Influence of Nanotoxicity on Human Health and Environment: The Alternative Strategies

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Contents

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1 Introduction

Nanotechnology allows the manipulation and application of engineered particles or systems that have at least one dimension less than 100 nm in length (Stander and Theodore 2011). New industries in collaboration with university research departments are being formed and are finding so many investors eager to back their ideas and products. There is no doubt that governments and major industrial companies are committing significant resources for research into the expansion of nanometre scale processes, materials and products. Growing exploration of nanotechnology has resulted in the discovery of many distinctive properties of nanomaterials such as superior catalytic, optical, magnetic, mechanical and electrical properties when compared to conventional formulations of the same material (Ferrari 2005; Pattan and Kaul 2014). Nanomaterials are progressively more being used for commercial purposes and in consumer products leading to increased direct and indirect exposure in humans (Pattan and Kaul 2014). In the field of medicine, nanoparticles are purposefully injected into the human body. For drug delivery and imaging nanomaterials are often deliberately coated with biomolecules such as protein, DNA and monoclonal antibodies to aim particular cells (Lewinski et al. 2008; Nalwa 2014). The novel physicochemical properties of these engineered nanomaterials may initiate new mechanisms of injury and toxicological effects due to destructive interactions of nanomaterials with biological systems and the environment (Ray et al. 2009; Yan et al. 2015). Even though less studied than human health, there is also basis for concern regarding environmental impacts and areas such as ecotoxicology, environmental chemistry, behaviour and fate are areas of concentrated current research (Zhu et al. 2008). Nanomaterials may potentially impact the environment in three possible ways: (1) direct effect on invertebrates, micro-organisms, fish and other species; (2) interaction with other pollutants, that may transform the bioavailability of toxic compounds and nutrients; and (3) changes to non-living environmental structures (Dhawan and Sharma 2010). Understanding the environmental and human health impacts of nanomaterials is a crucial stage for the responsible development of nanotechnology and to gain full benefit of its applications. As nanotechnology matures, questions are being aroused regarding whether the products or materials of nanotechnology will provide hazards to human health or the environment and whether the manufacturing of these materials will spawn new hazards or waste streams. Considerate the environmental and human health impact of nanomaterials is a fundamental stage for the liable development nanotechnology and to gain full advantage of its applications (Yadav et al. 2014).

Alternatively, green nanoscience has been described as the progress of clean technologies to reduce possible environmental and human health risks coupled with the production and use of nanomaterials and to promote replacement of existing products with new nano-products that are further environmentally friendly all over their life cycle (Hutchison 2008). Green nanoscience is the successful integration of green chemistry and nanoscience that brings the collective approaches and methods to build up greener products, processes, and applications (Iavicoli et al. 2014).

Recently green nanoscience is booming in the developing fields of nanoelectronics, nanocomposites and thermoelectric (Marconnet et al. 2011). Therefore, green chemistry and nanoscience are promising fields that take advantage of molecular-level design and have massive potential to overcome the adverse impacts of nanoparticles and nanomaterials on health and environment (Iavicoli et al. 2014). If the global research community can take advantage of green nanoscience then we can surely look forward to the advent of safe nanotechnologies. In this review we have summarized the adverse effects of different nanoparticles to human health and environment along with alternative strategies to overcome ill impacts.

2 Nanotoxicology

Nanotoxicology and nano-risk have been drawing increasing attention of toxicologists and regulatory scientists as the manufacturing of nanomaterials increases (Dhawan and Sharma 2010). As shown in Fig. 1, a number of hazardous exposure conditions are encountered by the workers occupied in nanotechnology activities. In fact, nanomaterials may have significant, still unknown, hazards properties that can pose risks for a broad range of workers: researchers, laboratory technicians, cleaners, production workers, transportation, storage and retail workers, employees in disposal and waste facilities and potentially, emergency responders who deal with spills and disasters of nanomaterials and may be differently exposed to these potential, innovative xenobiotics (Iavicoli et al. 2014). Thus the branch of nanotoxicology deals with the study relating to the toxicity of the nano materials, as it is essential to know the toxicity of nano material before using it for a variety of applications (Gao et al. 2015a; Donaldson and Poland 2013; Haynes 2010). In addition, the effects and impacts on human health also needs to be reviewed accordingly.

The International Council on Nanotechnology (ICON) has created a database of all the publications of several nano materials along with their impact on environmental health and safety. This highlights on the exciting trends associated with the field of nanotoxicology. In addition, it is involved in proposing reliable, robust, and data-assured test protocols for nanomaterials in human and environmental risk assessment (Donaldson and Poland 2013). The utmost challenge faced in the field of nanotoxicology now-a-days is the recognition as well as the estimation of the deleterious effects of a variety of engineered nanomaterials with their dissimilar physiochemical properties, which are regularly being manufactured and launched for versatile applications (Hutchison 2008). It is not very easy to discover the exact hazard denominations of nanoparticles due to different causes, for instance, we are not specific which physico-chemical property of the nanoparticles is influencing the toxicity (Di Bona et al. 2015). The extreme changes in biological, chemical and other properties that can formulate nanotechnology applications are so exciting, however, also may value examination to determine any effects on product safety, effectiveness, or other characteristics. Moreover, currently no clear processes and regulatory guidelines on the evaluation or testing of nanoparticulate materials are available.

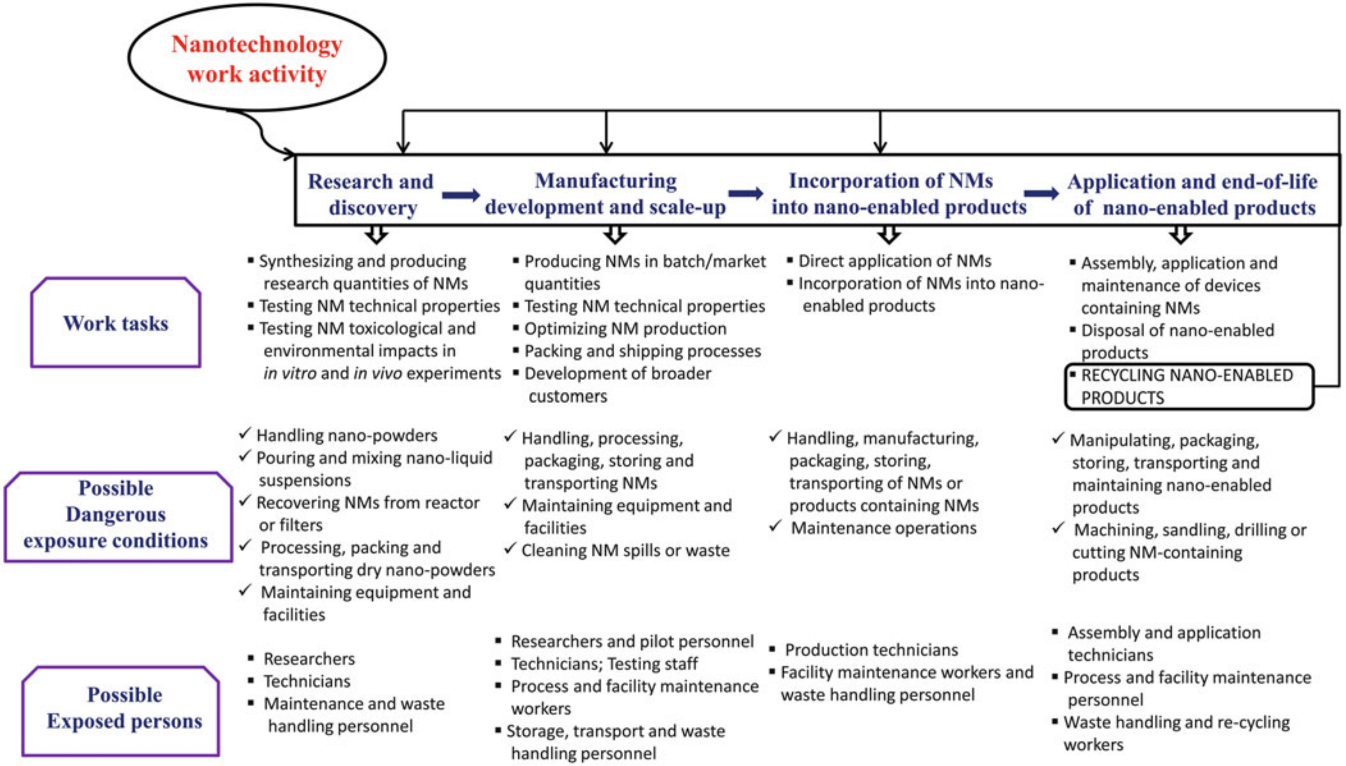

Fig. 1 Assessment of potentially hazardous exposure conditions for workers involved in nanotechnology activities (Source: Iavicoli et al. 2014)

2.1 Physicochemical Properties of Nanomaterial–Toxicity Relationship

As stated earlier, nanotechnology is a quick growing field that offers materials that have new dimensions, novel properties, and a broader array of applications but the basis of the toxicity of engineered nanoparticles is still unclear (Kumar et al. 2012). Till date, research results are more evocative than definitive and no quantitative structure–activity relationship models are existing. Physicochemical properties such as small size, specific surface area, structure, aspect ratio, morphology, solubility, chemical composition, reactivity, photochemistry, production of reactive species and surface properties (i.e. charge and coating) can be of prime importance (Yadav et al. 2014). In fact, the very similar properties that guide to the technical advantages of nanotechnology also lead to unique biological effects. For instance, size is the key feature determining the scope of uptake and toxicity of many nanomaterials, which have been shown to be size dependent (Oberdorster 2010). The dimension of nanoparticles may have vital impact on where nanoparticles end up in the human body and other organisms (Kumar et al. 2012). In humans, large inhalable nanomaterials of any composition with particle size above 2.5 μm have a tendency to deposit mostly in the nose and throat while smaller nanoparticles with particle size less than 2.5 μm can locate their way to the upper airways (Alfaro-Moreno et al. 2007). Shape and size of the nanoparticles has been shown to have a distinct effect on the biological activity. Pal and his group reported that silver nanoparticles undergo shape-dependent interaction with *E. coli* (Pal et al. 2007). In another study, Journeay et al. (2008) confirmed that water-soluble rosette nanotube structures exhibit low pulmonary toxicity due to their biologically stimulated design and self-assembled architecture. The smallest particles can make a way into deeper alveolar region and might penetrate to various parts of the respiratory tract (Kovacic and Somanathan 2009). Because of their small size, nanomaterials can possibly pass through the lungs into the bloodstream and to be taken up by cells, reaching potentially susceptible sites such as liver, spleen, kidney and heart (Sturm 2015). In case of anatase TiO_2 nanomaterial, it was revealed that modification to a fiber structure of greater than 15 μm formed a highly toxic particle that initiated an inflammatory response by alveolar macrophages and that length may be a vital determinant of nanomaterial biocompatibility (Hamilton et al. 2009). Physico-chemical characterization and their interaction with biological media are essential for widely used metal oxides and carbon nanomaterials (Landsiedel et al. 2010; Štengl et al. 2016). In one of the investigations by Schaeublin and his group, 1.5 nm sized gold nanoparticles exhibited their action on cellular processes like the charged NPs initiating cell death through apoptosis and neutral NPs leading to necrosis in HaCaT cells (Schaeublin et al. 2012). It was observed that surface charge was a key determinant of their action on cellular processes (Beddoes et al. 2015). Figure 2 illustrates a range of possible physicochemical properties of engineered nanomaterials leading to nanotoxicology.

Further, the size and shape of nanomaterials is the main factor in influencing their uptake across the gill membrane or the gastrointestinal tract (GI) of aquatic

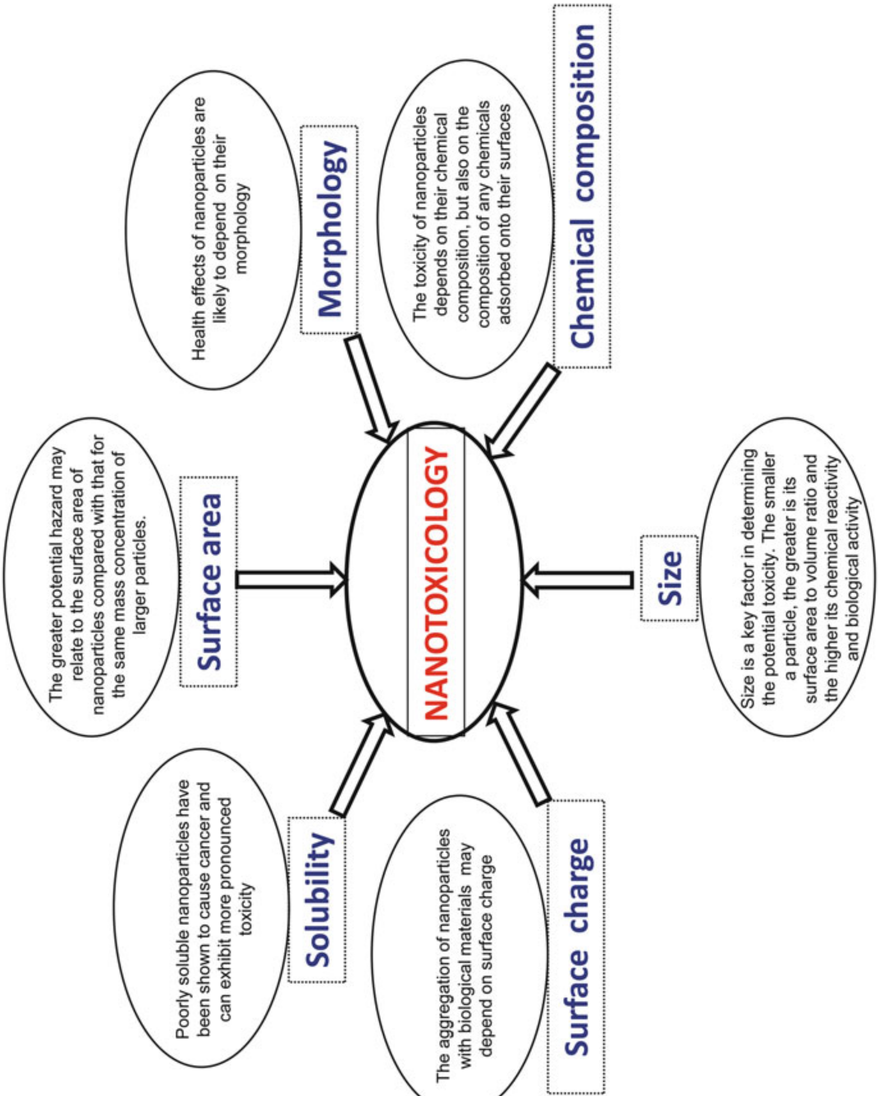

Fig. 2 Physicochemical properties of engineered nanomaterials leading to nanotoxicology

and terrestrial organisms. It has been observed that the absolute limit for passive diffusion through fish gills is about 1 nm (Batley et al. 2013). Surface charge and particle composition are also key factors for determining the uptake and toxicity of nanomaterials (Fan et al. 2015). Mineral particle stimulated apoptosis was dependent on particle size, while surface reactivity and composition were found to be most essential for the proinflammatory potential of the particles (Pattan and Kaul 2014). The aspect ratio of engineered nanoparticles along with biological persistence is likely to be an important factor for their toxicology. Fibres longer than 20 μm cannot be phagocytosed by alveolar macrophages, causing reduced clearance and accumulation. Poland and group have reported that dependent on structure, the carbon nanotubes (CNTs) perform in a similar manner to asbestos and may have an even superior biological activity and therefore is hazardous (Poland et al. 2008). Some of the reported morphologies of engineered nanoparticles have been summarized in Table 1. Therefore, nanomaterials are composed of primary

Table 1 Some of the reported morphologies of engineered nanoparticles

Morphologies of engineered nanoparticles	
 *Spherical* Generally in small crystalline particles and non-crystalline structures	 *Rod or wire* May have a series of cross sections like cubic, circular and pentagonal
 *Discotic* Thin flat plates regularly broader than 10 nm. May be a variety of shapes including hexagonal and irregular	 *Geometric solid* Usually in crystalline particles may be a array of shapes like cubic, tetrahydral and icosahedral
 *Dendritic* Comprises of nanoscale wires the dendrite may be larger than 100 nm	 *Tetrapod* Shaped by the enlargement of hexagonal phase rods from cubic seed crystals
 *Dumbell* Produced by the development of one materials only at the ends of the rod of another material	 *Tear drop* An extension of the spherical shape

and agglomerated particles that can vary in size, shape, charge, crystalline, chemical composition, surface properties and all these characteristics have been optional to influence the toxicity of nanomaterials. As a result, several efforts are made to increase the knowledge on the toxicity-determining characteristics of nanomaterials to categorize them into hazard groups in order to facilitate risk assessment (Braakhuis et al. 2014; Arts et al. 2015).

3 Potential Human Health Effects of Nanomaterials

Nanoparticles have the same dimensions as biological molecules such as proteins. Currently, exposure to nanoparticles is increased, and because of uncertainty regarding their toxic characteristics, concerns have arisen that such materials pretence novel health risks for consumers, workers, and the environment (Braakhuis et al. 2015). An extensive literature states that some of the nanoparticles may have an adverse effect and there is a cause for concern as to their effect on human health, which has largely developed out the ample literature on the health impacts of nanoparticles. This is mainly due to the several features that may contribute to the toxicity of nanomaterials. For instance, an organism's reaction to a particular nanomaterial may be related to the mass of the administered dose, or it may be related to other factors, together with the number of particles, shape, electrical charge, and coating, or a mixture of physiochemical properties (Buzea et al. 2007). Currently, there is no consensus within the scientific community on what characteristic may be the most important in elucidating this dose-response relationship for each type of nanomaterial. This lack of agreement is comprehensible, given that studies evaluating the health effects of nanomaterials show a range of findings and highlight the unfortunate generalization of responses across all types of nanomaterials.

Nanoparticles can interact with complex networks of immune cells located within and beneath epithelial surfaces and these NPs can act as allergens during the neonatal period, triggering the immune system to induce allergic inflammation in later life stages (Sly and Schüepp 2012). Detrimental cardiovascular consequences due to NPs exposure have been reported in epidemiological studies (Liou et al. 2012). Wang and their group reported that nano-cerium-element doped titanium dioxide induces apoptosis of Bel 7402 human hepatoma cells in the presence of visible light (Wang et al. 2007). Nanoparticles like zinc oxide and sunscreen titanium dioxide can cause oxidative damage to DNA in vitro and in cultured human fibroblasts (Dunford and Salinaro 1997). Inhaled ultrafine particles (UFPs) can increase access to the blood stream and can then be dispersed to other organs in the body; this has been shown for synthetically produced nanoparticles such as C^{60} fullerenes which accumulate in the liver (Hougaard et al. 2015). Even big particles outside the 'nano' range can enter the stratum corneum of human skin and get to the epidermis and occasionally the dermis and may be taken up into the lymphatic system (Smulders et al. 2015; Tinkle et al. 2003). There is a strong

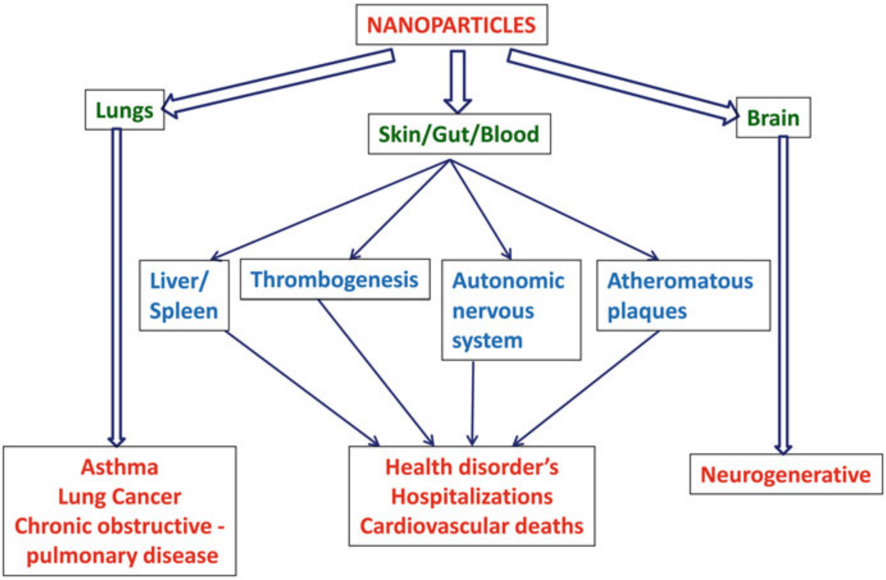

Fig. 3 Systematic health effects of nanoparticles on human body

possibility that nanoparticles can be assimilated into the body through the lungs, skin and gastrointestinal tract (Smulders et al. 2015). Additionally, several studies have been conducted in investigating the dissolution of nanoparticles in artificial body fluids such as fluids representing the environment of the stomach, blood and airways and found adverse influences (Stebounova et al. 2011; Leo et al. 2013). Figure 3 gives an illustrated picture of systematic health effects of nanoparticles on human body.

3.1 Major Modes of Exposure

There are numerous exposure scenarios depending on the particulars of manufacture, use and discarding. All through these scenarios, the levels of exposure, the population exposed, the duration of exposure and the nature of the material to which people are exposed are completely different (Civeira et al. 2015). In an industrial situation, exposure to nanomaterials can happen to workers at all phases of material life cycle. During the development of a new material, it is possible that material will be manufactured under strongly controlled conditions, usually in very little quantities. Once the material moves into commercial production, exposures can occur potentially during synthesis of the material or in downstream activities such as packaging, transport, recovery and storage (Leo et al. 2013). Nanomaterials may also be integrated into a composite material, which may be consequently re-engineered or reprocessed by cutting, finishing and sawing. Once again in

Table 2 Common exposure routes of humans to engineered nanoparticles present in consumer products

Route	Types of consumer products
Skin (Dermal)	Sunscreen (lotion)
	Skin care (lotion)
	Paints and coatings
	Sealants
	Air freshners (spray)
Lungs (inhalation)	Paints and coatings
	Skin care (spray)
	Sunscreen (spray)
	Food additives and colourings
Gastrointestinal tract	Food supplement
	Health supplements
	Food packaging

these conditions the potential for exposure exists. Release of nanomaterials into the environment is possible as waste or industrial pollution, directly into the air, soil or water systems or due to purposeful release in applications such as remediation of contaminated lands. Hence, humans may become exposed as a result of nanomaterial contamination in air, water or the food chain, or during the use of commercial products containing nanomaterials (Buzea et al. 2007). In view of human exposure for all of these scenarios, it is compulsory to think about the route of entry into the human body. Following are the some of the various human exposure routes in detail and Table 2 illustrates the common exposure routes of humans to engineered nanoparticles.

3.1.1 Skin

The significance of dermal exposure to dangerous substances continues to rise (Mackevica and Foss 2015). Detrimental effects arising from skin exposure may either happen locally within the skin or alternatively the substance may be absorbed through the skin and circulated via the bloodstream, probably causing systemic effects (Warheit and Donner 2015). Skin is the major primary defence organ in human body and directly comes into contact with many lethal agents. Skin exposure to engineered nanomaterials can also occur during the purposeful application of topical creams and other drug treatments (Hagens et al. 2007). Information on in vivo uptake of Ag nano particles due to dermal exposure are limited partly caused by the lack of appropriate analytical approaches for the determination of Ag in biological matrices, but strongly needed to enable risk assessment of skin exposure to nano silver containing products (Bianco et al. 2015; Völker et al. 2013). However, nanosilver-based dressings and surgical sutures have received approval for clinical application and good control of wound infection is attained; their dermal toxicity is still a matter of scientific dispute and worry. Ryman-Rasmussen et al. (2006) confirmed that quantum dots with various physicochemical properties could go through the intact stratum corneum barrier and get localized within the epidermal and dermal layers. Nano-titanium dioxide (TiO_2) is one of the most frequently used materials being synthesized and due to the extensive application of TiO_2 nanoparticles and their inclusion in many commercial products, the increased exposure of human beings to nanoparticles is possible. These TiO_2 particles could get through the human stratum corneum and get to epidermis and even dermis (Shakeel et al. 2016; Lademann et al. 1999). Rouse et al. (2007) demonstrated that fullerene-based peptides were capable of penetrating intact skin and mechanical stressors could make easy their traversal into the dermis. Monteiro-Riviere et al. (2005) proved that epidermal keratinocytes are able to phagocytising an array of engineered nanoparticles and setting off inflammatory responses. Intradermally taken quantum dots could penetrate subcutaneous lymphatics and regional lymph nodes (Gopee et al. 2007). It has been proved that engineered nanoparticles like quantum dots, single or multi-wall carbon nanotubes with nanoscale titania and surface coating have lethal effects on fibroblasts and epidermal keratinocytes and are competent of altering their gene or protein expression (Haliullin et al. 2015).

3.1.2 Respiratory Tract

The respiratory system provides a major doorway for ambient particulate materials and the diseases resulting from airborne particle materials like asbestos, quartz, and carbon have long been keenly investigated in clinical and environmental medicine (Pelclova et al. 2016). In recent times, the pathogenic effects and pathology of inhaled engineered nanoparticles are seized the attention of researchers. Nanoparticles deposition in the pulmonary system differs considerably according to the granulometry of nanoparticles and their airborne behaviour (Ma et al. 2015). Particle granulometry has a foremost impact on the pulmonary deposition site (Witschger and Fabries 2005; Ma et al. 2015). In many nanoparticle production processes, the granulometry can also vary significantly according to the stage of production. These differences in nanoparticle distribution in the lungs may have major consequences on the health effects of inhaled nanoparticle particles and the elimination mechanisms involved (Zhang et al. 2005; Ma et al. 2015). In the alveolar region, the macrophages will take up the insoluble particles by phagocytosis. However, the effectiveness of phagocytosis is badly dependent on nanoparticle shape and size. Several studies have proved that unagglomerated polyethylene nanoparticles of general nano scale size deposited in the alveolar region are not phagocyted efficiently by the macrophages (Keller et al. 2014). However, the macrophages are especially efficient for coarser particles in the one to three micrometre range. After the deposition of nanoparticles in the alveolar region they are absorbed across the lung epithelium, later they enter the blood and lymph to reach cells in the lymph nodes bone marrow, spleen and heart (Nurkiewicz et al. 2006). Further targets after translocation include the sensory nerve endings surrounded in the airway epithelia, followed by ganglia and the central nervous system by means of axons (Simkó and Mattsson 2014). Soto et al. (2007) demonstrated that aggregated silver nanoparticles and some other nanomaterials are cytotoxic to alveolar macrophage cells as well as epithelial lung cells. It was proved by both inhalation and instillation experiments that nanoparticles were taken up by alveolar macrophages to some extent and aggregated silver particles persevere there for up to 7 days. Results of in vitro studies indicate a dose-dependent programmed cell death included by oxidative stress as main possible pathway of toxicity by silver nanoparticles (Völker et al. 2013). In addition, silver nanoparticles may influence cellular enzymes by interference with free thiol groups and mimicry of endogenous ions. Cena et al. (2015) conducted a field study to estimate the amount of Cr, Mn, and Ni deposited in the respiratory system of welders in two amenities. Even though each worker wore a nanoparticle respiratory deposition (NRD) sampler during gas metal arc welding (GMAW) of mild and stainless steel and flux-cored arc welding (FCAW) of mild steel and several welders also wore side-by-side NRD samplers and closed-face filter cassettes for total particulate samples. The NRD sampler estimates the aerosol's nano-fraction deposited in the respiratory system. The obtained results proved that most of the Cr and more than half of the Ni and Mn in the fumes were in the fraction smaller than 300 nm.

3.1.3 Gastrointestinal Tract

Gastrointestinal tract acts as an organ system responsible for consuming and digesting foodstuffs, absorbing nutrients, as well as expelling waste. Nanomaterials can reach the gastrointestinal tract by ingesting directly in water, food, cosmetics, drugs and drug delivery devices or after mucociliary clearance from the respiratory tract via nasal region (Mann et al. 2012; Som et al. 2011). In addition, increased utilisation of nanoparticles may lead to increased environmental contamination and unintentional ingestion via water, food animals, or fish (Bergin and Witzmann 2013). It is measured that the exogenous sources of ingestion exposure mainly results from hand to mouth contact in the workplace. On the other hand, NPS can be ingested directly via food, water, drinking, drugs and drug delivery systems. Besides, NPs cleared from respiratory tract via the mucociliary escalator can then be ingested into the gastrointestinal tract. Thus, gastrointestinal tract is considered as vital target for nanoparticles exposure (Liu et al. 2013). Assessment of nanoparticles must taken into deliberation not only for absorption and extra-intestinal organ accumulation but also the potential for altered gut microbes and the effects of this perturbation on the host (Bergin and Witzmann 2013). Chen et al. (2006) reported the acute toxicity of copper particles (bulk) and nanocopper in mice and discovered that nanocopper was several folds lethal than bulk copper. Nanocopper was also reported to source pathological damage to kidney, liver and spleen. Russell-Jones (2000) proposed the usage of biodegradable nanoparticles in the delivery of oral vaccines for antigens known to be susceptible to proteolysis. In fact, studies on toxicity of nanomaterials after oral ingestion are very limited and very little work has been done till now on gastrointestinal tract exposure.

Gastrointestinal tract is a highly complex environment and understanding of the fate of ingested NPs requires consideration of multiple factors. Many features have been identified that are significant to interpretation of nanoparticles ingestion studies and these studies include physicochemical characterisation of nanoparticles and reporting of metadata from in vivo studies. Moreover, a characteristic somewhat exceptional to the ingestion route is the possible for toxic effects related to interactions with the gut microbiome. In the end, although doses higher than distinctive exposures are a standard and essential part of toxicity studies for establishing dose range parameters, these doses should be reasonably based and critically compared to probable exposure levels (Bergin and Witzmann 2013).

3.2 *Effects of Carbon Nano Tubes on Human Health*

Carbon nanotubes are a novel form of carbon molecule and are an important new class of technological materials that have numerous novel and useful properties (Donaldson et al. 2006, 2010). Surrounded by hexagonal complex of carbon atoms, these hollow cylinders can have diameter around 0.7 nm in size and reach some millimeters in length. They are single layered or multilayered and are chemically and thermally very stable. Their manufacturing normally involves the presence of metals, the ultimate content of which in the product will depend on the product's conditions of manufacturing and subsequent purification (Awasthi et al. 2013). The composite materials containing CNTs may have incredible strength, potentially sufficient to allow the building of spacecraft structures, space elevators, artificial muscles, combat jackets, membranes for gas separation and land and sea vehicles (Kumar et al. 2010). Wang et al. (2004) reported that Hydroxylated single-walled carbon nanotubes administered by gavage in mice are spread to most of the organs and tissues, apart from the brain. Pantarotto et al. (2004) investigated the intracellular transfer of functionalized single-walled carbon nanotubes (SWCNT), i.e., conjugated with lysine, on human and mouse fibroblasts in vitro. They reported that these carbon nanotubes could pass through the cellular membrane and gather up in the cell and end up in the cell nucleus. In an investigation by Monteiro-Riviere et al. (2005) multi-walled carbon nanotubes (MWCNT) were found in the cytoplasmic vacuoles of human epidermal keratocytes in vitro, leading a decline in cell viability and a considerable increase in an inflammation marker (interleukin-8). This reveals the capability of MWCNT to penetrate the cell membrane. Cui et al. (2005) confirmed that SWCNT can hold back cell proliferation, initiate apoptosis and reduce adherence of human embryonic kidney cells in vitro. Shvedova et al. (2003) proved through their investigation that the exposure to unrefined SWCNT can direct to an increase in cutaneous toxicity in exposed workers. In addition, CNTs are also reported to induce human fibroblast (Tian et al. (2006) and T-lymphocyte apoptosis (Bottini et al. 2006) and show cytotoxicity in alveolar macrophages as well (Jia et al. 2005). In differing to this Liu et al. (2009) reported absence of any obvious toxicity of properly functionalized and purified

CNTs. Engineered nanomaterials causes stress in the cellular environment which disturb the oxidative balance resulting in high concentrations of intracellular reactive oxygen species (ROS). Despite the potential impacts of carbon nanotubes (CNTs), on human health and the environment, they have been receiving more and more attention in the recent past, existing information on the toxicity of CNTs.

3.3 *Effects of Inorganic Nanoparticles on Human Health*

Among the various nanomaterials, inorganic nanoparticles are very significant in current technologies. Because they can be easily and cheaply synthesized and mass produced. In addition, they are more readily integrated into applications (Auffan et al. 2009). Insoluble inorganic nanoparticles can be made up of pure metals or a variety of inorganic products or alloys. Their nanometric size differentiates them from the same products usually found on a larger scale (Tee et al. 2015). These inorganic nanoparticles exhibit electrical, mechanical and other properties that do not survive when in larger dimensions (Sharma et al. 2015). Drug sensitization with various inorganic nanoparticles (NPs) has established to be a capable and a developing strategy in the field of nanomedicine. For instance, Rose Bengal (RB), a notable photosensitizer, triggers the formation of ROS under green light irradiation and as a result it induces cytotoxicity and cell death (Chaudhuri et al. 2015). Acticoat™ consists of a polyester or nylon mesh, trapping polyethylene and includes a silver nanocrystal coating. This product has been used for several years to speed up healing of injuries and decrease bacterial colonization. In the occurrence of moisture, the product liberates ions and silver radicals that would be accountable for antibacterial action. In an in vitro study of cultured human keratinocytes, Lam et al. (2004) observed a significant decrease in cell viability and conclude cytotoxicity of silver nanoparticles released by Acticoat™. Braydich-Stolle et al. (2009), demonstrated that 100 % anatase nanoparticles, in spite of of size, induce cell necrosis and membrane leakage, but they do not generate ROS. In contrast, the rutile nanoparticles initiate apoptosis through formation of ROS. Therefore, it seems that links between size and crystal structure may have a role in mediating nanoparticle toxicity. Lucarelli et al. (2004) conducted in vitro studies and reported that SiO_2 and cobalt (Co) nanoparticles displayed significant proinflammatory action for the activity of human marrow monocytes. Yao et al. (2015) determined the influence of particle size and concentration of gold nanoparticles (AuNPs) on their absorption, accumulation, and cytotoxicity in model intestinal epithelial cells. As the mean particle diameter of the AuNPs decreased (from 100 to 50 to 15 nm), their rate of absorption by the intestinal epithelium cells increased, but their cellular accumulation in the epithelial cells decreased. Moreover, accumulation of AuNPs caused cytotoxicity in the intestinal epithelial cells, which was evidenced by depolarization of mitochondria membranes and the results provide an important insights into the relationship between the dimensions of AuNPs and their gastrointestinal uptake and potential cytotoxicity (Yao et al. 2015).

Platinum drugs as anti-cancer therapeutics are held in particularly high in consideration. Regardless of their success, there are drawbacks associated with the use of platinum drugs. Their dose-limiting toxicity, their limited activity against an array of common cancers and patient resistance to Pt-based therapeutic regimes are some examples (Parker et al. 2016). Peters et al. (2004) examined the viability and behaviour of human endothelial cells in vivo and observed that PVC, TiO_2, SiO_2 and Co nanoparticles were incorporated into the cell vacuoles. Inorganic elements are an undeniable part of living organisms; therefore, the synthesis, stability, and toxicity of engineered metal nanoparticles (ENPs) have been broadly studied during the past two decades. But research on the formation, fate, and ecological effects of naturally-occurring nanoparticles (NNPs) has become a focus of attention only recently (Sharma et al. 2015).

Organic nanoparticles can be normally described as solid particles composed of organic compounds mainly lipids or polymeric compounds (Lambert et al. 2014). Over the past decades, this type of nanoparticles has met an immense development and intensive investigations due to their high potentialities in a wide spectrum of industrial areas ranging from electronic to photonic, conducting materials to sensors, medicine to biotechnology, and so forth (Grimsdale et al. 2009; Niu et al. 2009; Chen et al. 2015). In addition, organic nanoparticles can also be materials connecting with entrapment, encapsulation or surface adsorption of active biological substances (Kashi et al. 2012). The results are promising regarding the therapeutic aspects organic nanoparticles, mostly for polymeric nanoparticles, but the information is insufficient relating to their toxicity in the work environment because of the unusual route used and the limited information concerning their toxicological assessment. As per the literature available, very limited and incomplete data is present on human health hazards related organic nanoparticles. But when it comes to the animal studies there is sufficient data to prove the adverse effects of organic nanoparticles (Liu et al. 2014; Lehto et al. 2014; Kim et al. 2006; Lockman et al. 2004; Alvarez-Román et al. 2004).

3.4 *Effects of Quantum Dots on Human Health*

Quantum dots (QDs) are very tiny particules on the order of a nanometer in size and are composed of a hundred to a thousand atoms. They are a type of fluorescent label with applications in biological molecules, cells and in vivo imaging (Yuan et al. 2015). Although the applications of these QDs are rising, there are concerns about their potential ill effects to human health. But, the toxicity connected with these nanoparticles and the underlying mechanisms have not been systematically assessed (Nguyen et al. 2015). Kirchner et al. (2005) uncovered the cytotoxicity of ZnS and CdSe nanocrystal solutions for human fibroblasts and tumour cells. Cytotoxicity was higher if the nanocrystals were coated with mercaptopropionic acid, an unstable coating. Phosphosilicate, PEG-silica and polymer-coated inert gold nanoparticles also have a cytotoxic effect (Gambardella et al. 2015). The investigators concluded that the toxic effect may be associated to the straight effect of precipitated particles on the cells. Shiohara et al. (2004) demonstrated the in vitro cytotoxicity of ZnS and CdSe quantum dots layered with sheep serum albumin and mercaptoundecanoic acid. Human hepatocytes, primate kidney cells and cervical cancer cells were also exposed to these quantum dots and noticed a decrease in the viability of the cell lines. In a study, double-stranded DNA was incubated in a cadmium selenide solution encapsulated in zinc sulphite functionalized with surface biotin. Ultraviolet (UV) radiation was also applied. The outcome of this study showed that the quantum dots altered the DNA by releasing SO_2 free radicals, resulting from ZnS oxidation. The proportion of DNA alterations varied according to the application of UV (Green and Howman 2005). Lovric et al. (2005) recommended that the location of QDs could be relevant to the toxic and adverse cellular responses linked with these highly fluorescent NPs. In spite of this, an understanding of the actual cellular process of the uptake and sub-cellular localisation and distribution of QDs is limited. In a study by Nguyen et al. (2015) CdTe-QD caused disruption of mitochondrial membrane potential, increased intracellular calcium levels, impaired cellular respiration, and decreased adenosine triphosphate synthesis. Even with the apparent benefits proposed by QDs, sensitive concerns have been lifted as to their exposure to humans and what impact they might have upon human health.

3.5 Effects of Nanospheres, Nanoshells and Nanocapsules on Human Health

A wide variety of insoluble organic polymers are employed in the production of nanocapsules, nanospheres and nanoshells. Some of these structures are manufactured to allow integration with other substances, often medications. The exterior of these nanoparticles can also be altered to interact purposely with certain sites of the body. Because of their nanometric size, these nanoparticles can circulate in a living organism, serve as a drug vector or fix to specific cells. In a study by Favi et al. (2015) rod-shaped silver nanorods (AgNRs) and gold nanorods (AuNRs) were fabricated by electron beam physical vapor deposition (EBPVD), and their cytotoxicity toward human skin fibroblasts were assessed and the results showed the maximum toxicity with fibroblast cells by both types of nanorods. Torres-Lugo et al. (2002) showed the in vitro cytotoxicity and a reversible alteration of the electrical resistance of the epithelial cells by hydrogel nanospheres. Cahouet et al. (2002) intravenously introduced nanocapsules with a lipid core and a shell composed of 2-hydroxy-polyethylene glycol (PEG) stearate and lecithin in rats. The nanocapsules were stained with technetium-99 and iodine-125. The authors observed a longer persistence of the nanocapsules in the blood compartment than expected. The nanocapsules were dispersed in the animals' stomach liver, intestines, and penis, but there was no considerable cerebral distribution. Like this, cytotoxic effects of nanospheres, nanoshells and nanocapsules on cell membrane, mitochondrial function, prooxidant/antioxidant status, enzyme leakage, DNA, and other biochemical endpoints were elucidated by many researchers (El-Ansary et al. 2015; Perez et al. 2015; Jeannet et al. 2015; Liu et al. 2013). Researchers highlight the need for caution during the use and disposal of such manufactured nanomaterials to prevent unintended environmental impacts.

3.6 Effects of Fullerenes on Human Health

Fullerenes are carbon allotropes similar in structure to graphene but rolled up to form closed-cage, hollow spheres. The use of fullerenes have expanded significant consideration due to their anti-oxidant and radical scavenging characters and their current applications comprise targeted drug delivery, energy application, polymer adaptations and cosmetic products. The fabrication of fullerenes and their use in consumer products is expected to increase in future (Aschberger et al. 2010). Totsuka et al. (2009) manufactured nano/microparticles such as fullerenes (C60), carbon black (CB) and ceramic fiber that are being widely used because of their desirable properties in industrial, medical and cosmetic fields. However, these manufactured products, CB, C60 and kaolin, were shown to be genotoxic in in vitro assay systems. Functionalization of fullerenes with hydroxyl groups (fullerenols) can boost the solubility and potential for cellular interaction, but the health and safety effects of varying degrees of fullerene hydroxylation in biological systems is inadequately understood. Existing reports regarding the toxicity and inflammatory potential of fullerenols give contradictory conclusions. To further clarify the potential for toxicity of fullerenols, human epidermal keratinocytes (HEK) were exposed to fullerenols (low ($C_{60}(OH)_{20}$), medium ($C_{60}(OH)_{24}$), and high ($C_{60}(OH)_{32}$) at concentrations ranging from 0.000544 to 42.5 μg/mL for 24 and 48 h. The findings suggest that extrapolation across similar NP will be dependent upon surface chemistry and concentration which may affect the degree of agglomeration and thus leads to biological effects (Saathoff et al. 2011).

Santos et al. (2014) observed the balance between hydrophilicity and hydrophobicity resulting from the surface chemistry of fullerene nanoparticles, rather than the cluster size or the surface charge acquired by fullerenes in water, influences their membrane interactions and consequently their effects on mitochondrial bioenergetics. Sayes et al. (2004) demonstrated the cytotoxicity (CL50) of four water-soluble fullerenes on human cells like hepatic caricinoma cells and fibroblasts in vitro. They confirmed that toxicity differ with the nature of the functional group. Some studies report risks of oxidative damage and toxicity, particularly when cells were exposed to the photoexcited form of fullerene. The present knowledge of the lethal effects of fullerene nanoparticles is relatively inadequate. Toxic effects have already been recognized at the pulmonary, reproductive, cardiac, renal, cutaneous and cellular levels (Injac et al. 2013). The acknowledged toxic effects on humans and the physicochemical characteristics of fullerene nanoparticles give good evidence that through nanoparticles there is risk of occupational disease in researchers and students who develop these products and in workers who manufacture, transform or use nanoparticles.

4 Nanoecotoxicology-Potential Biological Effects

Little is identified about the fate and behaviour of synthetic nanomaterials in the environment, and appropriate methods to detect them in complex environmental media are only in the progress stage. Nanoecotoxicology is a sub-discipline of ecotoxicology and particularly aims to identify and predict effects drawn by nano sized materials on ecosystems. To attain this objective, nanoecotoxicology needs to take into consideration the entry routes and fate of nanomaterials in the abiotic and biotic environment to define exposure (Oughton et al. 2008; Kahru and Ivask 2013). Furthermore needs to recognize those interactions of nanomaterials with biota that alter the proper function of cells comprising an organism, thus impacting populations, which in turn can lead to changes in community structure and function. Collectively, this information can be used to evaluate the risk that nanomaterials in a given environment (Stone et al. 2010). Figure 4 gives a detailed sorting of

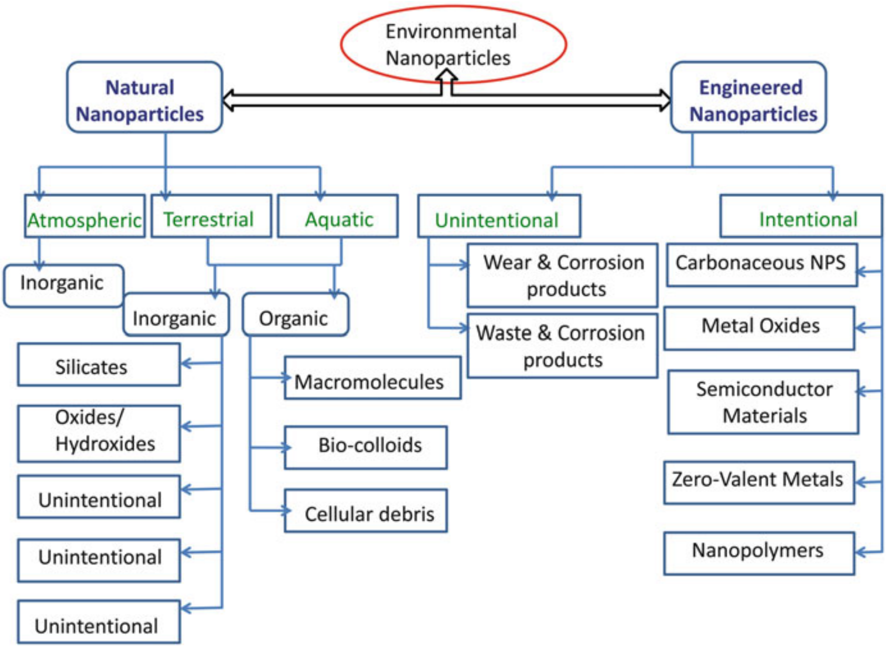

Fig. 4 Categorization of nanoparticles present in the environments

nanoparticles existing in the environments. Despite of a rising considerate that synthetic NPs should be evaluated for their probable environmental hazard prior their use in products and following inevitable release into the environment. There are currently few data on the toxicity of nanomaterials to environmentally relevant species, limiting the quantitative risk assessment of NPs (Kahru and Dubourguier 2010). As manufactured nanomaterials are used in many commercially available consumer products, production of nanomaterials is increasing and the environmental exposure to these materials is evident. It is clear that the physicochemical properties as well as the structure and morphology of nanomaterials have a high influence on toxicity (Sigg et al. 2014). Therefore, environmental risk assessments of engineered nanoparticles require thorough characterization of nanoparticles and their aggregates. In addition, quantitative analytical methods are required to assess environmental concentrations and enable both effect and exposure assessments. Many methods still need optimization and development, especially for new types of nanoparticles, but extensive experience can be gained from the fields of environmental chemistry of natural nanomaterials and from fundamental colloid chemistry (Hassellöv et al. 2008).

Based on the ecotoxicological data previously available and mitigating factors, hazard assessment is conducted. Further, chronic testing is compulsory to improve the risk assessment process if the substance is classified as Persistent, Bioaccummulative, Toxic (PBT). The greater part of present studies of the toxicity of nanomaterials have been carried out on a limited number of nanomaterials and aquatic species, generally at high concentration and over short exposure time. Fullerenol $C_{60}(OH)_{24}$ and Nanoclusters of C_{60} have been shown to create reactive oxygen species in water under polychromatic light and UV (Pickering and Wiesner 2005). Literature on potential toxicity of nanomaterials on terrestrial species like plants, micro-organisms and soil invertebrates is growing rapidly (Handy et al. 2008). Nanomaterials have the ability to unite substantial fractions of pollutants such as trace metals and organics. In the environment, contaminants adsorb to natural solid phases like nanoparticles. Nanomaterials have the capability to combine with substantial fractions of contaminants such as organics and trace metals (Behra and Krug 2008) Carbon nanotubes and Zero-valent iron oxides have been applied for the remediation of organic pollutants and used for the immobilization of organic compounds and metals. Nanoparticles in altered form may be more bioavailable and may be taken up through cell membranes more easily (Sigg et al. 2014; Rickerby and Morrison 2007).

Some of the biological effects of nanomaterials dispersed in the environment including the ecological and evolutionary effects of nanomaterials on terrestrial and aquatic ecosystems such as: species interactions, circulation of nanomaterials and their by-products within ecosystems, factors that influence bioaccumulation and biomagnification of nanomaterials in food network, biotic processes that influence the persistence and chemical transformations of nanomaterials in the environment, and the way and existence of effects on ecosystems (Rickerby and Morrison 2007; Kahru and Dubourguier 2010) Therefore, from the environment nanomaterials have the ability to interact with metabolic networks, cellular constituents and living

Table 3 In vivo observed effects induced by engineered nanoparticles that are supported by in vitro evidences

In vivo observed effects supported by in vitro evidences	
In vitro evidence	*In vivo observed evidences*
Increased cytotoxicity on exposed cell cultures	Chronic obstructive pulmonary disease (COPD)
Proliferative stimuli induced by extracts of DEP components	Hyperplasia
Macrophage-dendritic transepithelial cells network alterations in the Gap Junction Intercellular Communication (GJIC)	Particle translocation
Endothelial cell activation by direct contact with particles or indirectly induced in co-cultures where pneumocytes, macrophages, and other cell are exposed. Changes in the TEER values related to tight junctions	Systemic and endothelial dysfunction
ROS increases via NADPH-oxidase in lung epithelial cell exposed to PM	Oxidative stress
Secretion of IL-1b, IL-6, IL-8, TNFa, MCP-1, and so forth, by lung cells, macrophages, and cocultures	Local and systemic inflammation

tissues including interactions at the organ, cellular molecular and systemic levels. Engineered nanoparticles can effects on organism ontogeny and multi-generational life histories (Lv et al. 2015). In vivo observed effects induced by engineered nanoparticles are summarized in Table 3 and the multiple scenarios through which nanoparticles enter into environment and humans are exemplified in Fig. 5.

4.1 Environmental Issues

Nanotechnology is a transformative technology revolutionizing many areas including energy, security, information technology, agriculture, environmental protection, and healthcare (Gao et al. 2015b). Scientific activities related to the development of nanomaterials have been remarkable and the number of peer-reviewed papers related to the topic has shown an exponential growth over the last decade. Currently there are more than 60 countries that have already launched national nanotechnology programs. But definitely the victory or failure of nanotechnology may well depend on the skill to address environmental issues. Responsible Research and Innovation provides a framework for judging the ethical qualities of innovation processes, however guidance for researchers on how to implement such practices is limited. The propose of any research should be anticipatory, exploring in advance and expecting potential technological impacts; reflective, by examining objectives and purposes of technologies as well as the uncertainties in risk assessment; deliberative, the idea that public and diverse stakeholders' perspectives are actively considered during design processes and, lastly; responsive, the actual alteration and shaping of technological trajectories in response to deliberation and reflection (Spruit et al. 2015). Many researchers are

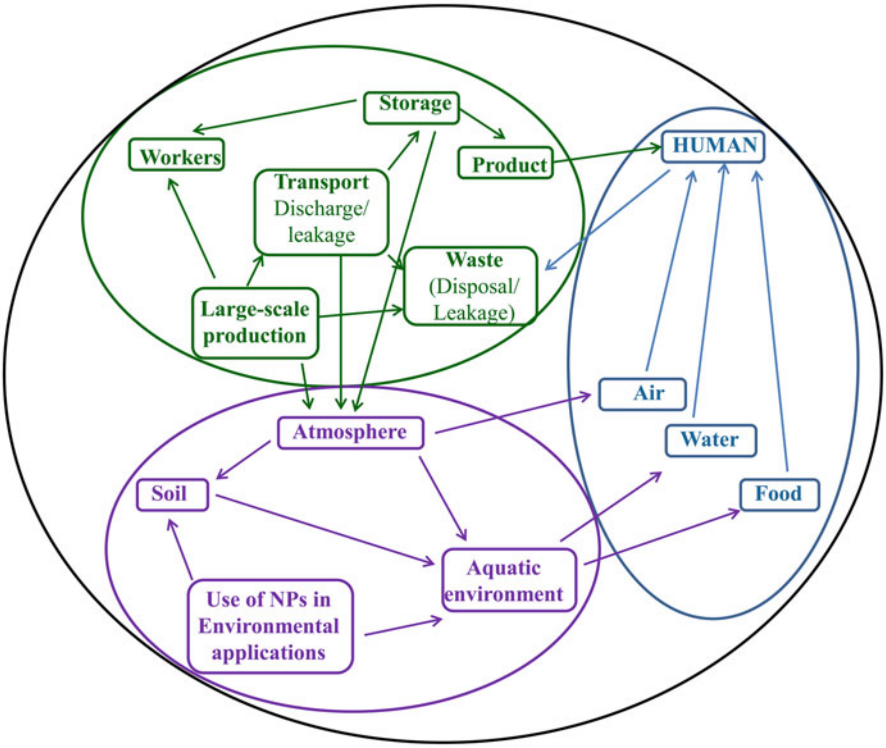

Fig. 5 Multiple scenarios through which nanoparticles enter into environment and humans

working hard to provide answers to many key environmental issues, including the following:

- How far industry and society can expect hazardous material to be delivered into the environment during either the production or use of nanoproducts?
- What are the possible environmental problems linked with this nanotechnology?
- Could nanoapplications show the way to environmental degradation, predominantly from bioaccumulation of nanoproducts in living tissue?
- What effects will regulations have on this nanotechnology?

Investigations on nanoparticles influence on ecology shows a certain hazard potential of some nanomaterials. Even though scientific uncertainties still exist, the precautionary principle should be applied in the sense of preventive risk minimization. Environmental inputs should be avoided to the extent possible. Ecotoxicological research should be progressively more focus on the environmental relevance of the materials and consider the complexity of natural systems. As the result of their minute size and elevated specific surface areas, chemical reactivities sensitive to exposed surface sites will likely be magnified with these products (Loux et al. 2011).

4.2 Environmental Fate of Nanomaterials in Air

In air the fate processes for ultrafine particles are well described many researchers (Stone et al. 2010; Lowry et al. 2012). But there are still some key issues to be addressed with regards to disclosing the processes governing their behaviour, transport and fate (Meesters et al. 2013; Hartmann et al. 2014). Nanoparticles will have high mobility and will mix rapidly in aerosol systems. Engineered nanoparticles suspended in air will most likely be exposed to sunlight, and particularly to UV wavelengths of light, to a much larger degree than for the other environmental compartments (Mitrano et al. 2015). This amplifies the possibilities for photochemical transformations. In addition, the deposition of nanoparticles in air depends on the gravitational settling velocity, which is proportional to the diameter of the particle. As a result, smaller nanoparticle in air will deposit at a much slower rate than larger particles. Agglomeration will therefore significantly enhance the deposition of engineering nanomaterials. In comparison to photochemical reactions, agglomeration and deposition, other processes are assessed to be of much less significance or even to be inappropriate for nanomaterials in the air (Loux et al. 2011; Soni et al. 2015). To find out the fate and behaviour of nanomaterials in the environment requires the understanding of potential sources of nanomaterials and their degradation, transformation, and existence. The fate of nanomaterials in the environment is expected to differ with the physical and chemical properties of the nanomaterials, containing medium, interaction of nanomaterials and other environmental pollutants.

Atmospheric nanomaterials have three major sources: (1) primary emission, refers to those that are openly released from road traffic exhaust and industrial combustion; (2) secondary emission, refers to those that are produced in the atmosphere from the compression of low volatility vapours produced from the oxidation of atmospheric gases; and (3) formation at the time of diesel exhaust dilution (Baalousha and Lead 2009). The lack of data about engineered nanomaterials in the atmosphere is due to the nonexistence of methods capable of discriminating engineered nanomaterials from the background concentration from other sources which is alike to the condition in aquatic and terrestrial environments (Baalousha and Lead 2009). From the literature it is known that fine, ultrafine particles, and nanomaterials can go through several processes in the atmosphere (Tiwari and Marr 2010; Gouin et al. 2011). Some nanomaterials can produce by condensation of low volatility compounds or reduce in size by evaporation of adsorbed water or other volatiles, resulting in the deviation in particle size distribution but not the overall numeral concentration. Atmospheric nanomaterials can combine resulting in an increase in particle dimension with a decrease in the numeral concentration (Gidhagen et al. 2004). Sometimes nanoparticles can also be missing from the atmosphere by dry and wet deposition, both of which are capable for extremely small particles of natural origin and so presumably also for engineered nanomaterials. This results in a decline in particle numeral concentration and a change in particle size distribution to larger sizes (Clarke et al. 2004).

4.3 Environmental Fate of Nanomaterials in Water

The fate of nanomaterials in the aquatic environment can be influenced by different processes, such as aggregation and disaggregation, diffusion, interaction between nanoparticles and natural water components, transformation, biotic and abiotic degradation and photoreaction (Vale et al. 2015). The fate and behaviour of engineered nanomaterials released into the aquatic environment can be understood with the help of existing literature on the fate and behaviour of natural colloidal particles. Currently, nanomaterials are extensively recommended for wastewater treatments due to their exceptional properties. Some studies report the various advantages of nanotechnology in the remediation of wastewaters, but inadequate research has been directed toward the fate and potential impacts of the solid residues produced after the application of such technologies (Nogueira et al. 2015). In a study, researchers examined the aggregation and sedimentation kinetics behaviors of citrate- (Cit-AgNPs) and polyvinylpyrrolidone-coated silver nanoparticles (PVP-AgNPs) in calcium chloride ($CaCl_2$) solutions, emphasizing the effects of particle size and type of coating material on both behaviors. As the ionic strength increased, Cit-AgNPs aggregated rapidly and settled down, while PVP-AgNPs did not aggregate, even at an ionic strength of 10 mM $CaCl_2$, due to likely steric hindrance effects of PVP coating. Interestingly, PVP-AgNPs sedimented without aggregating within week and this inclination seems to have relevance to the particle size. These results suggest that the particle size and type of coating material play important roles in determining nanoparticle fate in water (Jang et al. 2014). In addition, nanomaterials released into the water bodies may interact with aquatic organisms and induce adverse effects at different levels of biological organization. These potential ecotoxicological risks of ENMs to aquatic organisms have recently been reviewed (Rocha et al. 2015; Grillo et al. 2015; Baker et al. 2014; Corsi et al. 2014; Ma and Lin 2013; Matranga and Corsi 2012) but their mode of action and biological risk remain unclear.

Therefore, in aquatic environment nanoparticles may interact with natural organic matter, natural colloids and suspended particulate matter, resulting in aggregation and potentially sedimentation from solution. Sedimentation and aggregation may represent a pathway for the carrying of nanoparticles from the water column to benthic sediments. The nanoparticles in aquatic environment are bioaccumulated by deposit and filter feeding organisms. Research on such interactions have not been fully studied till date due to the fact that robust and sensitive analytical methods are not yet available for detecting and characterizing nanoparticles in complex environmental matrices such as natural waters and soils (Tiede et al. 2015) but may considerably affect nanoparticle fate and toxicity.

4.4 Environmental Fate of Nanomaterials in Soil

Soil is the matrix of a multilayer food web structure and it is a complex interface between gases-solid-water-organic/inorganic matters and organisms. Nanomaterials are small enough to pass through soil pores (Mukhopadhyay 2014). They can adhere to soil particles due to their high surface area and become immobilized (Michael et al. 2008). Large aggregates of nanomaterials can be immobilized by sedimentation, filtration, or straining in smaller pores (Mukhopadhyay 2014). At present few reports are available on the transport and fate of nanomaterials in the natural porous environment. It is reported that transport is moderately fast and influenced by the type of nanomaterials (Li et al. 2006; Boxall et al. 2007). While toxicity mechanisms have not yet been totally clarified for most nanoparticles, probable mechanisms include disruption of membranes or membrane potential, oxidation of proteins, genotoxicity, interruption of energy transduction, formation of reactive oxygen species, and release of toxic constituents (Zharov et al. 2006). These toxicity mechanisms may result from various factors such as: high surface area to volume ratio, surface charge, hydrophobic and lipophilic groups may permit them to interrelate with proteins and membranes, complementary effects of nanostructures which cause inhibition of enzyme activity, bioaccumulation and chemical composition which amplify their reactivity (Jafar and Hamzeh 2013). Polymers and surfactants enhance the transport of nanoparticles. Many researchers are investigating the role of natural organic matter in nanoparticle facilitated transport. The properties of the soil matrix may influence the diffusion and mobility of nanoparticles. The mobility of nanoparticles in soils depends on nanoparticle's physical–chemical properties; characteristics of the soil and environment; and the interaction of nanoparticles with natural colloidal material. List of some existing ENPs and their health and environmental effects are summarized in Table 4.

5 Global Strategies Designed to Address Human Health and/or Environmental Safety Aspects of Nanomaterials

The concern over the possible adverse influences of nanomaterials on living systems has given rise to 'nanotoxicology' (Dhawan et al. 2009; Schulte et al. 2016). However, nanotoxicology has lagged far behind nanotechnology due to a number of experimental challenges and problems faced in designing studies involving toxicological assessment of nanomaterials. Globally, many organizations initiated research programmes or strategies designed to address human health and/or environmental safety aspects of nanomaterials (Dobrovolskaia et al. 2016). A summary of global organizations and their objectives were illustrated in Table 4. The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 34 industrialised nations in North and South America, Europe and the Asia and Pacific region, as

Table 4 List of some existing ENPs and their health and environmental effects

Nanoparticle	Environmental effects	Health effects
Carbon nanotubes	Cause indirect effects upon contact with the surface of the environmental organisms; environmental damage	Apoptosis; decreased cell viability; lung toxicity; oxidative stress; retarded cell growth; skin irritation etc.
Fullerenes	Effects on soil organisms and enzymes; aquatic ecosystems; binding of chemicals to fullerenes may affect the toxicity of other environmental contaminants	Retarded cell growth; decreased cell viability; oxidative stress and apoptosis etc.
Heterogeneous nanostructures	Toxicity depends on multiple physicochemical as well as environmental factors; adverse influence of ecosystem etc.	Arrest of cell growth and sometimes even cell death; chromatin condensation; free radical formation
Nanosilver	Undergoes several transformations when it is released into the environment and shows adverse effects	Alterations of the non-specific immune responses; altered cell signalling; apoptosis; necrosis of cells; oxidative stress etc.
Nanostructured flame retardants	Persistent and tend to accumulate in the environment; toxic to plants, wildlife etc.	Oxidative stress; fibrosis; cardiovascular effects; cytotoxicity; carcinogenic etc.
Polymeric nanoparticles	Potential hazardous factor for environmental exposure	Oxidative stress; inflammation; alteration in cellular morphology and functioning etc.
Silicon based nanoparticles	Potential hazardous factor for environmental exposure; adverse influence of ecosystem etc.	Cardiovascular effects; cytotoxicity; increase oxidative stress etc.
TiO_2 nanoparticles	Disrupt an aquatic ecosystem's carbon and nitrogen cycles; stress photosynthetic organisms	Excessive exposure in human may result in increased oxidative stress; retarded cell growth; slight changes in lungs etc.

well as the European Commission (EC), meet to coordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems (Rashidi et al. 2015). One of the objectives of OECD include the valuation of risk assessment approaches for manufactured nanomaterials through information exchange and the identification of opportunities to fortify and improve risk assessment capacity. Promoting policies and modern technologies for sustainable economic growth and employment, increasing standards of living, and trade liberalization is principal aims of the OECD. Drawing on facts and real-life experience, OECD recommend policies designed to improve the quality of people's lives (Rashidi et al. 2015). In addition, the OECD is also working for a stronger, cleaner, and fairer economy.

The National Institute for Occupational Safety and Health (NIOSH) established the Nanotechnology Research Center (NTRC) in 2004 to address the occupational safety and health concerns that might be associated with this engineered nanomaterials (Fischman et al. 2011). It is working in parallel with the development and implementation of commercial nanotechnology through conducting strategic planning and research, partnering with public and private-sector colleagues from the United States and abroad, and, making information widely available. The NIOSH goal is to provide national and world leadership for incorporating research outputs about the implications and applications of nanotechnology into good occupational safety and health practice for the advantage of all nanotechnology workers. NIOSH has developed a strategic plan for coordinating nanotechnology research and for use as a guide for the development of new research efforts (Kuempel et al. 2012; Brenner et al. 2016).

The NanoSafety Cluster, a cluster of projects funded by the EC, recognized the need for a computational infrastructure for toxicological data management of engineered nanomaterials (ENMs) (Jeliazkova et al. 2015). It is an EC programme to maximise the synergies between the past, ongoing and future FP7 nanosafety projects. Each of these projects addresses important aspects of nanosafety, including toxicology, ecotoxicology, exposure assessment, risk assessment, standardisation, and mechanisms of interaction. There are currently almost 40 such projects. In 2014, the NanoSafety Cluster conducted a Key Global NanoSafety Database Survey which is first in a biannual continuous effort and attempt to accumulate, organise and share up-to-date information about NanoSafety related databases worldwide. The resulting list of databases will continuously be updated with innovative valuable insight along its development (Oomen et al. 2014; Guadagnini et al. 2015). The Strategic Research Agenda (SRA) has been developed by members of the European NanoSafety Cluster, a forum for ongoing FP6 and FP7 projects covering all features of nanosafety. The implementation of the SRA is expected to afford a major step forward in the expansion of safe and sustainable nanomaterials (Kermanizadeh et al. 2016). In addition to these organizations, other organizations like Federal Institute for Materials Research and Testing (BAM), Federal Ministry of Education and Research (BMBF), Federal Environment Agency (Umweltbundesamt, UBA), Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR), Federal Institute of Occupational Safety and Health (BAuA), Federal Research Institute of Nutrition and Food (Max Rubner-Institut, MRI), MODENA COST etc. are contributing their efforts to address human health and/or environmental safety aspects of nanomaterials through different strategies as summarized in Table 5.

6 Green Nanoscience and Its Assurance

Many research and activist groups have expressed worries and concerns about nanotechnology toxicity to human and environment (Polshettiwar et al. 2012; Hutchison 2008). Conflicting research conclusions have increased concerns about nanomaterial safety. Ambiguous answers regarding nanomaterial safety and toxicity are available which make to think nanotechnology as a boon and or as a curse. There is an improved and intensified attention on addressing the Environmental Health and Safety (EHS) concerns interrelated to nanotechnologies by both

Table 5 Global strategies to address human health and/or environmental safety aspects of nanomaterials

Organization	Objectives
The Organisation for Economic Co-operation and Development (OECD)	• Evaluation of risk assessment approaches for manufactured nanomaterials through information exchange and the identification of opportunities to strengthen and enhance risk assessment capacity
National Institute for Occupational Safety and Health (NIOSH)	• Development and implementation of commercial nanotechnology through conducting strategic planning and research to provide national and world leadership for incorporating research findings about the implications and applications of nanotechnology into good occupational safety and health practice.
EU NanoSafetyCluster	• It works on the projects addressing all aspects of nanosafety including toxicology, ecotoxicology, exposure assessment, mechanisms of interaction, risk assessment and standardisation. • Conducts workshops and seminars to educate people particularly all nanotechnology workers
Federal Institute for Materials Research and Testing (BAM)	• BAM is involved in EU-funded (FP7) projects: – *NanoDefine* (FP7): The aim of NanoDefine is to support the governance challenges associated with the implementation of the nanomaterial legislation by addressing the issues on the availability of suitable measuring techniques, reference material, validated methods, acceptable for all stakeholders and delivering an integrated and interdisciplinary approach. – *NanoValid* (FP7): The main objective of NanoValid is the development of new reference methods and certified reference materials, including methods for characterization, detection/quantification, dispersion control and labeling, as well as hazard identification, exposure and risk assessment of ENs
Federal Ministry of Education and Research (BMBF)	• NanoCare—Safe handling of Manufactured Nanomaterials • Studying the effects of ENM on humans and the environment
Federal Environment Agency (Umweltbundesamt, UBA)	• NanoCare—Safe Handling of Manufactured Nanomaterials • Investigating Impacts on Health and the Environment

(continued)

Table 5 (continued)

Organization	Objectives
Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR)	• To demonstrate and establish new principles and ideas based on data from value chain implementation studies • To establish Safe-by-Design as a fundamental pillar in the validation of a novel manufactured nanomaterial • Establishing nanomaterial grouping/ classification strategies according to toxicity and biological effects for supporting risk assessment • Grouping of nanostructured materials for protection of workers, consumers, the environment and risk minimisation
Federal Institute of Occupational Safety and Health (BAuA)	• Grouping of nanostructured materials for protection of workers, consumers, the environment and risk minimization
Federal Research Institute of Nutrition and Food (Max Rubner-Institut, MRI)	• Detection and characterization of nanomaterials in complex matrices such as food etc. • Research on nano-sized carrier systems for bioactive compounds • Interaction of nanomaterials with compounds of the food matrix
Modena Cost	• The specific objectives are to study the synthesis of engineered nanomaterials (ENM) with controlled composition, size, area and nano-texture and • To develop of strategies to immobilise ENM in matrices, on substrates with minimum effect on the desired properties and surface reactivity and identify the relevant datasets for Quantitative Nanostructure-Toxicity Relationships (QNTR) modelling

scientists and policymakers (Hussain et al. 2015; Hutchison 2008). The focus on nanomaterial environmental health and safety depicts the requirement for a research agenda that can minimize nanomaterial hazards. As an ultimate answer to many of the concerns about nanotechnology toxicity and safety, green nanoscience has evolved as an approach to determine and implement the design rules for safer, greener nanomaterials for more efficient processes (Hussain et al. 2015). With green nanoscience we can design and process the materials that can eradicate hazards throughout the material's life cycle. Since green nanoscience offers significant promise as solutions to long-standing environmental, health and technological challenges (Hussain et al. 2015; Hutchison 2008; Nath and Banerjee 2013). Both the government and private industry are gearing up to invest billions of dollars in research and development of green nanoscience. Even though this green nano science is growing slowly, there are principal groups that have enunciated and illustrated the concepts of green nano with recent conferences and symposia highlighting work that is currently being conducted.

Green nanoscience is an integrated approach of green chemistry and nanotechnology that aims to generate and apply design rules proactively for greener nanomaterials and to develop potential synthetic strategies to manufacture nanomaterials reproducibly with definite structure, composition and purity. The following are the fundamental objectives of green nanoscience.

- To develop safer and greener substitute materials that can be used if a nanomaterial is found to be lethal or bioaccumulative in commercial or near-commercial phase.
- Discover the design rules for novel nanomaterial groups that have attractive properties and an elevated level of safety.
- Diminish the hazard and increases the potentiality of nanomaterials production.

Green nanoscience can provide further benefits. It can encourage innovation through the investigation of new materials with greener properties. Green nanoscience facilitates commercialization by reducing insecurity about material safety and providing more potential production approaches (Mckenzie and Hutchison 2004). It protects our investment in nanotechnology from the threats of public or consumer doubts about the unsure risks of the technology. Merging green chemistry and nanoscience will have noteworthy impact on the processes and products of the future. To maturely build up nanotechnology, we must evaluate, through new nanomaterials, appropriate metrics and nano manufacturing processes and relate these findings to direct this upcoming industry. The employment of nanomaterials in green chemistry to meet its goals will definitely offer new opportunities to develop superior safe products and green processes with low impact on the environment and human health. The integration of these two emerging fields provides even greater opportunity for reducing the impact of new technologies on the environment and human health. As asserted by many environmental scientists, if nanotechnology is to be the key to the future, then it should be developed with sustainability.

Green nanoscience employs the familiar twelve principles of green chemistry to the design, production, and application of nanomaterials (Hutchison 2008; Anastas and Warner 1998). Green nanoscience, similar to green chemistry, struggles to trim down or abolish hazards to human health and the environment through safe product design and process optimization. To practice those principles, it is essential to acquire the knowledge like mechanistic understanding, synthetic methods, characterization tools and strategies and bio or eco testing procedures. As a result we can acquire steps on time to find substitute for materials that are not safe to design new materials and to manufacture materials which are reliable and potential (Eckelman et al. 2008). The twelve principles of green chemistry which are applied in green nano science are; avoiding the generation of waste, atom economy, less hazardous chemical synthesis, designing safer materials, safer solvents and auxiliaries, design for energy efficiency, use of renewable feedstock's, eliminate the use of derivatives, catalysis which can improve the selectivity of reactions and reduces the amount of energy necessary to initiate a reaction, design for degradation, real-time analysis for pollution prevention, inherently safer chemistry which involves the process to evaluate the environmental issues associated with a product production. With these principles, green chemistry offers potential benefits in process development and manufacturing as well as product design of green nanoparticles. At present, numerous green nanoparticles with well-defined chemical composition, size, and morphology have been synthesized by different methods and their applications in many progressive technological areas have been explored (Hussain et al. 2015; Vinothkannan et al. 2015; Saini et al. 2015; Mashwani et al. 2015; Emmanuel et al. 2014).

Green chemistry has huge potential in navigating the responsible development of nanotechnology through the design of greener nanomaterials and the discovery of green nano producing methods. It provides potential benefits in process development and production as well as product design (Hutchison 2008). As several preparation processes for the molecular building blocks of nanotechnology engage high energy necessities or hazardous chemicals, the development of safe and greener processes for the manufacture of these materials is crucial. Several examples have been described where the risks of nanoparticle production have been drastically reduced by process redesign (Bazaka et al. 2016). Weare et al. (2000) developed an efficient and less hazardous production process for phosphine-stabilized gold nanoparticles that produces superior amounts of particles, in less time, in milder conditions, while using less hazardous reagents than the conventional preparation. The amino acid asparagine was used as a benign reducing and stabilizing agent for the production of monodisperse gold nanoparticles (AuNPs) using green chemistry principles. With an increasing concentration of amino acid asparagine (0.5–10 mM), the absorbance intensity at 525 nm increased; however, no effects on the color, size, or shape of the AuNPs were observed (Ghodake et al. 2015). The benefits of producing gold nanoparticles in supercritical CO_2 a greener solvent is safer and greener than is traditionally used solvent. Silver nanoparticles and Monodisperse gold have been manufactured through the use of living plants and in microorganisms (Ahmad et al. 2003). The application of micro reactors to manufacture nanoparticles in a rapid, continuous process results in improved energy efficiency, reduced waste, and increased control of product properties. Park et al. (2015) report a novel fluid-based fluorescent CD paints (C-paints) derived from polyethylene glycol and produced in quantum yields of up to ~14 %.

The sustainable synthesis of gold nanoparticles from gold ions was conducted with caffeic acid as a green reducing agent (Seo et al. 2015). In this study, newly synthesized gold nanoparticles exhibited catalytic activity toward the reduction of 4-nitrophenol to 4-aminophenol in the presence of sodium borohydride. The addition of metal oxide or metal into polymers make coatings that may sooner or later replace environmentally-harmful chromate coatings conventionally used for corrosion resistance (Štengl et al. 2016). Nanocomposite polymers based on biopolymers like chitosan and starch, intercalated with nanolayered clay has produced biodegradable polymers with the physical and mechanical characteristics that equal engineering plastics (Yong et al. 2015). In each of the above examples, green chemical strategies have offered opportunities for the improvement of synthetic methods that are more potential, reduce waste, and have enhanced health and environmental impacts (Geetha et al. 2015). Some of the green chemistry approaches in nanoproduction are evaluations of possible environmental and toxicological effects of nanoscale materials before they are included into technologies provide an opportunity to reduce negative consequences and encourage a sustainable nanotechnology industry. The improvement of low-waste methods and high-precision of nanoproduction will be crucial to commercialization.

Nanoscience provides new tools for green chemistry through novel design strategies and new nanostructured materials that are based on improved control of chemical and physical structure (Zhao et al. 2014). Devices with components of nanometer dimension are naturally lighter and faster, use less power, and often have improved performance. The novel chemical, optical, and electronic properties of these materials and the predictable high degree of control over these characteristics offer new scenario for greener materials and safe processes (Reddy et al. 2012). Green nanoscience grants various opportunities for better environmental technology through novel nanostructured materials with applications in remediation, sensing and pollution eradication. Nanoscale sensors based on nanowires or nanoparticles provide more rapid response time, give lower detection limits and make on-site, real-time detection possible. Several different types of inorganic nanoparticles have shown assurance as catalysts for photodegradation of pollutants in air, water, and soil. These nanomaterials are further the aims of green chemistry through superior advancement in evaluation and removal of hazards. Since green nanotechnology applications might involve a clean production process, such as synthesizing nanoparticles with sunlight or the recycling of industrial waste products into nanomaterials, such as turning diesel soot into carbon nanotubes, nanoscience applications in green chemistry can develop environmental remediation processes (Nath and Banerjee 2013). Another common function of green chemistry that is used in nanoscience is for increasing efficiency. Many nanostructured materials with particular preferred properties present more efficient material and energy consumption (Hussain et al. 2015). Catalysis by nanoscale metal complexes carries on to be an active area of research in both green chemistry and nanoscience (Kim et al. 2014). An additional tool that nanoscience offers green chemistry is dematerialization, a waste-reduction approach wherein nanoscale materials are used to replace macroscale counterparts. Considerable reductions in waste have been achieved through the use of molecular monolayers as an alternative of thick polymer films as masks for lithography and through nanoscale deposition of polymer electrolytes for non-lithographic patterning of metal oxide films. Nanoscience along with green chemistry has led to new potential catalysts where the catalyst is maintained in a nanoframework, which increases the, selectivity, catalytic activity and stability. Nanocomposite materials, which possess nano-scale components boost strength without adding weight, supply increased energy efficiency because of their lighter weight (Camargo et al. 2009). Thermoelectric devices made up of green nanoparticles are able to provide energy-efficient cooling or converting waste heat into electricity. Despite the benefits that nanomaterials are already providing in pollution prevention, remediation and well-organized use of resources, possibly the greatest contribution to green chemistry will be the novel production strategies available through nanoscience. Functional group assisted processes, such as self-assembly, can spectacularly decrease waste generation and energy requirements.

The nanomaterials of issue are those that are liberally dispersed or those that may become displaced from a bulk material during the usage of a material that contains embedded nanostructures. Although several hundreds of reports on nanomaterial hazards have been present in the literature, still it remains uncertain which characteristics of nanomaterials contribute to specific hazards (Winkler 2015; Bumbudsanpharoke et al. 2015). To develop the design rules for greener and safe nanomaterials; compositionally, structurally and well-defined nanomaterials are selected to study hypotheses regarding the influence of nano-structure on biological impact (Kumar et al. 2015). Systematic characterization and tests of purity are desirable to ensure that impacts can be interconnected to structural features (Ghodake et al. 2016). Biological testing is carried out to decide impacts and the mechanisms of action for exact endpoints. New hypotheses are proposed that contribute to materials design. Subsequent iterations of this process lead to enhanced understanding of the activity or structure relationships and to "design rules" for greener and safer nanomaterials (Balbus et al. 2007). To design new nanomaterials two approaches would be prudent; first avoid compositions which are toxic in nature; and second, thinking about the hazards of micrometer-scale and molecular materials of the targeted composition and keep away from compositions bracketed by smaller and larger materials with known hazards.

In terms of greener and safer nanomanfacturing, one would like to avoid use of toxic materials and reduce the production of hazardous by-product. Efficiency is also key factor to minimizing impact and improve manufacturability, that is, by increasing material efficiency, throughput, precise product control, and avoiding waste (Kaur et al. 2014). Nanoparticles with characteristics that depend particularly on each of their structural features like size, shape, composition surface coating etc., might be referred as fine nanomaterials (Kuhn et al. 2015). The recent methods of nanoparticle manufacturing of fine nanomaterials are usually depended upon the initial "discovery" routes. They regularly involve higher reactive and lethal reagents and have deprived efficiencies. The hazards and inefficiencies of these routes create significant risks during production and severely restrict production throughput. For these causes, the manufacture of nanoscale materials and devices is field where green chemistry principles can and should be readily applied to direct process improvement and innovation. Several examples are known that demonstrate the application of those principles and show how greener approaches often improve the manufacturability of the material by reducing costs, improving throughput and avoiding waste (Yan et al. 2016; Wang et al. 2015).

Therefore in consistence with universal efforts to minimize the generation of toxic waste and to develop energy-effective production, green chemistry and biochemical processes are increasingly integrating with contemporary developments in science and technology (Nath and Banerjee 2013). Green nanotechnology as a result aims to the application of green chemistry principles in designing nanoscale products, and the development of nanomaterial production methods with reduced toxic waste generation and safer applications. Hence, the definitive possible for green chemistry and nanoscience may lie in an integrated move towards the progress of 'green nanoscience'.

7 Green Nanotechnology-Challenges

As stated earlier, green nanotechnology is primarily focused on the application of the principles of green chemistry and sustainability. The highest levels of acceptance and benefits for society can be achieved if technological development of nanotechnology is attached with the evaluation of societal, environmental and economic impacts, posing the basis for complete sustainability evaluation of different NPs with the same functionality (Iavicoli et al. 2014). The health and safety concerns nanoparticles raised due to their unique physicochemical properties drew initial attention to their sustainability implications (Linkov et al. 2015). In addition to the recent immense progress, there are few challenges specific to green nanotechnology is that the science, the testing, the regulatory strategy, and even the processes required for commercial production are all being developed and deployed at the same time. There are still no clear guiding principles for researchers in preliminary discovery phases of green nanoscience. Many green nanomaterials require new commercial production techniques, which increases the need for basic research, engineering research, and coordination of the two between the industrial and research communities. Toxicology and analysis protocols need to be developed and constantly updated to reflect advances in the science. Regulatory uncertainty persists, and green nanotechnologies often face higher regulatory barriers than existing or conventional chemicals (Cinelli et al. 2016). The end-market demand is unclear, especially since there are only an inadequate number of commercial grade products that can be compared to conventional materials in terms of performance. A lot of research was then conducted to evaluate the impacts of NPs on sustainability, including life cycle assessments, economic and social impact assessments (Dobon et al. 2011) and broad development of criteria sets for a variety of risks, profits and sustainability implications.

8 Summary and Conclusion

Nanotechnology continues to offer new materials and applications that will benefit society. But, recently the stunning developments in nanotechnology have been with issues regarding to their potential effect on human health and the environment. There are no particular regulations on nanoparticles apart from existing regulations covering the similar material in bulk form. Difficulties abound in developing such regulations, further than self-imposed regulations by responsible companies, because of the likelihood of different properties exhibited by any one type of nanoparticle, which are tuneable by varying their size, shape and surface properties. Green nanoscience i.e green chemistry principles incorporated into nanotechnologies can answer many question posed by about whether the products or materials of nanotechnology will present hazards to human health or the environment and whether the production of these materials will generate new hazards. Merging green chemistry and nanoscience will have noteworthy impact on the products and processes of the future. To maturely develop nanotechnology, we must review, through appropriate metrics, new nanomaterials and nano-manufacturing processes and employ these findings to guide this promising industry. The use of nanomaterials to achieve the goals of green chemistry will provide new opportunity to build up superior products and processes with reduced impact on the environment and human health. The combination of these two emerging fields provides even superior opportunities for reducing the impact of new technologies on the environment and society.

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