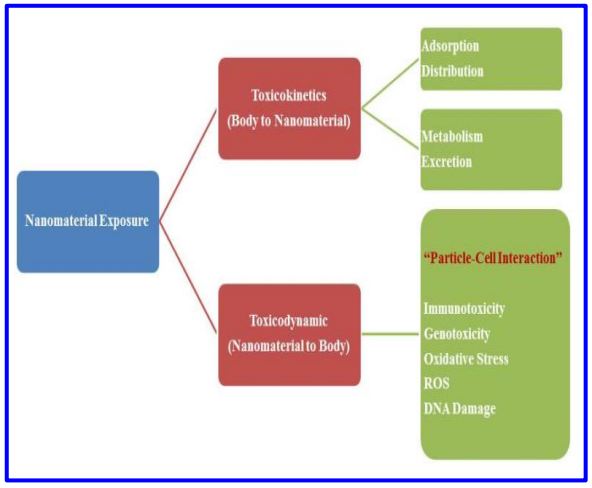

Fig. 2: Toxicodynamic and Toxicokinetics of Nanomaterial

On the contrary, Toxicodynamic studies aim to study the effect of nanomaterial on the body (Moore, 2007). It deals with the "Particle-Cell Interaction". Immunotoxicity, oxidative stress and generation of Reactive Oxygen Species (ROS) are the examples of effect of nanomaterial on body (Hoet, 2009). Both *in vivo* and *in vitro* studies have shown

that nanoparticles of various compositions create reactive oxygen species. Reactive oxygen species have been shown to damage cells by per oxidizing lipids, altering proteins, disrupting DNA, interfering with signaling functions and modulating gene transcription (Howard and Debra, 2005). Oxidative stress is a response to cell injury, and can also occur as an effect of cell respiration, metabolism, ischemia/reperfusion, inflammation, and metabolism of foreign compounds (Fischer and Chan, 2007). Table 2 shows the various types of engineered nanoparticles and their effect on human body (Bleckmann *et al.* 2007).

Table 2. Types of Nanomaterial and their effect on human body.

Nanomaterial	Effects	References
Fullerenes	Blood-brain-barrier penetration, Distribution in the kidneys, bone, spleen, and liver by 48 hrs	Oberdörster, 2004; Seabra *et al.* 2014; Merel *et al.* 2012.
Single Walled Carbon nanotubes (SWCNT)	Cellular toxicity, Endocytosis, intra-cytoplasmic localization, extensive cell death.	Chen *et al.* 2010; Schierz *et al.* 2014; Chapman *et al.* 2007; Meike *et al.* 2008; Buford *et al.* 2007.
Multi Walled Carbon nanotubes (MWCNT)	Toxicity and decrease in cell viability, Dispersion in the lung and induction of an inflammatory and fibrotic response.	Buford *et al.* 2007; Jonathan *et al.* 2012; Jessica *et al.* 2009.
Titanium Dioxide	DNA damage induction by sunlight illuminated TiO_2, Pro-inflammatory effects, pulmonary inflammation, production of reactive oxygen species (ROS)	Shvedova *et al.* 2010; Gevdeep *et al.* 2009; Ronald *et al.* 2010; Jonathan *et al.* 2012; Bermudez *et al.* 2004; Masanori *et al.* 2012; Isabella *et al.* 2012; McKinney *et al.* 2012.
Iron Oxide	Decreased MTT activity and DNA content, Adhesion to plasma membrane	Singh *et al.* 2009.
Cerium Dioxides	Size-dependent internalization of the particle, Decreased MTT activity and DNA content, production of reactive oxygen species (ROS)	Hawthorne *et al.* 2014; Flemming *et al.* 2011.
Copper Nanoparticles	Target organs of copper nanoparticles: kidney, spleen, and liver	Shi *et al.* 2014; Chang *et al.* 2012; Donaldson *et al.* 2002.
Gold Nanoparticles	Slight decrease in cell metabolic activity and/or proliferation induced by water-soluble gold nanoparticles.	Unrine *et al.* 2012; Jin *et al.* 2012; Khan *et al.* 2014.
Quantum Dots	Penetration of the stratum corneum barrier localization of QD in the underlying epidermal and dermal layers. CDSE-Decrease in MTT viability after treatment with uncoated UV irradiated or chemically oxidized CdSe QD.	Werlin *et al.*2010; Tarl *et al.* 2012.

2.3 Environmental Risk

The sources, fate, transport and toxicity of engineered nanomaterials have been a major focus of environmental health and safety research over the past decade (Lewicka, 2011). The fundamental properties concerning the environmental fate of nanomaterials are not well understood as there are less available studies (European Commission, 2004). The increasing use and production of nano based materials leads to the environmental exposure, including the traditional exposure routes for assessment of conventional chemicals, for example production wastes (liquid, solid, airborne), release from products during the product life and during the waste cycle (Dionysion, 2004). Although there are many different kinds of nanomaterial, concerns have mainly been raised about free nanoparticles. Free nanoparticles could either get into the environment through direct outlet to the environment or through the degradation of nanomaterial and can remain in the environment for the extended period of time (Howard and Debra, 2005).

2.3.1 Toxicity through environmental exposure

Environmental nanotoxicology emphasizes ecological interactions at population, community, and ecosystem levels. Eco-nanotoxicology powerfully links exposure and engineered nanomaterial's (ENM) chemical properties, biochemical mechanisms and the ecological and physical processes that regulate ecosystem-level impacts and ecosystem services **(**Martin, 2008; Holden *et al.* 2013). Uncertainties in health, ecology and the environment effects associated with exposure to engineered nanomaterial raise questions about potential risks from the exposures. However, the health concerns focus on respiratory health; epidemiological studies show clear effects of ultrafine particles on respiratory illness such as inflammation, coughing, wheezing etc., (Handy, 2007; Donaldson and Seaton, 2008). Nanoparticles such as titanium dioxide, zinc oxide and silver, consumer products such as cosmetics, creams and detergents, is a key source and discharges assumed to increase with the development of nanotechnology (Danail *et al.* 2012). Environmental technologies using nanotechnology lead to direct interactions of intentionally produced nanomaterial with chemically complex mixtures present within a variety of environmental media such as soil, water, ambient air, and combustion emissions (Helinor *et al.* 2012). The health effects associated with these interactions are unknown. There is need to assess the health and environmental risks associated with environmental applications of nanotechnology (Tsuji *et al.* 2006). Nanoparticles exposure to the environment is interrelated, depicts in fig.3. Life cycle assessment is necessary to study the interaction and exposure of nanoparticle in the environment.

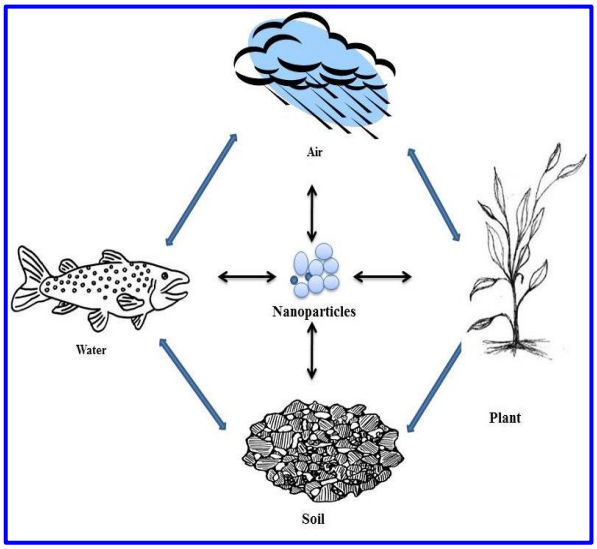

Fig. 3: Nanoparticle Exposure in the environment.

The main routes through which the nanomaterial exposes to environment are:

A) Soil

Soil is characterized by the presence of terrestrial ecosystems, the largest component contributing to the biodiversity. The interaction of nanomaterial with soil is of highly critical in nature due to the ultrafine and extremely small scale dimensions of nanomaterial (Werlin *et al.* 2010). The behaviour of nanomaterial as toxicants *via* their interactions with soil is quiet tough toanalysed because of highly diverse nature of soil particles in many different chemical and physical forms. The interactions of nanoparticles is different and unpredictable in different soil textures such as that of soil media, soil organic matter, soil solutions and soil pre-existing wastes (Peralta-Videa *et al.* 2010). Nanomaterial released to soil is likely to vary depending upon the physical and chemical characteristics of the nanomaterial. The nanosized particles tend to sorb to sediment and soil particles and are immobilized due to their high surface area to mass ratio. The strength of the sorption of any intentionally produced nanoparticle to soil will be dependent on its size, chemistry, applied particle surface treatment, and the conditions under which it is applied (Unrine *et al.* 2012). No studies have been published investigating the sorption of nanomaterial to soil and sediment particles in the water column. Various soil factors such as pH, ionic strength, zeta potential and soil texture play key roles in dictating the eventual fate of the nanoparticles being released as wastes in a particular kind of habitat. Although little is known about the biodegradation of nanomaterial, which may result in changes in their physical structure or surface characteristics, and the majority of nanomaterials are not expected to biodegrade, bioaccumulation is an essential characteristic of nanomaterial to explore.

B) Air

The amount of nanoparticles in the air can be surprisingly similar in urban and rural areas, with as much as 106-108 np/L (nanoparticles per liter) of air depending on conditions (Balbus *et al.* 2007; O'Brein, 2008). In rural areas, nanoparticles generally originate from the oxidation of volatile compounds ofbiogenic or anthropogenic origin, including secondary organic aerosols. In urban areas, the primary sources of these particles are diesel engines or cars with defective or cold catalytic converters.Several processes influence the fate of airborne nanomaterial added to their initial dimensional and chemical characteristics, the length of time the particles remain airborne, the nature of their interaction with other airborne particles or molecules, and the distance that they may travel prior to removal (Nel, 2005). Airborne particles are classified by size and behaviour into three groups or modes: the coagulation mode (diameters <80 nm), the accumulation mode (diameters >80 nm and <2 μm), and the coarse mode (diameters >2 μm). Particles in the coagulation mode are short-lived because they rapidly coagulate to form larger particles. Particles in the coarse mode are subject to gravitational settling. Nanoparticles can travel great distances in air by Brownian diffusion and are respirable and can depositin the alveolar regions of the lung and from there it can disperse to the other part of the body.

C) Water

The interactions of nanoparticles with water are the key to evaluate the aquatic nanotoxicity of the nanomaterial. Another route of exposure to the environment is from wastewater overflow or if there is an outlet from the wastewater treatment plant where nanoparticles are not effectively held back or degraded. Additional routes of environmental exposure are spills from production, transport, and disposal of nanomaterial or its products (Flemming *et al.* 2011). While many of the potential routes of exposure are uncertain, which need confirmation, the direct application of nanoparticles, such as nano zero valent iron (NZVI) for remediation of polluted areas or groundwater is one route of exposure that will certainly lead to environmental exposure. Although, remediation with the help of free nanoparticles is one of the most promising environmental nanotechnologies, it might also be the one raising the most concerns. The Royal society and The Royal Academy of Engineering recommend that the use of free nanoparticles in environmental applications such as remediation should be prohibited until it has been shown that the benefits outweigh the risks. The most prominent way nanoparticles enter the environment is as a by-product of industrial production, where they can be transferred as industrial waste, through either the air or fluid waste streams. Other sources of nano pollution are consumer products, biological excretion, and destruction of nanoparticle containing infrastructure.

2.3.2 Nano-Ecotoxicological concerns

Nanomaterials affect aquatic and terrestrial organisms differently than larger particle. Furthermore, use of nanomaterials in the environment result in novel byproducts that also pose risks. Based on analogy to physico-chemical properties of larger molecules of the same material, it is possible to estimate the tendency of nanomaterial to cross cell membranes and bio-accumulate (Hawthorne *et al.* 2014). Though, current studies have been limited to a very small number of nanomaterials and target organisms.

A) Aquatic ecosystem effects

Studies have been conducted on a limited number of nanoscale materials, and on a limited number of aquatic species. There has been no chronic or full life-cycle studies reported till yet.In aquatic ecosystems, nanoparticles generally referred as colloids comprises of organic materials like fulvic and humic acids form after the degradation of various natural complexes, proteins and peptides as a result of breakdown of dead organic matters and many inorganic species such as oxides of manganese and hydrous iron. An important aspect of the engineered nanomaterial's is their tendency to get agglomerated and aggregate, when agglomerates, particles are held together by relatively weak forces, including Vander-Waals forces, electrostatic forces and surface tension. Nanoparticles also form a group of strongly associated particles that cannot easily be re-dispersed by mechanical means, and in this case the collection is known as an aggregate (Schierz *et al.* 2014). They form aggregates which are random in nature and enter the food chain through aquatic organisms. They persist more in the sea water and this tendency further results in exhibition of novel effects as the behaviour of aggregated complexes will be significantly different from those of the individual nanoparticles. For example, Oberdorster *et al.* (2004) studied effects of fullerenes in the brain of juvenile largemouth bass and concluded that C60 fullerenes induce oxidative stress, based on their observations that (a) there was a trend for reduced lipid per-oxidation in the liver and gill, (b) significant lipid per-oxidation was found in brains and (c) the metabolic enzyme glutathione s-transferease (GST) was marginally depleted in the gill. Toxicity studies and structure-activity relationship predictions for carbon black and suspended clay particles suggest that some suspended natural nano-sized particles in the aquatic environment have low toxicity to aquatic organisms, with effects thresholds ranging from tens to thousands of parts per million (Merel and Richard, 2012).

B) Terrestrial ecosystem effects

To date, very few studies have been conducted to assess potential toxicity of nanomaterial's to ecological terrestrial test species such as plants, wildlife, soil invertebrates and soil microorganisms (Judy *et al.* 2011). The same properties of nanomaterial's that regulate uptake in aquatic organisms limit uptake of nanoparticles by plant roots by reducing passive transport at lower molecular weight and size or transport through plant leaves and stomata (Lin and Xing, 2008). Species tested included commercially important species used in ecological risk assessments of pesticides: corn (*Zea mays*), cucumber (*Cucumis sativus*), soybean (*Glycine max*), cabbage (*Brassica oleracea*) and carrot (*Daucus corota*). Fundamentally, ability to infer the toxicity information from conventional substances to nanomaterial's will require thorough knowledge about uptake, distribution and excretion rates as well as modes of toxic action (Dietze and Herth, 2011).

3. BIODEGRADABILITY, BIOAVAILABILITY AND BIOACCUMULATION OF NANOMATERIAL

In addition to the impact of various nanoparticles within the domains of biodiversity on the earth, the final phenomenon of biodegradation, bioaccumulation and biopersistance should be given a fair consideration while discussing about the toxic effects (Shi *et al.* 2014). The potential for and possible mechanisms of biodegradation of nano-sized particles have just begun to be investigated. Many of the nanomaterials in current use are composed of inherently non-biodegradable inorganic chemicals, such as ceramics, metals and metal oxides, and are not expected to biodegrade (Lioy *et al.* 2010). Researchers at Rice University's Center for Biological and Environmental Nanotechnology have shown that nanomaterial can accumulate in living things over time, with ever-increasing concentrations in microbes, in the worms that eat the microbes and in animals higher up the food chain. Bacteria and living cells can take up nano-sized particles, providing the basis for potential bioaccumulation in the food chain. Nanoparticles can easily enter to the food chain and can cause severe harm to human and environment (Klaine *et al.* 2008). The potential for biodegradation will depend strongly on the chemical and physical nature of the particle. Contamination of the human food chain with nanomaterials will depend partly on environmental quality and whether or not materials contaminate agricultural land, and also on the use of certain nanoparticles in farming (Handy, 2007; Chen *et al.* 2010). Environmental fate processes may be too slow for effective removal of persistent nanomaterials before they can be taken up by an organism.

In a study, the researchers examined how well existing methods of water purification would remove nanoparticles, specifically metal oxides, from commercial drinking water and concluded that removal of nanomaterial by coagulation, flocculation, and sedimentation processes was comparatively difficult and if they are difficult to remove from water using current industrial purification techniques it stands to reason that their introduction to natural water sources could pose a serious problem to both health and the environment (Boczkowski and Hoet, 2010). Earlier studies in 2002 by Rice University's CBEN (Centre for Biological and Environmental Nanotechnology) showed that nanoparticles accumulated in the bodies of lab animals and other studies showed fullerenes travel freely through soil and could be absorbed by earthworms. This is a potential link up the food chain to humans and presents one of the possible dangers of nanotechnology. Other nanoparticles have also been shown to have adverse effects like a research revealed *cadmium selenide* (CdS) nanoparticles, also called quantum dots, can cause cadmium poisoning in humans (Werlin *et al.* 2010). Another study showed gold nanoparticles might move through a mother's placenta to the foetus. Determination of toxicity of nanomaterial in different stages of food chains must be surveyed and estimated in order to obtain a more appropriate picture of the effects of the nanoparticulates on environment as well as human health.

4. RISK ASSESSMENT

Risk assessment is the evaluation of scientific information on the hazardous properties of a variety of agents, the dose-response relationship and the extent of exposure of humans and environmental targets (Moore, 2007). To understand the risks of nanomaterial to animals and humans, it is important to grasp some basic facts about nanomaterial (i) the risks of nanomaterial vary according to the route of exposure, such as dermal, oral, respiratory and intravenous, (ii) as there is tremendous diversity among nanomaterial, it is not possible to make any generalizations about the safety of all nanomaterial; one must consider each type of material separately, (iii) the risks of exposure to manufactured nanomaterial may be different from the risks of exposure to the naturally occurring nanoscale materials, since humans have had millions of years of evolution to adapt to natural exposures and (iv) the size, shape and physico-chemical properties of nanomaterial are very dependent on their microenvironment and change once they enter an organism (Oberdörster, 2010). Risk evaluation of nanoparticle can be defined as: "The process intended to calculate or estimate the risk to a given target organism, system or population, including the identification of attendant uncertainties, following

exposure to the particular agent, taking into account the inherent characteristic of the agent of concern as well as the characteristics of the specific target system". Risk has both objective and subjective dimensions (Service, 2006). Risk analysis is a process for controlling situations where an organism, system, or population could be exposed to a hazard. The risk analysis process consists of three components: risk assessment, risk management and risk communication (WHO, 2004; Jo, 2008). Risk assessment is thus a key part of risk analysis (Danail *et al.* 2012). The Traditional risk assessment methodology comprises the following stages:

A) Exposure assessment

Exposure assessments must aim to summarize, both quantitatively and qualitatively, information on the duration, frequency, concentration and material of exposure of humans or the environment (Helinor *et al.* 2012). An exposure assessment aims to understand the amount of the material to which consumers or the environment is exposed. Greater information on human exposure levels in different scenarios (occupational and consumer) to inform risk assessment; this will require development and validation of measurement strategies and exposure scenarios. Methods and standards for dustiness testing should be developed that are tailored for manufactured nanomaterial; they should include determination of size distribution and agglomeration state of the released particles (Francisco *et al.* 2010). Such information could be included in material safety data sheets for improved exposure risk assessment**.**

B) Hazard Identification

To understand what are the adverse health and environmental effects associated with particular nanoparticles (Service, 2004).

C) Hazard Characterization

To determine the amount of nanomaterial needed to provoke a response (the dose–response function). Systematic studies on how particle size, physico-chemical parameters and fictionalization of ENP affect toxicity (Holsapple *et al.* 2005). This would allow effective comparative hazard assessments to be carried out.

D) Risk Characterization

The fact that smaller a material, the greater is its toxicity is not always true and needs a fresh consideration. In this sense, nanomaterials are just like ordinary chemicals that are sometimes harmful depending on their usage and concentration while at other times, they are fine in terms of their utility (Service, 2008).

Since the risks of human exposure to nanomaterial have not been well studied at this time, understanding and predicting risks is the most significant challenge for risk minimization.

5. GOVERNING BODY

Internationally harmonized standards and methods are necessary for the evaluation of environmental, health and safety risks (Stone *et al.* 2014). The OECD (Organization for Economic Co-operation and Development), the standardization bodies and the European Committee for Standardization (CEN) have established working groups and technical committees that play a key role in the development of measurement standards and formally recognized test methods and guidelines for nanomaterials (Thomas and Sayre, 2005). In 2006, the OECD established the Working Party on Manufactured Nanomaterial's (WPMN), to promote international co-operation in the health, safety and environmental issues of manufactured nanomaterials. It is the main forum for international co-operation in this area for the development of test methods needed for the proper implementation of regulation.

The supreme comprehensive horizontal piece of legislation relevant to nanomaterials is the EU chemicals legislation, REACH (Registration, Evaluation, Authorization and Restriction of Chemicals). Concerns that have been expressed about REACH relate to its applicability for the chemical safety assessment of nanomaterials because of the lack of knowledge about their physico-chemical features and effects on human health and the environment (The Royal Society and the Royal Academy of Engineering (UK), 2004). In 2013, the European Parliament and the Council have adopted the new Cosmetic Products Regulation, which will enter into force and which introduces various provisions specific to nanomaterial. These provisions include a notification obligation for manufacturers about the presence of nanomaterial's in cosmetics not subject to prior authorization; a possibility for the Commission to request a safety assessment for such materials by the Scientific Committee for Consumer Safety: and a labeling requirement for nanomaterial ingredients. This means that in the list of ingredients the names of such substances shall be followed by the word 'nano' in brackets (Steffen *et al.* 2008). The National Nanotechnology Initiative (NNI) supports a broad range of research and development including fundamental research on the unique phenomena and processes that occur at the nano scale, the design and discovery of new nanoscale materials, and the development of nanotechnology-based devices and systems. Twenty-four federal agencies currently participate in the NNI, eleven of which have budgets dedicated to nanotechnology research and

development. The other thirteen agencies have made nanotechnology relevant to their missions or regulatory roles. Nine federal agencies are investing in implications research including the National Science Foundation, the National Institutes of Health, the National Institute of Occupational Health and Safety, and the Environmental Protection Agency. The Organization for Economic Cooperation and Development (OECD) is currently engaging the topic of the implications of engineered nanomaterial's among its members under the auspices of the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology (Chemicals Committee) (US Environmental Protection Agency, 2007). The OECD Chemicals Committee has identified this international forum for ensuring global cooperation, coordination and communication between member countries, nonmembers, industry and NGOs on nanotechnology issues.

6. SOCIETAL AND ETHICAL IMPLICATION OF NANOTECHNOLOGY

Roco and Brainbridge of the National Nanotechnology Initiative stated in 2001: "Over the next 10-20 years, nanotechnology will fundamentally transform science, technology and society". The public reaction to nanotechnology so far has been mixed. While there have not been many well-organized protests against nanotechnology, some environmental groups have raised concerns (Cobb and Macoubrie, 2004). Nanotechnology raises many ethical and social issues that are associated with many emerging technologies, such as questions concerning risks to human beings and the environment and access to the technology and several new questions, such as the use of nanotechnology to enhance human traits (Etzkowitz, 2001). As nanotechnology is an emerging field and most of its applications are still speculative, there is much debate about what positive and negative effects that nanotechnology might have (Papov, 2004). The implication for nano science and nanotechnology to the society will go beyond the boundaries of the science itself (Burgi and Pradeep, 2006). Renowned science fiction author Asimov said that "The Saddest aspect of life right now is that science gathers knowledge faster than society gathers wisdom". As the APEC Centre for Technology Foresight observes, If nanotechnology is going to revolutionize manufacturing, health care, energy supply, communications and probably defence, then it will transform labour and the workplace, the medical system, the transportation and power infrastructures and the military. None of these latter will be changed without significant social disruption.

There is an urgent need to regulate some of the aspects of nanotech products. Nanotechnology presents a wide range of problems and opportunities, not just diverse issues, but different kinds of issues (O'Brien and Cummins, 2008). An important aim of ethical investigation is to anticipate ethical problems – preventable harms, conflicts about justice and fairness, and issues concerning respect for persons likely to arise from specific nano initiatives. A second important aim is to substitute sensitivity to ethical issues and responsibilities at every level of decision making by both technical and policy people (Moor and Weckert, 2004). These issues must be addressed by more than one kind of organization, based on more than one system of ethics. Guardian ethics, embodying force and caution, will be necessary to avoid the worst risks and dangers of nanotechnology (Thomas and Sayre, 2005). Commercial ethics, designed to maximize profit, will be most effective in funding development, solving problems and building markets. Information ethics are well suited for situations that allow unlimited benefit from unlimited copying; the full potential of almost-free nanotech-based manufacturing cannot be achieved without them (Hansen *et al.* 2008). As a consequence, we must consider about the ethical implications of the use of nanomaterial's and the different pros and cons associated with it. This is the chief reason for the increasing and stimulating impetus being received by nanotoxicology in different countries of the world. The broadness in scope presents difficulties for understanding the legal and ethical implications of nanotechnology because nanotechnology may represent a collection of technologies, each have different characteristics and applications (Zhou, 2003; Abbott and Maynard, 2010). While anticipating all the ethical issues arising from nanotechnology and its application is difficult, some ethical issues are so commonplace in any emerging technology that we can safely assume that we will encounter the same issues for nanotechnology (Roco, 2009). Such areas include environment and safety, equity, and potential conflict of interest arising from the interactions among government, industries, universities and intellectual property ownership. Issues in nanoethics would include how to safeguard privacy in a world with nano-snooping devices, to what extent the manipulation of human beings should be permitted, and how to minimize the risk of runaway nanobots (Etzkowitz, 2001).

7. CONCLUSION

Nanotechnology is a "double-edge sword", "the same property that makes nanoparticle useful for new applications are also the properties that can increase their harmfulness". Almost without exception, every single study of nanoparticle toxicology issues a warning to the exposure to all the various nanoparticles until more conclusive studies can be made. Additional research focused on the physicochemical properties of nanomaterial and their

potential impact on humans and the environment will be critical to the responsible development of nanotechnology. Particular care must be taken in nanomedicine, since in this area is where greater exposure would be present.There is a growing global debate on the ethical, legal and social aspects of nanotechnology, in particular the potential risks to human health and the environment posed by engineered nanomaterial. Nanotechnology is still mainly a solution looking for problems to solve, including sustainable development issues. Although nanotechnology carries great promise, unwise or malicious use could seriously threaten the survival of the human race. The importance of nanotechnology to the economy and to our future wellbeing is beyond debate, but its potential adverse impacts need to be studied along the same lines. A discipline of nanotoxicology would make an important contribution to the development of a sustainable and safe nanotechnology.

ACKNOWLEDGMENT

The Author acknowledges University Grant Commission-Maulana Azad National Fellowship (UGC-MANF) for providing the fellowship.

FUNDING

This research received grant from UGC-MANF

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

COPYRIGHT

REFERENCES

Abbott, L. C. and Maynard, A. D., Exposure assessment approaches for engineered nanomaterials. *Risk Anal*, 30(11), 1634-44(2010). doi: 10.1111/j.1539-6924.2010.01446.x

Abdelhalim, M. A. K., Exposure to gold nanoparticles produces cardiac tissue damage that depends on the size and duration of exposure, Lipids in Health and Disease, (2011). doi: 10.1186/1476-511X-10-205

Ajayan, P. M. and Zhou, O. Z., Applications of Carbon Nanotubes, *Topics Appl. Phys*. 80, 391–425(2001). doi:10.1007/3-540-39947-x_14

Aleksandr, B. S., Vincent, A. H., Gert, R., Kensei, E., Steve, H., Michael T. P., Iseult, L., Wei-En-Fu., Thomas, P. J. L. and Andreas, F. T., Nanoscale reference materials for environmental, health and safety measurements: needs, gaps and opportunities, Nanotozicology, 1325-1337(2012). doi:10.3109/17435390.2012.739664.

Amy, K. M. and Kent, E. P., Health effects of inhaled engineered and incidental nanoparticles, *Critical Reviews in Toxicology*, 39(8), 629-658(2009). doi:10.1080/10408440903133788

Bakand, S. Hayes, A. and Dechsakulthorn, F., Nanoparticles: a review of particle toxicology following inhalation exposure, *Inhalation Toxicology*, 24(2), 125–135(2012). doi: 10.3109/08958378.2010.642021.

Balbus, J. M., Maynard, A. D., Colvin, V. L., Castranova, V., Daston, G. P., Dension, R. A., Dreher, K. L., Goering, P. L., Goldberg, A. M., Kulinowski, K. M., Monteiro-Riviere, N. A., Oberdorster, G., Omenn, G. S., Pinkerton, K. E., Ramos, K. S., Rest, K. M., Sass, J. B., Silbergeld, E. K. and Wong, B. A., Hazard assessment for nanoparticles: Report from an interdisciplinary workshop, *Environmental Health Perspectives*, 115(11), 1654-1659(2007). doi: 10.1289/ehp.10327

Bermudez, E., Mangum, J. B., Wong, B. A., Asgharian, B., Hext, P. M., Warheit, D. B. and Everitt, J. I., Pulmonary responses of mice, rats and hamsters to subchronic inhalation of ultrafine titanium dioxide particles, *Toxicological Sciences*, 77, 347 – 357(2004). doi:10.1093/toxsci/kfh019

Bernd, N. and Thomas, D. B., Occurrence, behaviour and effects of nanoparticles in the environment, *Environmental Pollution*, 150(1), 5-22(2007). doi:10.1016/j.envpol.2007.06.006

Besley, J., Current research on public perceptions of nanotechnology, *Emerging Health Threats J.*, 3, 8(2010). doi:10.3134/ehtj.10.164

Bleckmann, C. A., Cellular interaction of different forms of aluminium nanoparticles in rat alveolar macrophages, *J. Phy. Chem*., B, 111(25), 7353-7359(2007). doi: 10.1021/jp068938n

Boczkowski, J. and Hoet, P., What's new in nanotoxicology? Implications for public health from a brief review of the 2008 literature, *Nanotoxicology*, 4(1),1-14(2010). doi:10.3109/17435390903428844

Buford, C., Hamilton, R. F. and Holian, A., A comparison of dispersing media for various engineered carbon nanoparticles, *Particle and Fibre Toxicology*, 4(6), (2007). doi:10.1186/1743-8977-4-6

Burgi, R. J. and Pradeep, T., Societal implications of nanoscience and nanotechnology in developing countries, *Current Science*, 90(5), 10, 645(2006). doi:10.1007/s11051-004-2336-5

Chang, Y. N., Zhang, M., Xia, L., Zhang, J. and Xing, G., The Toxic Effects and Mechanisms of CuO and ZnO Nanoparticles, *Materials*, 5, 2850-2871(2012). doi:10.3390/ma5122850.

Chapman, R., Cardiovascular effects of pulmonary exposure to single-wall carbon nanotubes, *Environmental Health Perspectives*, 115(3), 6(2007).

Chen, R., Ratnikova, T. A., Stone, M. B., Lin, S., Lard, M., Huang, G., Hudson, J. S. and Ke, P, U., Differential uptake of carbon nanoparticles by plant and mammalian cells, *Small.*, 6(5), 612–617(2010). doi:10.1002/smll.200901911

Chidambaram, M. and Krishnasamy, K., Nanotoxicology: Toxicity of engineered nanoparticles and approaches to produce safer nanotherapeutics, *Int. J. Pharm. Sci.*, 2, 4, 117-122(2012).

Clift, M. J., Gehr, P. and Rutishauser, B. R., Nanotoxicology: A perspective and discussion of whether or not in vitro testing is a valid alternative, *Arch. Toxicol.*, 85, 723–731, (2011). doi:10.1007/s00204-010-0560-6.

Cobb, M. D. and Macoubrie, J., Public perception about Nanotechnology: Risks, benefits and trust, *J. Nanopart. Res*., 6, 395–405(2004). doi:10.1007/s11051-004-3394-4

Colvin, V., The potential environmental impact of engineered nanomaterial's, *Nat. Biotechnol.*, 21(10); 1166-1170(2003). doi:10.1038/nbt875

Colvin, V., Responsible nanotechnology, *Looking beyond the good news*, 1-4(2008).

Danail, R. H., Alex, Z., Christy, F. and Panagiotis, I., (2012) A weight of evidence approach for hazard screening of engineered nanomaterial's. Nanotoxicology. doi:10.3109/17435390.2012.750695

Danail, R. H., Stefania, G., Andrea, C. and Antonio, M., Risk assessment of engineered nanomaterial's: A review of available data and approaches from a regulatory perspective. *Nanotoxicology*, 6(8), 880-898(2012). doi:10.3109/17435390.2011.626534

Das, T. K. and Prusty, S., Recent advances in applications of graphene, *Int. J. Chemical Sci. Appl*., 4(1), 39-55(2013). doi: 10.1039/c5py00777a

Dawson, K. A., Anna, S. and Iseult, L., Nanotoxicology, Nanoparticles reconstruct lipids; *Nature's Nanotech*., (2008). doi:10.1038/nnano.426

Deguchi, S. H., Koki, M. and Sada-atsuYamazaki, T., Stabilization of C60 nanoparticles by protein adsorption and its implications for toxicity studies, *Chemical Research in Toxicology*, 20(6), 4(2007). doi: 10.1021/tx6003198

DeJong, W. H. and Borm, P. J., Drug delivery and nanoparticles: Applications and hazards. *Int. J. Nanomedicine*., 3(2), 133-49(2008).

Dietze, K. J. and Herth, S., Plant nanotoxicology. *Trends in Plant Science*, 16(11), 82–589(2011). doi: 10.1016/j.tplants.2011.08.003

Dionysion, D. D., Environmental Application and Implication of Nanotechnology and Nanomaterial. *J. Environ. Eng.*, 723-724(2004). doi.org/10.1061/(ASCE)0733-9372(2004)130:7(723)

Dobrovolskaia, M. A. and McNeil, S. E., Immunological properties of engineered nanomaterial's. Nat Nanotechnol, 2(8):469-78(2007). doi:10.1038/nnano.2007.223

Donaldson, K., Nanotoxicology. Occupational and Environmental Medicine, 61(9), 727–728(2004). doi:10.1136/oem.2004.013243

Donaldson, K., Mills, N., Newby, D, E., MacNee, W. and Stone, V., Toxicology of Nanoparticles in Environmental Air Pollution, *Nanotechnologies for the Life Sciences*, (2007). doi: 10.1002/9783527610419.ntls0059

Donaldson, K. and Seaton, A., A short history of the toxicology of inhaled particles, Particle and Fibre Toxicology, 913, (2008). doi:10.1186/1743-8977-9-13

Donaldson, K., Stone, V., Clouter, A. and Renwick, L., Ultrafine Particles, *Occupational and Environmental Medicine*, 58(3), 211–216(2001). doi:10.1136/oem.58.3.211

Donaldson, K. and Tran, C. L., Inflammation caused by particles and fibers, *Inhalation Toxicology*, 14(1), 5–27(2002). doi:10.1080/089583701753338613

Etzkowitz, H., Nano-science and society: Finding a social basis for science policy, *In: Societal Implications of Nanoscience and Nanotechnology*, ed. By Roco, M. C., Bainbridge, W. S., Kluwer, Dordrecht, 121–128(2001).

Fischer, H. C., Chan, W. C., Nanotoxicity: The growing need for in vivo study, *Curr. Opin. Biotechnol*, 18(6), 565-71(2007). doi:10.1016/j.copbio.2007.11.008

Flemming, R., Exposure, Health and ecological effects review of engineered nanoscale cerium and cerium oxide associated with its use as a fuel additive. *Critical Reviews in Toxicology*, 41(3), 213-229(2011). doi: 10.3109/10408444.2010.529105

Francisco, B., Manuel, A., Jone, U. and Jesus, S., Reported nanosafety practices in research laboratories worldwide. *Nature's Nanotech*., (2010). doi:10.1038/nnano.

Garnett, M. C. and Kallinteri, P., Nanomedicines and nanotoxicology: some physiological principles. *Occupational Medicine*, 56, 307–311(2006). doi:10.1093/occmed/kql052.

Gevdeep, B., Nanoparticles can cause DNA damage across a cellular barrier, 313(2009). doi:10.1038/nnano.

Günter, O., Vicki, S. and Ken, D., Toxicology of nanoparticles: A historical perspective, 1(1), 2-25(2007). doi:10.1080/17435390701314761

Gupta, S, M. and Tripathi, M., A review of TiO_2 nanoparticles, *Physical Chemistry*, 56(16), 1639–1657(2011). doi: 10.1007/s11434-011-4476.

Handy, R, D. and Shaw, B, J., Toxic effects of nanoparticles and nanomaterial's: Implications for public health, risk assessment and the public perception of nanotechnology. *Health, Risk and Society*, 9(2), 125-144(2007). doi:10.1080/13698570701306807

Hansen, S. F., Michelson, E. S., Kamper, A., Borling, P., Stuer-Lauridsen, F. and Baun, A., Categorization framework to aid exposure assessment of nanomaterials in consumer products. *Ecotoxicology*, 17(5), 438-47(2008). doi: 10.1007/s10646-008-0210-4.

Hawthorne, J., De la Torre Roche, R., Xing, B., Newman, L, A., Ma, X., Majumdar, S., Gardea-Torresdey, J. and White, J, C., Particle-size dependent accumulation and trophic transfer of cerium oxide through a terrestrial food chain, *Environ. Sci. Technol*., 18, 48(22), 13102-9(2014). doi: 10.1021/es503792f.

Health Effects Institute Working Group. Diesel exhaust: a critical analysis of emissions, exposureand health effects. Special Report of the Institute's Diesel Working Group. Project on Emerging Nanotechnologies is supported by The Pew Charitable Trusts(1995).

Helinor, J., Giulio, P. and Stefano, Z., Engineered nanomaterial risk, Lessons learnt from completed nanotoxicology studies: potential solutions to current and future challenges, *Critical Reviews in Toxicology*, 43(1), 1-20(2012). doi:10.3109/10408444.2012.738187

Hirose, A., Research strategy for evaluation methods of the manufactured nanomaterial's in NIHS and importance of the chronic health effects studies. *Int. J. Nanomedicine.*, (127), 15-25(2009).

Hoet, P., Legiest, B., Geys, J. and Nemery, B., Do nanomedicines require novel safety assessments to ensure their safety for long-term human use? *Drug Saf*., 32(8), 625-36(2009). doi: 10.2165/00002018-200932080-00002

Holden, Patricia A., Roger M. Nisbet, Hunter S. Lenihan, Robert J. Miller, Gary N. Cherr, Joshua P. Schimel, and Jorge L. Gardea Torresdey, Ecological Nanotoxicology: Integrating Nanomaterial Hazard Considerations Across the Subcellular, Population, Community, and Ecosystems Levels, *Accounts of Chemical Research*(201 3). doi: 10.1021/ar300069t

Holl. M. M. B., Nanotoxicology: a personal perspective, Wiley Interdisciplinary Reviews Nanomedicine and Nanobiotechnology(2009). doi: 10.1002/wnan.27.

Holsapple, M. P., Research strategies for safety evaluation of nanomaterial's, part II: toxicological and safety evaluation of nanomaterial's, current challenges and data needs. *Toxicol. Sci.*, 88(1), 12-7(2005). doi: 10.1093/toxsci/kfi293

Howard, M. K. and Debra, L. L., Smaller is not always better: nanotechnology yields nanotoxicology, *Am. J. Physiol. Lung. Cell Mol. Physiol*., 289, L696–L697(2005). doi: 10.1152/ajplung.00277.2005

Hubbs, A. F., R. R. Mercer, S. A. Benkovic, J. Harkema, K. Sriram, D. Schwegler-Berry, M. P. Goravanahally, T. R. Nurkiewicz, V. Castranova, and L. M. Sargent. "Nanotoxicology--A Pathologist's Perspective", Toxicologic Pathology, (2011). doi:10.1177/0192623310390705

Hubert, R. and Birgit, S. K., The European commission's recommendation on the definition of nanomaterial makes an impact, *Nanotoxicology*., (2012). doi: 10.3109/17435390.2012.724724.

Isabella, D. A., Flavia, B., Comparative study of ZnO and TiO_2 nanoparticles: physicochemical characterisation and toxicological effects on human colon carcinoma cells, *Nanotoxicology*.,(2012). doi:10.3109/17435390.2012.741724

Jamiesona, T., Bakhshia, R., Petrovaa, D., Pococka R., Imanib, M. and Seifalian, A. M., Biological applications of quantum dots *Biomaterials*., 28, 4717 – 4732(2007). doi:10.1016/j.biomaterials.2007.07.014

Jessica, P. R., Mark, F. C., Arnold, R. B. and Jeanette, K., Inhaled carbon nanotubes reach the sub pleural tissue in mice, *Nature's Nanotech*., (2009). doi:10.1038/nnano.305.

Jin, S. K., Genotoxicity, acute oral and dermal toxicity, eye and dermal irritation and corrosion and skin sensitisation evaluation of silver nanoparticles, *Nanotoxicology*.,(2012). doi:10.3109/17435390.2012.676099

Joachim, C., To be or not to be nano, *Nature Materials*, 4,107(2005). doi:10.1038/nmat1319

Jonathan, G., Ananth, T. and George, D. D., DNA damage of macrophages induced by metal nanoparticulates using an air–liquid interface exposure model, *Nanotoxicology*.,(2012). doi: 10.3109/17435390.2012.682354

Jones, M. A., Gunsolus, I. L., Murphy, C. J. and Haynes, C. L., Toxicity of Engineered Nanoparticles in the Environment, *Anal. Chem.*, 85, 3036 −3049(2013). doi.org/10.1021/ac303636s

Judy, J. D., Unrine, J. M. and Bertsch, P. M., Evidence for biomagnification of gold nanoparticles within a terrestrial food chain, *Environmental Science and Technology*, 45, 776-781(2011). doi: 10.1021/es103031a

Kagan, V. E., Bayir, H., Shvedova, A. A., Nanomedicine and nanotoxicology: two sides of the same coin, *Nanomedicine*, 1(4), 313(2005). doi:10.1016/j.nano.2005.10.003

Kevin, L. and Dreher., Health and Environmental Impact of Nanotechnology: Toxicological Assessment of Manufactured Nanoparticles, *Toxicological Sciences.*, 77, 3–5(2004). doi: 10.1093/toxsci/kfh041

Kevin, W. P., Maria, P., Brij, M. M. and Stephen, M. R., Characterization of the size, shape and state of dispersion of nanoparticles for toxicological studies, 1(1), 42-51(2007). doi:10.1080/17435390701314902

Khan, A. K., Rashid, R., Murtaza, G. and Zahra, A., Gold Nanoparticles: Synthesis and Applications in Drug Delivery, *Tropical Journal of Pharmaceutical Research*, 13(7), 1169-1177(2014). doi.org/10.4314/tjpr.v13i7.23

Khara, D. G., Igor, L., Steffen, F. H., Anders, B., Environmental risk analysis for nanomaterial's: Review and evaluation of frameworks, *Nanotoxicology*, 6(2), 196-212(2012). doi:10.3109/17435390.2011.569095

Klaine, S. J., Alvarez, P. J., Batley, G. E., Fernandes, T. F., Handy, R. D. and Lyon, D. Y., Nanomaterials in the environment: behavior, fate, bioavailability and effects, *Environ. Toxicol. Chem*., 27(9), 1825-51(2008). doi: 10.1897/08-090.1

Kołodziejczak-Radzimska, A. and Jesionowski, T., Zinc oxide-From synthesis to application: A Review, *Materials.*, 7, 2833-2881(2014). doi:10.3390/ma7042833

Lewicka, Z. A. "The structure, composition, and dimensions of TiO2 and ZnO nanomaterials in commercial sunscreens", Journal of Nanoparticle Research, (2011). doi:10.1007/s11051-011-0438-4

Lin, D. and Xing, B., Root Uptake and Phytotoxicity of ZnO Nanoparticles. *Environ. Sci. Technol*., 42 (15), 5580–5585(2008). doi: 10.1021/es800422x

Linkov, I. Nanotoxicology and nanomedicine: making hard decisions, Nanomedicine: Nanotechnology, Biology, and Medicine, 200806 doi:10.1016/j.nano.2008.01.001

Lioy, P. J., Nazarenko, Y., Han, T. W., Lioy, M. J. and Mainelis, G., Nanotechnology and exposure science: what is needed to fill the research and data gaps for consumer products. *Int. J. Occup. Environ. Health*., 16(4), 378-87(2010). doi: 10.1179/107735210799160057

Logothetidis, S., Nanostructured Materials and their applications, *NanoScience and Technology.*, doi: 10.1007/978-3-642-22227-6 1.

Lonkar, S. P. and Abdala, A. A., Applications of graphene in catalysis, *Thermodyn. Catal*., 5, 2(2014). doi: 10.4172/2157-7544.1000132

Manke, A., Wang, L. and Rojanasakul, Y., Mechanisms of nanoparticle-induced oxidative stress and toxicity, *BioMed Research International.*, 942916, 15(2013). doi: 10.1155/2013/942916.

Marina, A. D., Dori, R. G. and James, L. W., Evaluation of nanoparticle immunotoxicity, *Nature's Nanotech*., (2009). doi:10.1038/nnano.175.

Marina, A. D. and Scott, E. M., Immunological properties of engineered nanomaterial's, *Nature's Nanotech*., (2007). doi: 10.1038/nnano. 223

Martin, S., Nanoecotoxicology: Environmental risks of nanomaterial's, *Nature's Nanotech*., (2008). doi:10.1038/nnano.145.

Masanori, H., Hiroko, F., Shigehisa, E. and Junko, M., Comparison of acute oxidative stress on rat lung induced by nano and fine-scale, soluble and insoluble metal oxide particles: NiO and TiO_2, *Inhalation Toxicology*, 24(7), 391-400(2012). doi: 10.3109/08958378.2012.682321.

Maxine, M., Environmental, health and safety issues: Nanoparticles in the real world, *Nature's Nanotech*., (2011). doi:10.1038/nnano.169

Maynard, A. D., Warheit, D. B. and Philbert, M. A., The new toxicology of sophisticated Materials, Nanotoxicology and Beyond, *Toxicol. Sci*., 120, S109-S129(2011). doi: 10.1093/toxsci/kfq372.

McKinney, W., Jackson, M. and Sager, T. M., Pulmonary and cardiovascular responses of rats to inhalation of a commercial antimicrobial spray containing titanium dioxide nanoparticles, *Inhalation Toxicology*., 24(7), 447-457(2012). doi: 10.3109/08958378.2012.685111.

Meike, L. S., Nozomi, N., Corrine, R. D. and Nadine, K., A pilot toxicology study of single-walled carbon nanotubes in a small sample of mice, *Nature's Nanotech*., (2008). doi:10.1038/nnano.68.

Mélanie, A., Towards a definition of inorganic nanoparticles from an environmental, health and safety perspective, *Nature's Nanotech*., (2009). doi:10.1038/nnano.242.

Merel, J. C. and Richard, D. H., C_{60} exposure induced tissue damage and gene expression alterations in the earthworm *Lumbricus rubellus*, Nanotoxicology, (2012). doi: 10.3109/17435390.2012.668569

Mitka, M., Committee calls for framework to assess the safety of nanotechnology materials, *JAMA*, 307(11), 1123-4(2012). doi: 10.1001/jama.2012.289

Moor, J. and Weckert, J., Nanoethics: Assessing the nanoscale from an ethical point of view, *Discovering the Nanoscale*, *Amsterdam: IOS Press*(2004).

Moore, R., Nanomedicine and risk: further perspectives, *Med. Device Technol*., 18(6), 28-9(2007).

Mueller, N. C., Braun, J., Bruns, J., Černík, M., Rissing, P., Rickerby, D. and Nowack, B., Application of nanoscale zero valent iron (NZVI) for groundwater remediation in Europe, *Environ. Sci. Pollut. Res.*, 19, 550–558(2012). doi: 10.1007/s11356-011-0576-3.

Nanotoxicology and in vitro studies: The need of the hour, *Toxicology and Applied Pharmacology*, doi:10.1016/j.taap.2011.11.010

National Science Foundation. Societal Implications of Nanoscience and Nanotechnology, USA National Science Foundation(2001). doi:10.1007/s11051-004-2336-5

Nel, A., Atmosphere, Air Pollution-Related Illness: *Effects of Particles. Science*, 308(5723), 804–806(2005). doi: 10.1126/science.1108752

Oberdorster, E., Manufactured nanomaterial's (Fullerenes, C60) induce oxidative stress in the brain of Juvenile Largemouth Bass, *Environmental Health Perspectives*, 112, 1058-1062(2004). doi: 10.1289/ehp.7021

Oberdörster, G., Safety assessment for nanotechnology and nanomedicine: Concepts of nanotoxicology, *J. Intern. Med*., 267(1):89-105(2010). doi: 10.1111/j.1365-2796.2009.02187.x

Oberdorster, G., Translocation of Inhaled Ultrafine Particles to the Brain. *Inhalation Toxicology*, 16(6–7):437–445(2004). doi: 10.1080/08958370490439597

Oberdorster, G., Oberdorster, E. and Oberdorster, J., Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles. *Environmental Health Perspectives*, 113(7), 823–839(2005).

Oberdorster, G. and Utell, M. J., Ultrafine particles in the urban air: To the respiratory tract and beyond? *Environmental Health Perspectives*, 110(8):A440–A441(2002).

O'Brien, N. and Cummins, E., Recent developments in nanotechnology and risk assessment strategies for addressing public and environmental health concerns, *Hum. Ecol. Risk Assess*, 14(3):568-92(2008). doi:10.1080/10807030802074261

Paul, A. S. and Fabio, S., Ethical and Scientific Issues of Nanotechnology in the workplace(2010). doi:10.1590/s1413-81232007000500030

Peralta-Videa, J. R., Zhao, L., Lopez-Moreno, M. L., De la, R. G., Hong, J. and Gardea-Torresdey, J. L., Nanomaterials and the environment: A review for the biennium 2008-2010, *J. Hazard Mater*., 186:1-15(2010). doi:10.1016/j.jhazmat.2010.11.020

Poonam, T. and Sheefali, M., In vitro methods for Nano toxicity Assessment: Advantages and Applications, *Archives of Applied Science Research*, 3 (2):389-4(2011).

Popov, V. N., Carbon nanotubes: properties and application, *Materials Science and Engineering R* 43:61–102(2004). doi:10.1016/j.mser.2003.10.001

Powell, M. C., New risk or old risk, high risk or no risk? How scientists' standpoints shape their nanotechnology risk frames, Health Risk and Society(2007). doi:10.1080/13698570701306872

Renata, B. and Harald, K., Nanoecotoxicology: Nanoparticles at large, *Nature's Nanotech.*, (2008). doi:10.1038/nnano.113.

Resnik, D. B.. "Ethical issues in clinical trials involving nanomedicine", *Contemporary Clinical Trials*, (2007). doi:10.1016/j.cct.2006.11.001

Roco., It's not just about nanotoxicology, *Nat Nanotechnol.*, 4(10):615(2009). doi:10.1038/nnano.2009.280

Roco, M. C., Broader Societal Implications of Nanotechnology, *J. Nanoparticle Research*, 5, 181-189(2003). doi:10.1023/a:1025548512438

Ronald, D. G., Pieter, B., Joke, H. and Jan, M., The changes in hazard classification and product notification procedures of the new European CLP and Cosmetics Regulations, *Clinical Toxicology*, 48(1), 28-33(2010). doi: 10.3109/15563650903376097.

Roszek, B., De Jong, W. H. and Geertsma, R. E., Nanotechnology in medical applications: state-of-the-art in materials and devices. RIVM report 265001001(2005).

Ruhung, W., Generation of toxic degradation products by sonication of Pluronic dispersants: implications for nanotoxicity testing, *Nanotoxicology*(2012). doi:10.3109/17435390.2012.736547

Sametband, M., Shweky, I., Banin, U., Mandler, D. and Almog, J., Application of nanoparticles for the enhancement of latent fingerprints, *Chem. Commun*., 1142–1144(2007). doi: 10.1039/b618966k

Schierz, A., Espinasse, B., Wiesner, M. R., Bisesi, J. H., Attwood, T. S. and Ferguson, P. L., Fate of single walled carbon nanotubes in wetland ecosystems, *Environ. Sci. Nano.*, 1, 574-583(2014). doi: 10.1039/c4en00063c

Seabra, A. B., Paula, A. J., deLima, R., Alves, O. L. and Durán, N., Nanotoxicity of graphene and graphene oxide, *Chem. Res. Toxicol.*, 27 (2), 159–168(2014). doi: 10.1021/tx400385x

Senić, Z., Bauk, S., Vitorović-Todorović, M., Pajić, N., Samolov, A. and Rajić, D., Application of TiO_2 Nanoparticles for obtaining self decontaminating smart textiles, *Scientific Technical Review*, 61(3-4) 63-72(2011).

Service, R. F., Nanotoxicology, Nanotechnology grows up, *Science*, 304(5678), 1732–1734(2004).

Service, R. F., Science policy, Priorities needed for nano-risk research and development, *Science*, 314(5796):45(2006).

Service, R. F., Science policy, Report faults U.S. strategy for nanotoxicology research, *Science*, 322(5909):1779(2008). doi: 10.1126/science.322.5909.1779a.

Sharma, H. S., Ali, S. F., Hussain, S. M. and Schlager, J. J., Influence of engineered nanoparticles from metals on the blood-brain barrier permeability, cerebral blood flow, brain edema and neurotoxicity. An experimental study in the rat and mice using biochemical and morphological approaches. *J. Nanosci Nanotechnol*., 9: 5055-5072(2009). doi:10.1166/jnn.2009.gr09

Shi, J., Peng, C., Yang, Y., Yang, J., Zhang, H., Yuan X. Chen and Hu, T., Phytotoxicity and accumulation of copper oxide nanoparticles to the Cu-tolerant plant Elsholtzia splendens. *Nanotoxicology*, 8(2), 179-188(2014). doi:10.3109/17435390.2013.766768

Shvedova, A. A., Kagan, V. E., Fadeel, B., Annu, R., Close encounters of the small kind: adverse effects of man-made materials interfacing with the nano-cosmos of biological systems, *Pharmacol Toxicol.*, 50:63-88(2010). doi: 10.1146/annurev.pharmtox.010909.105819

Singh, N., Manshian, B., Jenkins, G. J., Griffiths, S. M., Williams, P. M. and Maffeis, T. G., NanoGenotoxicology: the DNA damaging potential of engineered nanomaterials. Biomaterials; 30(23-24):3891-914(2009). doi: 10.1016/j.biomaterials.2009.04.009.

Steffen, H., Andrew, M., Anders, B. and Joel, A. T., Late lessons from early warnings for nanotechnology, *Nature's Nanotech*.(2008) doi:10.1038/nnano.1987.

Stone, V., ITS-NANO - Prioritising nanosafety research to develop a stakeholder driven intelligent testing strategy, *Particle and Fibre Toxicology*, 11:9(2014). doi:10.1186/1743-8977-11-9

Suh, W. H., Suslick, K. S., Stucky, G. D. and Suh, Y, H., Nanotechnology, nanotoxicology and neuroscience. *Prog. Neurobiol.*, 87(3):133-70(2009). doi:10.1016/j.pneurobio.2008.09.009

Susan, D.,. Knowledge gaps in risk assessment of nanosilica in food: evaluation of the dissolution and toxicity of different forms of silica, *Nanotoxicology*(2012). doi:10.3109/17435390.2012.662250

Susan, D., Petra, K., Ruud, J. B. P. and Daniëlle, P. K. L., Presence and risks of nanosilica in food products, *Nanotoxicology*, 5(3), 393-405(2011). doi:10.3109/17435390.2010.519836

Tarl, W. P., Nancy, A., Alfred, O., Jeffrey, E. and Xianfeng, C., Quantum dot penetration into viable human skin, 6(2), 173-180(2012). doi:10.3109/17435390.2011.569092

The Royal Society and the Royal Academy of Engineering (UK), Nanoscience and Nanotechnologies, *Opportunities and uncertainties*, (2004).

Thomas, K. and Sayre, P., Research strategies for safety evaluation of nanomaterial's, Part I: evaluating the human health implications of exposure to nanoscale materials, *Toxicol. Sci*., 87(2):316-21(2005). doi: 10.1093/toxsci/kfi270

Thomas, K., Research strategies for safety evaluation of nanomaterials, Part VIII: International efforts to develop risk-based safety evaluations for nanomaterials, *Toxicological Sciences*, (2006). doi: 10.1093/toxsci/kfj211

Tsuji, J. S., Research strategies for safety evaluation of nanomaterial's, part IV: risk assessment of nanoparticles, *Toxicol. Sci*., 89(1):42-50(2006). doi: 10.5487/tr.2015.31.2.157

Unfried, K., Cellular responses to nanoparticles: Target structures and mechanisms, *Nanotoxicology*, (2007). doi:10.1080/00222930701314932

Unrine, J. M., Shoults-Wilson, W. A., Zhurbick, O., Bertsch, P. M. and Tsusko, O. V., Trophic transfer of Au nanoparticles from soil along a simulated terrestrial food chain, *Environmental Science and Technology*, 46: 9753-9760(2012). doi: 10.1021/es3025325

US Environmental Protection Agency, Nanotechnology white paper, Washington, DC: Science Policy Council, *U.S. Environmental Protection Agency*(2007)..

US Occupational Hazards; Protecting Nanotech, Workers from Health risks, 1-2(2008).

USEPA (Environmental Protection Agency), (2003). www.epa.gov/tio/database.

Vicki, S. and Ken, D., Nanotoxicology: Signs of stress. *Nature's Nanotech*.,(2006). doi:10.1038/nnano.69.

Wan Yaacob, W. Z., Kamaruzaman, N. and Samsudin, A. R., Development of nano-zero valent iron for the remediation of contaminated water, *Chemical Engineering Transaction*., 28, 25-30(2012).

Wason, M. S. and Zhao, J., Cerium oxide nanoparticles: potential applications for cancer and other diseases, *Am. J. Transl. Res.*, 5(2):126-131(2013).

Werlin, J. H,, Biomagnification of cadmium selenide quantum dots in a simple experimental microbial food chain. Nature's Nanotech, (2010). doi:10.1038/nnano.251.

Yadav, B. C. and Kumar, R., Structure, properties and applications of fullerenes, *Int. J. Nanotechnol. and Appl.*, 2(1):15–24(2008)..

Zholdakova, Z. I,, Sinitsyna, O. O., Kharchevnikova, N. V., General and specific aspects of the toxic properties of nanoparticles and other chemical substances in the context of classical toxicology, Gig Sanit, (6):12-6(2008).

Zhou, W., Ethics of nanobiotechnology at the frontline, *Santa Clara Computer and High Technology, L*, (2003).

Zhu, Motao, Guangjun Nie, Huan Meng, TianXia, Andre Nel, and Yuliang Zhao, Physicochemical properties determine nanomaterial cellular uptake, Transport and Fate, *Accounts of Chemical Research*, (2013). doi: 10.1021/ar300031y