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REVIEW ARTICLE

Impact of nanoparticles on human and environment: review of toxicity factors, exposures, control strategies, and future prospects

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Abstract Nanotechnology has revolutionized the world through introduction of a unique class of materials and consumer products in many arenas. It has led to production of innovative materials and devices. Despite of their unique advantages and applications in domestic and industrial sectors, use of materials with dimensions in nanometers has raised the issue of safety for workers, consumers, and human environment. Because of their small size and other unique characteristics, nanoparticles have ability to harm human and wildlife by interacting through various mechanisms. We have reviewed the characteristics of nanoparticles which form the basis of their toxicity. This paper also reviews possible routes of exposure of nanoparticles to human body. Dermal contact, inhalation, and ingestion have been discussed in detail. As very limited data is available for long-term human exposures, there is a pressing need to develop the methods which can determine short and long-term effects of nanoparticles on human and environment. We also discuss in brief the strategies which can help to control human exposures to toxic nanoparticles. We have outlined the current status of toxicological studies dealing with nanoparticles, accomplishments, weaknesses, and future challenges.

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Introduction

Use of nanoparticles (NPs) has been extremely increased in domestic and industrial processes in recent years. These NPs show unique physical and chemical conduct because of their large surface to volume ratio, extremely small size, and size-dependent optical properties (Xiao et al. 2008). Metal nanoparticles (MNPs) possess special catalytic properties (Migowski and Dupont 2007) and during the past decade, area of nanocatalysis has gone through an explosive progression (Narayanan and El-Sayed 2005). Widespread applications of MNPs can be found in the fields of biotechnology (Sönnichsen et al. 2005), bio sensing (Wang et al. 2001; Kwon and Bard 2012), clinical diagnosis and therapy (Jain et al. 2012; Cheng et al. 2014), food safety (Ricke and Hanning 2013), water and sewage treatment (Patil and Parikh 2014).

Moreover, with the passage of time, more nanotechnology applications are focusing in areas of construction, paint, medicine, food, cosmetics, electronics, optics, textile, energy, and agriculture. New departments and units have been established in universities and research institutes to explore the field and many governments are investing huge amount of their budgets for research in nanotechnology. But at the same time, researchers and social community has raised their concerns about environmental impact and toxicity of nanomaterial-based products. Currently, studies in area of nanotoxicity are increasing and many researchers are of view that toxicity and fates of nanomaterial must be studied before giving too much attention to their applications. There is a serious lack of

information concerning the human health and environmental implications of manufactured nanomaterial particularly NPs.

With rapid growth of NPs-based products, there is a pressing need to identify their potential toxic effects to the human body and wildlife. People working in nanotechnology-based industries and research centers are more exposed to these engineered nanoparticles (ENPs) during their generation, transportation, and final applications in various products. NPs have achieved great importance in medicine and diagnostics and resulted in a new medicine branch known as nanomedicine. As they improve therapeutic index of drug, recently, more than 20 types of NPs are being used in clinical applications and various other types are under their development stages (Zhang et al. 2008). Use of NPs for drug delivery and diagnostic applications inside different organs of the human body may impose serious toxic and harm effects on the body. NPs-based temperature sensors are widely used for measurement of temperature changes in biochemical reactions, chemical reactions, and thermal fluid-based materials and so on. These sensors are normally composed of NPs like Cd, Te, and Se which are highly toxic metals and there is increased possibility of inclusion of these particles into solutions and also their release into environment (Matsuda et al. 2013).

Sources of NPs in environment comprise of both natural and anthropogenic. Anthropogenic sources are further classified into intentional and unintentional. Figure 1 describes sources of natural and synthetic NPs and their life cycle in environment. Here in this document, we review the characteristics which govern toxicity of NPs from the perspective of recent research in this area. We critically outline the routes and mechanisms of toxicity of NPs to the human. Control of exposure to NPs is suggested and at the end we conclude present status of studies dealing with toxicology of NPs.

ENPs can be classified into following four types

1. Inorganic NPs which include all metal and metal oxide NPs.
2. Organic NPs which include polymeric and biologically compatible NPs.
3. Carbon-based NPs include carbon nanotubes, graphene, carbon nanofibers, carbon black, carbon nanofoams, carbon rods, etc.
4. Organic–inorganic hybrid NPs

Basis for toxicity of nanoparticles

The most important point before prediction of toxicity of NPs is to gain knowledge about the factors and properties which play major role in promoting their toxicity. The way these particles interact with human body and environment will decide their fate and effects. The example of most interactive and direct application of NPs in human body is their use in drug delivery. Clearance and distribution of NPs is subject to their nature and properties (Alexis et al). Here, we briefly discuss properties of NPs which make them toxic.

Size

As NP size becomes small, the surface to volume ratio increases exponentially, which make these particles more reactive and toxic. Secondly, with decrease in size their ability to penetrate into plant and animal tissues increases. At such a small size, even common substances behave in uncommon ways. Some substances that do not conduct electricity or are fragile become excellent conductors when they are small enough. Penetration of NPs through different barriers of cells has large dependence on size. It is postulated that particles with size less than 35 nm can penetrate into blood–brain barrier and particles with size smaller than 40 nm can enter into nuclei of cells while those with size less than 100 nm can enter into cells by crossing cell membrane (Oberdörster et al. 2008; Dawson et al. 2009). Binding and post-binding stability of protein structures is also reported to depend on size of NPs (Fertsch-Gapp et al. 2011; Deng et al. 2012).

Silver nanoparticles (AgNPs) were observed to induce size-dependent cytotoxicity in human lungs cells due to significant release of Ag in cellular medium (Gliga et al. 2014). In vitro studies show that AgNPs induce a wide range of toxicities including inflammation, genotoxicity, cytotoxicity, and developmental toxicity based on size of particles (Park et al. 2011). Small-sized (<10 nm) TiO_2 NPs showed immune toxicity in rat's pulmonary system (Liu et al. 2010). Different sizes of TiO_2 NPs exhibit difference in toxicity to rat pulmonary system.

Size of NPs affects adsorption and catalytic activity of the proteins as it was reported by a study in which different-sized silica NPs were checked for their effects on adsorption and function of chicken egg lysozyme (Vertegel et al. 2004). Gold nanoparticles (AuNPs) functionalized with non-toxic groups showed acute and chronic toxicity based on their size (Bozich et al. 2014). Reduction of oxygen on Ag electrode follows a simple mechanism which involves two protons and two electrons. An intermediate product H_2O_2 is further reduced to water. But same reduction on NPs releases too much H_2O_2 which is an evidence form electrochemistry that AgNPs are more toxic compared to bulk Ag (Batchelor-mcauley et al. 2014). Nano-sized copper oxide (CuO) particles showed 10 to 20 times more toxicity than bulk CuO against protozoa *Tetrahymena thermophila* (Mortimer et al. 2010).

Size-dependent toxicity of NPs can be explained by some more examples. Cellular interaction studies indicated that small-sized (15 nm) AgNPs induced more toxicity to the cells by generating 10 times higher amounts of reactive oxygen

species compared to large-sized (30 and 55 nm) AgNPs (Carlson et al. 2008). AgNPs showed cytotoxicity to human lung cells at size of 10 nm which was independent of surface coating (Gliga et al. 2014). Five-nanometer-sized NPs exhibited more toxicity to nitrifying bacteria than their large-sized counterparts (Choi and Hu 2008). Rainbow trout fish was exposed to commercially available AgNPs of different sizes (10, 35, 600–1600 nm) in order to determine their fate and effects and the results revealed that high amounts of small-sized (10 nm) particles were accumulated in gill and liver tissues (Scown et al. 2010). Similarly, small-sized (1.4 nm) AuNPs induced 60 to 100 times more cytotoxicity to a variety of cells than large size (15 nm) NPs (Pan et al. 2007). Another study revealed that cellular uptake of carboxylic acid-functionalized polystyrene beads (PBs) was much quicker for 20 nm compared to 200 nm (Clift et al. 2008). Generalizing the size ranges of different NPs which can induce more toxicity is much difficult due to reason that there are no standard toxicity procedures followed by all researchers. Most of the reports differ from each other in toxicity aspects studied. A common feature revealed by all reports favor the postulate that small-sized NPs are more toxic compared to their large-sized counterparts. More examples explaining toxic effects of most common NPs in certain size ranges have been listed in Table 1.

Hence, size of NPs matters in order to determine their toxicity in living organisms. Cellular uptake, interaction mechanism, and intercellular stability are functions of NP size but still a clear-cut correlation cannot be developed based on available studies. In a summarized way, it can be said that

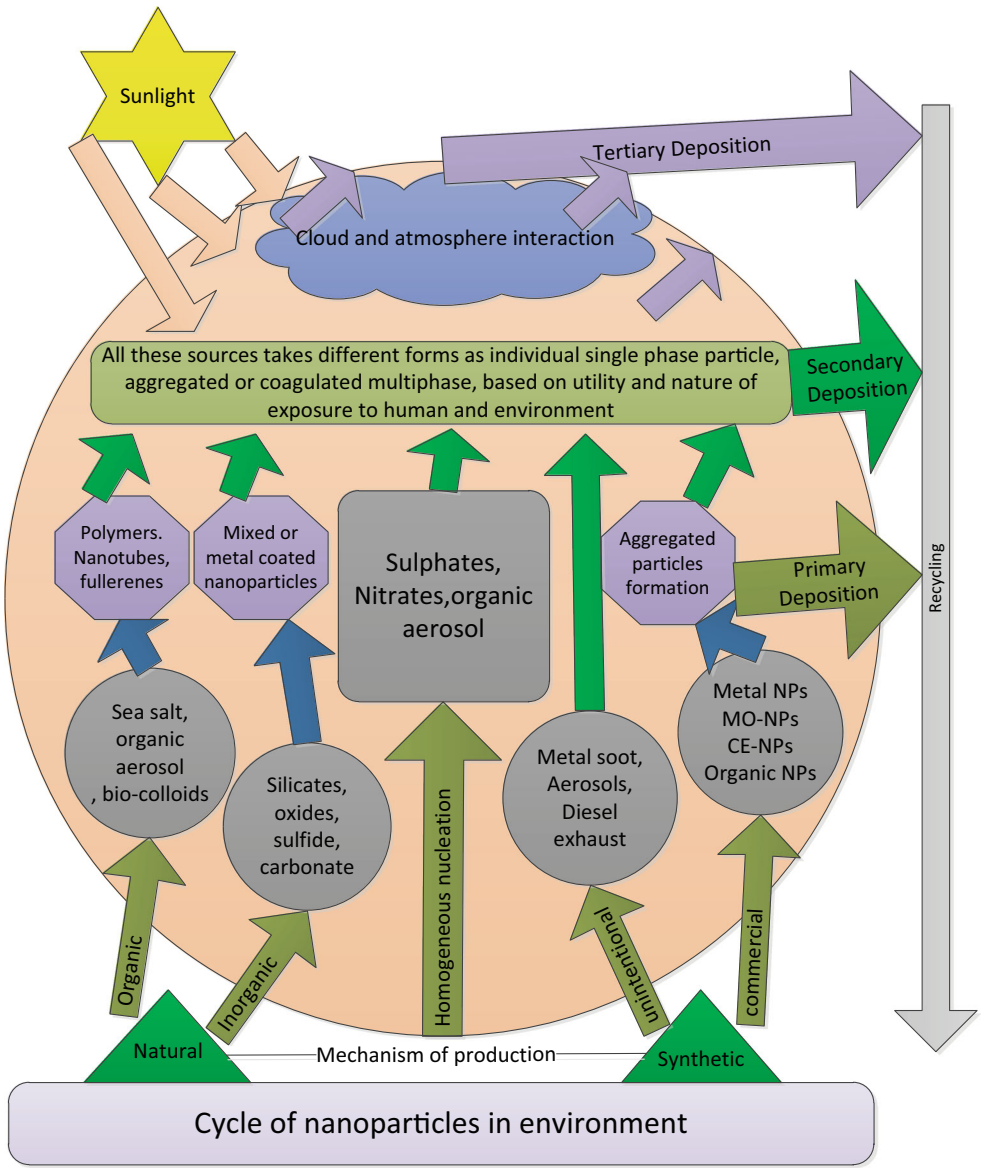

Fig. 1 Cycle of nanoparticles in environment

Table 1 Description of sources, tested target, important factors, and nature of toxic effects for various classes of common nanoparticles

NPs	Size distribution	Sources in environment	Testing Target	Important factors	Nature of toxicity	Reference
Ag NPs	13–15 nm	In domestic appliances as antimicrobial agent, plastics, paints, varnish, textile	Plants, bacteria, microalgae, aquatic species	Toxicity depends on surface properties, release of $Ag^{+,}$ and coating of Ag particles	Damage to cell membrane, disrupt ATP, DNA replication, release oxidative ROS	(Blaser et al. 2008; Sharma et al. 2014)
Au NPs	4–5 nm	Drug delivery, high-quality imaging, gene therapy, cancer therapy, wastewater treatment	*Daphnia magna*, rats	Functionalization greatly affects toxicity, acute and chronic exposure depends on ligands attached	Affects reproduction, in daphnia, mammals, algae, fishes, accumulates in liver, causing oxidative stress	(Umamaheswari et al. 2014; Bozich et al. 2014; Fraga et al. 2014)
TiO_2 NPs	40–100 nm	Sunscreen products, food products, paints, toothpaste medicine, agriculture products, effluent, sludge, watewater	Soil nematode, zebra fish, *Vicia narbonensis*, plants, soil,	Depends on surface chemistry, stability, residence, release of TiO_2 in wastewater	Negatively effects on wheat growth and soil enzyme actives, embryonic toxicity to fishes, phytotoxic effects, DNA fragmentation	(Khare et al. 2011; Du et al. 2011; Gondikas et al. 2014; Ruffini Castiglione et al. 2014; George et al. 2014)
CNTs NPs	20–200 nm	Water treatments, lubricants, electronics, sporting equipment, bioaccumulation in food chain to human health	Rat, human, zebrafish, rainbow trout, wheat, tomato, soil/sediments accumulation	Depends on particle size, shape, surface charge, functionalization, degradability, protein corona, and surface modifications	Human lungs, epithelial cells, Rat glioma cells, Embryos toxicity, cell proliferation, Gill accumulation, liver damage, brain, andintestine pathologies, respiratory toxicity, Phytotoxicity, seeds germination, inflammation	(Helland et al. 2008; Mueller and Nowack 2008; Khodakovskaya et al. 2009; Fraser et al. 2011; Kaiser et al. 2012; Han et al. 2012; Du et al. 2013; Lanone et al. 2013; Sarma et al. 2014)
Amino-polystyrene	20–60 nm	Medical applications, packaging of food materials, home appliances, IT and electronics materials, in construction material, toys applications	Adverse to environment and Human body	Toxicity is determined by functional group attached, Cationic polystyrene is more toxic, toxicity depends on pathway to cell and mitochondrial penetration, particle size, and exposure limit have major influence, highly resistant to metabolism	Highly toxic to macrophage, hepatoma, epithelial cells, cardiovascular endothelial, mitochondrial uptake, and cell death, ATP depletion, high concentration induces cell death	(Xia et al. 2008; Baun et al. 2008; Eidi et al. 2012; Elsabahy and Wooley 2012; Kim et al. 2013; Ware et al. 2014)
Quantum dots	Up to 515 nm	Photo luminescence medical applications, Use in plant bioimaging, Tracking different particles, drug delivery, and therapy	*Elliptio complanata*, monkeys, freshwater mussels	Depend on surface modifications, bioactivity, size, concentration, stability, environmental factors,	oxidative stress in plants, endothelial toxicity through activation of mitochondrial cells, cell viability decreased with increasing concentration of QD,	(Shiohara et al. 2004; Hoshino et al. 2004; Yu et al. 2006; Hardman 2007; Gagné et al. 2008; Valizadeh et al. 2012)

small size particles are more suspected to cellular internalization and show more toxicity than the larger ones (Hsiao and Huang 2011; Shang et al. 2014).

Shape

Shape of NPs also contributes to their toxic effects. Simulation-based computation showed that shape and charge on NPs can accelerate their translocation process through cell membranes up to 60 orders of magnitude (Nangia and Sureshkumar 2012). Different+shaped AgNPs are reported to affect the cells in a different way (Stoehr et al. 2011). When size and surface area is kept same for one type of NPs then their shape becomes more prominent in evaluation of toxicity. ZnO NPs in shape of nanorods induce more toxicity to human lung epithelium cells (A549) than spherical ZnO NPs (Hsiao and Huang 2011). Similarly, AuNPs with same functionalization showed that spherical particles contributed more to toxicity than rod-type particles and it might be due to more rapid release of functional molecules from spherical surface upon cellular interaction (Tarantola et al. 2011).

Nature

Nature of NPs is also one of the key factors which contribute to toxicity. As it is very well-known fact that all the materials in bulk have different toxic effects compared to nano-sized particles which range from negligible to very high, in the same manner nature of the NPs also affects their toxicity. Many studies favor this factor, for example AgNPs were found more toxic than CeO_2 NPs for a range of toxicity measuring tests (Gaiser et al. 2012). AgNPs induced higher toxicity to transparent embryos of zebrafish than gold NPs at the same size range and concentrations (Bar-Ilan et al. 2009). Different-natured NPs and biological assays describing their toxic effects have been listed in Table 2.

Reactivity

One major characteristic of NPs is their extremely high reactivity compared to other materials which led them to be used for catalysis. Reactive NPs start catalytic reactions within the cells and result in production of reactive oxygen species. As the particles do not go under degradation in catalytic processes, so chain of reactions can be expected within biological systems. This unusual reactivity makes NPs highly toxic (Stark 2011). Charge on NPs makes them more reactive towards cells and proteins compared to their neutral counterparts (Deng et al. 2013).

The main mechanism of particle-induced damage is the production of reactive oxygen species (Nel et al. 2006). As particle size shrinks, surface group's reactivity increases exponentially. Surface reactive groups may be of different kinds, e.g., hydrophilic, hydrophobic, or catalytic. These reactions often generate free radical oxygen species and these species are too reactive to induce oxidative stress in cells.

Mobility

NPs are solid particles which are capable of movement in the way gases and liquids move. While determining any toxic effects of NPs to human and environment, factors related to their mobility must be taken into account. Due to their high mobility and small size, NPs can diffuse into plant and animal cells with much ease. Diffusion of particles increases as their size decreases. Mobility is also one factor which helps in aggregation of NPs by bringing them close to each other.

Stability

Stability of NPs within biological system will depend on their nature, size, and concentration. System pH is important for stability of NPs. In biological systems' pH, most of the inorganic and organic NPs become soluble. In case of metals and metal oxide NPs, concentration of metal ions increases within the cells which lead to high stress within the cells. Presence of heavy metal ions can affect reactive oxygen species. Solubility of NPs in an environment is key parameter related to their stability and toxicity. Slightly soluble particles such as ZnO caused death of MSTO and 3T3 cells when exposed to concentration above than 15 ppm but in case of uncoated iron oxide NPs response was dependent on cell type. In case of insoluble NPs such as ceria, zirconia, and titinia, cell activity and DNA quantity was reduced but at very high concentrations (Roy et al. 2003).

Surface chemistry and charge

Likewise, NPs are functionalized and fabricated with different organic moieties for applications in different areas. Studies showed that different functionalities create different charges over NP surfaces, e.g., –COOH functionalized NPs are considered positively charged while $–NH_2$ functionalized NPs are considered negatively charged. These functionalities do not change only charge but their way of action in biological systems. Cationic chains functionalized AuNPs were found moderate toxic while anionic chains functionalized AuNPs were found non-toxic (Goodman et al. 2004). Uncoated and coated with three different functionalities, AgNPs were exposed to bacillus species and results revealed that toxicity was highly dependent on surface charge (El Badawy et al. 2011).

Table 2 List of biological assays and their findings for assessment of toxicity of different natured nanoparticles

Nanoparticles	Important biological assays	Medium	Important findings	Ref.
AgNPs and bulk $AgNO_3$	1. LC50 2. Pharmaceutical rescue assay 3. ROS formation assay 4. Oxidative DNA damage measurement	Nematode, *Caenorhabditis elegans*	1. AgNPs and $AgNO_3$ possess sametoxicities. 2. PVP coated AgNPs have less toxicity but it size depended. Smaller AgNPs are more toxic. 3. AgNPs and $AgNO_3$ induce oxidative DNA damage.	(Ahn et al. 2014)
Citrate and humic acid capped AgNPs and $AgNO_3$	1. Exposure to different concentrations. 2. Ag uptake.	Eggs, larvae, juveniles and adults of P. dumerilii	1. Abnormal developments are higher in early stages of life. 2. Fertilized eggs are sensitive to all tested materials. 3. Highest cute toxicity was induced in Platynereis dumerilii by HA-AgNPs. 4. AgNPs are more toxic than $AgNO_3$.	(García-Alonso et al. 2014)
CuO, ZnO and Ag-TiO_2 NPs	Hatching	*Labeo rohita*	Higest hatching in CuO and ZnO nanoparticles while lowest in Ag-TiO_2	(Swain et al. 2014)
Cationic and anionc polystyrene NPs	1. MTT and phagocytic index (PI) assay 2. ROS production by the DCFH-DA	Macrophage NR8383 cells	1. Highest cytotoxicity was shown by aminated cationic PSNPs due to formation of ROS. 2. Effect was more prominent with small size particles. 3. Both negatively and positively charged PS NPs increased roughness of cell membrane.	(Bhattacharjee et al. 2014)
Zero valent aggregated CuO NPs	Antibacterial assay	*E, coli*	Toxicity of nanoparticles is affected by temperature, aeration rate, pH, concentration of NPs, and concentration of bacteria itself.	(Rispoli et al. 2010)
Cobalt ferrite NPs	Microphysiometer	Fibroblast cultures	1. Cytotoxic effects were observed. 2. Microphysiometer is a good method to find toxicity of nanoparticles	(Mariani et al. 2012)
CuO, NiO, ZnO and Sb_2O_3	Microbial toxicity	*Escherichia coli*, *Bacillus s ubtilis*, and *Streptococcus aureus*	1. Cuo NPs showed maximum toxicity. 2. Presence of heavy metal in NPs also contributes to toxicity. 3. When dissolved ions of the same metals tested for toxicity, negligible effects observed compared to metal oxide NPs.	(Baek and An 2011)
Nickel NPs	1. Mitochondrial function (MTT assay) 2. Reactive oxygen species (ROS) 3. Membrane leakage of lactate dehydrogenase (LDH assay),	Human lung epithelial A549 cells	1. Time-dependent decrease in mitochondrial function. 2. Dose- and time-dependent oxidative stress due to production of ROS.	(Ahamed 2011)
Biodegradable chitosan NPs	Exposure of zebrafish embryos to nanoparticles	Zebra fish embryo	1. Chitosan NPs at size of 200 nm cause various malformations in zebrafish embryo. 2. Exposure increased rate of cell death and reactive oxygen species.	(Hu et al. 2011)
COOH, plain and NH2 modified superparamagnetic NPs	1. MTT assay 2. DNA microarray analysis	Human heart, brain, and kidney cell lines	1. Toxicity is cell type dependent. 2. Bare particles induced more toxicity than coated ones.	(Mahmoudi et al. 2011)
ZnO NPs		1. human myeloblastic leukemia cells (HL60) 2. Normal peripheral blood mononuclear cells (PBMCs). 3. Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* 4. Gram-positive bacterium *Staphylococcus aureus*	1. Selective ability to kill cancerous cells 2. More antibacterial activity towards Gram-positive bacteria than Gram-negative.	(Premanathan et al. 2011)

NPs adsorb proteins on their surface and form nanoparticle-protein coronas. Such adsorptions depend on particle size and interaction between the groups on nanoparticle surface and amine groups of proteins (Saptarshi et al. 2013).

Daphnia magna toxicity assays for functionalized AuNPs showed that not only charge on the functionalized group adds to acute and chronic toxicity but also the type of the functionalized group plays a role in toxicity (Bozich et al. 2014). Toxicity, fate, and stability of AgNPs in any medium is highly dependent on the type of surface-coated organic groups (Sarma et al. 2014). Hydrophilic and hydrophobic monolayers-modified AuNPs were studied for their uptake, distribution, and toxicity in medika fish. It was found that hydrophilic particles were present in intestines of fish but no obvious health effects were observed while hydrophobic particles were spread into different organs of the fish, resulting in mortality of fish in less than 24 h (Zhu et al. 2010c).

Agglomeration/aggregation

NPs have ability to agglomerate in solutions. Extent of agglomeration depends on size, shape, concentration, charge, temperature, and type of NPs. Agglomerated NPs behave in a different way than the individual dispersed particles mainly because of changes in surface properties. Hence their way of interaction with cells and tendency of protein adsorption will be greatly affected (Skebo et al. 2007; Herzog et al. 2009). Aggregation largely affects cellular uptake and hence the toxicity. Cellular uptake of transferrin-coated AuNPs by HeLa and A 549 cells was decreased by 25 % upon aggregation but it increased by twofolds for MDA-MB 435 cell (Albanese and Chan 2011).

Medium and storage time

Medium in which NPs are synthesized or stored in, also play a role in determining their toxic effects. Change in ionic strength may change size and hence toxicity of nanoparticles. Citrate capped AgNPs showed media-dependent toxicity against (*Oncorhynchus mykiss*) gill, RTgill-W1 cell line (Yue et al. 2014).

Studies indicate that toxicity of NPs varies with their storage for longer time in any media. Dissolution studies were carried out for AgNPs which were stabilized with different organic functionalities. It was observed that particles dissolve into water with the passage of time but a limit is reached after some days. Toxicity of NPs solution containing dissolved Ag ions was enhanced against human mesenchymal stem cell and it was attributed to Ag ions which were released into aqueous media upon storage for several weeks (Kittler et al. 2010).

Common exposure routes and mechanisms of NPs to human body

The exposure of nanoparticle to environment and human can be described through different mechanisms. Primarily occupational exposures occur to workers (including engineers, scientists, and technicians) during the research-scale synthesis and commercial production of nanomaterial-based products. This exposure mainly results from handling of raw materials while carrying out reactions through the equipment. Characterization of resulting material, packing, and transportation can be other sources of this type of exposure. At the second stage, consumers are exposed to such nanomaterial during usage and application and it may lead to harmful and toxic effects (Tsuji et al. 2006). Here, we will discuss some detailed mechanisms of exposure of NPs to human body and their toxic effects. Complex biological terms are avoided in order to make this subject understandable for a range of scientific community dealing with nanoparticle applications. Interaction of NPs to human body can occur through following routes.

1. Penetration through skin nodes
2. Intake by respiratory system via inhalation
3. Intake by digestive system via ingestion

One most important issue is to understand the mechanism and extent of NPs exposure. Almost all the substances, from small heavy metals to macromolecules of organic compounds are toxic to cells, plants, and animals above a specific level.

Currently, the understanding of the mechanism of NPs diffusion into human system, uptake by cells and tissues, their way of distribution and possible health effects are imprecise and are being explored worldwide. Main routes of NPs exposure to human body are penetration through skin, ingestion through food materials and inhalation through respiration. These up taken particles penetrate to other organs through respiratory and blood circulation systems (Slivka et al. 1993; Brigger et al. 2002; Pattan and Kaul 2012). A schematic diagram of mechanism of human exposure to ENPs and their risk assessment is described in Fig. 2.

Penetration through skin

With the development of nanomaterial field especially applications of NPs in medicine, the risk of exposure to NPs through skin and their entrance into blood circulation is increased and it resulted in increased safety concerns. To

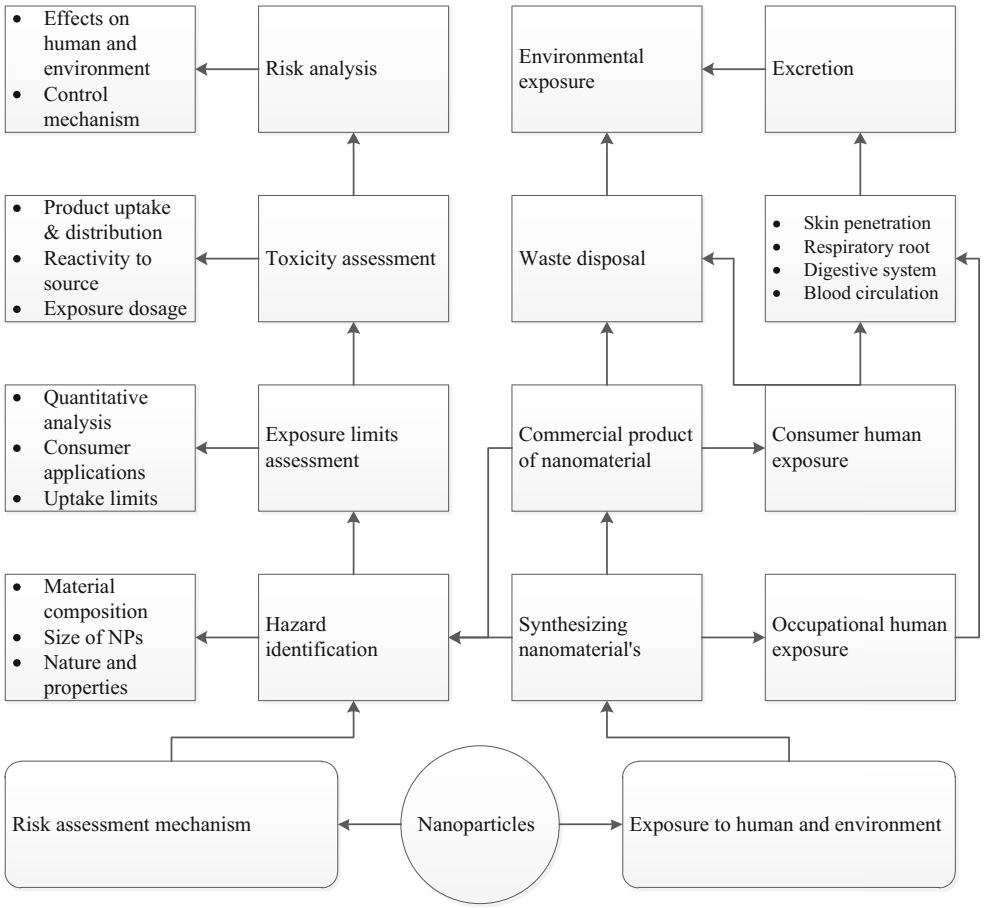

Fig. 2 Mechanism of human exposure and risk assessment of engineered nanoparticles

address these issues, a lot of attention is being paid to study of skin exposure mechanism, factors controlling penetration, penetration mechanism, and potential effects on skin (Liang et al. 2013).

The exposure of human skin to NPs can occur via intentional and unintentional means. Intentional exposure to NPs could be the result of applications of cosmetics products such as creams, lotions, and sunscreen containing coated NPs of TiO_2 and ZnO. These particles are thought to be activity enhancers for cosmetics. Unintentional exposure of NPs to human skin occurs through directly generated NPs during manufacturing, combustion, and disposal of used nanomaterial-based products (Oberdörster et al. 2005). Others sources of unintentional human and environmental exposure to NPs can be through vehicles tailpipe emissions, natural gas/powdered equipment (Rundell 2008), ultrafine particles generation during waxing of skin, welding fumes emissions (Zimmer et al. 2002) and emissions from coal, natural gas, and oil fired power plants.

There are two possible mechanism of NPs penetration into the skin, intercellular trans-epidermal mechanism, or diffusion through skin pores and hair cavities (Bennat and Müller-Goymann 2000). The main absorption of NPs may occur through several routes, including lipid-soluble particles which penetrate through intercellular lipid mechanism by stratum corneum cells, through transcellular cells pathway, hair follicle, and sweat ducts (Monteiro-riviere and Inman 2006). The concerns about penetration of NPs through skin and resulting toxic effects are highly debatable topics among researchers and scientists. These concerns include cytotoxicity of skin, toxicity during accumulation in skin for long time, metabolism with potential of toxicity and photo-activation of NPs when present at skin (Tsuji et al. 2006).

Human skin is an effective barrier towards NPs and other toxic chemicals; however, the presence of hair follicles and sweat glands makes this barrier susceptible by facilitating the penetration of small-sized NPs (Teow et al. 2011). Mostly NPs are less detected through viable skin while more penetration occurs to hair follicles when protective layer of skin is removed, damaged, or wounded (Mavon et al. 2007). TiO_2 NPs surface coating may indirectly damage the skin which results in NPs penetration into skin. The application of NPs in treating wounds and damage of skin accelerates penetration (Teow et al. 2011).

Antimicrobial properties of AgNPs have made these particles one of the most frequently utilized nanomaterial in skin care products (Miethling-graff et al. 2014). The toxicity of AgNPs have been reported to be mediated by the induction of

oxidative stress that is associated with decreased viability, the inhibition of mitochondrial activity and the initiation of apoptosis and cell death (Foldbjerg et al. 2009).

Many products often contain the substances which enhance penetration of material to skin (Finnin and Morgan 1999). Many nanoemulsions have good penetrating ability and they are used to deliver active ingredients to the deeper layers of skin. Particles which have size of 1,000 nm or smaller can penetrate to normal skin and this parameter is agreed by the researchers. But unfortunately, up to date, none of these products manufacturers have described the penetrating ability values. This is due to the fact that these particles are still not fully characterized from this point of view. It is unethical to manufacture and supply the when their toxicity and long-term effects are not well understood. A long-term study and animal testing is required to know all these parameters.

Once these particles find a way to enter the skin, now they can show their various toxic forms. They may be allergic, irritants, or can damage cellular or sub cellular parts of body, they may start some chemical reaction which leads to oxidation of material present in the body. Carbon nanotubes when incubated with keratinocytes in tissue culture caused mitochondrial dysfunction, oxidative phosphorylation, and generation of reactive oxygen species (Shvedova et al. 2003). Nanomaterials can also induce an injury response inside the skin leading to inflammation. They can denature proteins and unmask epitopes; for example, soot NPs from diesel exhaust promote antigen uptake by dendritic cells (Barlow et al. 2005). These NPs can even damage DNA and cell. NPs can form aggregates and sludge.

Even the penetration of very small concentration of NPs can influence in various ways. Use of NPs in undergarments or skin care products may result in entrance to female reproductive tract and can change the integrity of the reproductive lining. This may be a cause of infertility and one or sexually transmitted diseases. But these risks to the fetus have not yet been absolutely investigated. Skin, hair, and hygiene products containing nanomaterial are used by many young women in their daily routine. This issue of nanotechnology requires to be addressed immediately and needs attention of researchers.

Inhalation

Upon inhalation, NPs can penetrate deeper into lungs and interact with epithelium. This can cause inflammation and chronic effects by further penetration into interstitum and finally these NPs may transfer to lymph nodes (Donaldson et al. 1998). The behavior of inhaled particulate matter differs significantly than that of gases or volatile liquids. Particulate matter deposition on lungs is dependent on aerodynamics of particles physical–chemical characteristics, respiratory tract anatomy, and health status of host object or organ (Hoet et al. 2007).

Understanding aerosol inhalation requires the knowledge of particle transport mechanism, depositing in the lung, and clearance mechanism. Transport of particles into lungs and deposition in the respiratory tract are dependent on three main determinants including: the anatomic structure of the breathing tract, air flow patterns, and the flowing characteristics of particles (Bakand et al. 2012). Clearance time of deposited particles depends on how deep particles are penetrated into lungs. Similarly, particle-cell and particle–tissue interaction increases with deeper penetration. This interaction promotes adverse health effects. Once deposited, these very small-sized particles are able to cross the blood-air tissue barrier and translocate to blood streams through which they are transferred to other organs (Oberdörster et al. 2005). Still, insoluble particles reside inside the lungs for prolonged time period, which may cause cells destruction and biological disorder of tissues (Miller et al. 2005; Mühlfeld et al. 2008).

Extremely small particles are deposited in alveoli through diffusion mechanism where air flow is very small. Diffusion plays a predominant role in deposition of NPs deeper into the pulmonary region due to displacement, while they collide with air molecules (Borm et al. 2006)

For instance, the toxicity of CNTs is more adverse in case of inhalation, causing severe inflammation as compared to oral or dermal exposure which has mild effects (Foldvari and Bagonluri 2008). After inhalation, CNTs interact with cells, proteins, and tissues of biological organs and may retain their structure or metabolized depending on their physiochemical properties (Pichardo et al. 2012), from where translocation to various parts of body occurs through blood streams (Sharifi et al. 2012). Most effective factors determining toxicity of CNTs include dimensions, purity of material, functional groups attached, methods of production, and modification of these factors (Madani et al. 2014).

NPs can also induce nasal pathology. In such situation when nasal epithelial cells are exposed, they may become injured, and mucous membranes can be damaged. Smell sensation and nasal humidification ability reduces in such cases. Effects become more prominent as the NP size decreases. As the particles are very small, it becomes harder to eliminate these particles and ultimately defenses of the nasal air passages are eroded. In rodents, intranasal viral and metal NPs may take a path to the brain (Oberdörster et al. 2004). Such compromised nasal mucosal epithelium can facilitate entry of infectious or noxious agents into the brain, upper respiratory tract, and lungs.

The inhalation effects of NPs on lungs depend on the (1) dosage of nanoparticles, (2) deposition in lungs, (3) dimensional characteristics of particle, (4) persistence of particles, and (5) defense/clearance mechanism (Borm and Kreyling 2004). The deposition NPs in respiratory tract increases sharply as the size of particles is decreased. A major part of these particles is deposited in the gas exchange region and epithelial

terminal airways structures. From continuous inhalation, insoluble and non-degradable particles having more durability accumulate in the lungs; however, lungs have strong defensive system in the form of upper airways (mucociliary clearance) and lower airways, alveoli (macrophage clearance) to remove deposited nanoparticles. Soluble and degradable particles transport from alveolar to larynx and swallowed, digested, and excreted from human body. Since transport rate is slow, only about one third of these particles are cleared through this mechanism. Remaining particles have more pathogenic effects unless removed or degraded. Reactive nature of these particles may damage macrophages and epithelial cells leading towards inflammation of lungs (Gehr 2000). Inhalation of NPs and their transport and fate in lungs is schematically described in Fig. 3.

Most of the studies regarding mechanism of translocation of NPs to other organs are still very rare and conflicting (Borm and Kreyling 2004). Oberdörster and coworkers found rapid translocation of more than 50 % of C-13 (26-nm size) NPs towards the liver within 24 h of inhalation in a rat model (Oberdörster et al. 2002). However, Kreyling and coworkers observed translocation of only minute amount (<1 %) of iridium NPs (15–20 nm size) into rats' blood reaching not only towards liver but also into kidneys, spleen, heart, and brain (Kreyling et al. 2002). Nemmar et al. reported a rapid uptake of 3–5 % of carbon-based NPs within a minute of exposure into bloodstream and subsequent uptake by liver (Nemmar et al. 2001).

Ingestion

The research and knowledge related to applications and toxicity assessment of NPs in food-related materials and products is still not sufficient to completely correlate and describe ingestion process (Chaudhry et al. 2008). Ingestion of NPs is a major exposure route to human body (Foldbjerg and Autrup 2013). NPs directly or indirectly employed in food products and drugs are ingested orally and get absorbed through mechanism of gastrointestinal tract from where they enter in lymphatic cell tissues (Teow et al. 2011). Many factors are involved in controlling the absorption of NPs in gastrointestinal tract including size of particles, geometry, surface charge, ligand type, and attachment potential to ligand (Hillyer and Albrecht 2001). These ingested NPs depending upon their nature are either excreted if unstable or agglomerated by physical or chemical changes resulting in blockage of gastrointestinal tract leading to death (Wang et al. 2006). Absorption of ingested polystyrene NPs through gastrointestinal tract in rats has been reported in some studies (Jani et al. 1990).

NPs may accumulate in marine food from the waste disposed into water bodies and this polluted food may act as one possible source of ingestion (Ward and Kach 2009). Toxicity induced by ingested TiO_2 NPs results in damage of digestive gland cell membrane through oxidative stress mechanism (Valant et al. 2012). Gastrointestinal exposure may occur through direct ingestion or by mucociliary escalator transport (coughs and swallow). This ingestion may occur frequently by the use of food, water, drugs, and cosmetics. Such ingestion results in alteration of food metabolism and absorption as well as drug metabolism and absorption, or the composition of flora found in the gut. Permeability of the gastrointestinal tract may be changed by diseases with cutaneous manifestations.

NPs may behave differently when enter hepatic circulation. They can be hepatotoxic, or sludge in the biliary tree or the pancreatic ducts and may cause obstruction or gradual fibrosis. They may change the permeability of the gastrointestinal lining and can result in ulcers, weakening of the epithelium, cause metaplasia or dysplasia of the epithelium, malabsorption of nutrients, or in severe cases may lead to chronic bleeding. Parenteral nutrition basically uses very small-size emulsions of soy and lecithin. It is known that soybean oil is toxic to cell membranes in nanoemulsions. The toxicities of nanomaterials should be thoroughly evaluated before parenteral administration (Moreno et al. 2003). Recent research shows that CNTs which are parenteral soluble, excreted renally with 99.9 % efficiency. Moreover, soluble CNTs are more reactive and allergenic than insoluble ones. Nanotechnology-based production processes for vegetarian food which employ pesticides, water, soil purification sprays, and chemicals can be a cause of oral exposure of NPs to human body.

Environmental factors which govern toxicity of nanoparticles

Environmental factors can contribute to toxicity of nanoparticles. Weather conditions such as humidity, temperature, wind flow rate, geographical latitude, and nature of light may affect certain properties of NPs which drive their toxicity. At higher temperatures, NPs can disperse at increased rate compared to lower or normal temperatures. It is a well-known fact that NPs behave differently under different lights such as visible and ultra-violet. Wind speed can help these extremely small-sized particles to penetrate though plant and animal tissues. Some diseases have high incidence rates in one graphical location and same behavior can be expected from toxic nanoparticles.

Effects on aquatic environment

The aquatic environment is more prone to be contaminated with the NPs mainly due to increase in the consumer products like sunscreens and cosmetics which contain NPs like TiO_2 (Popov et al. 2005). NPs are toxic for the aquatic animals such as fish or daphnia and for unicellular organisms as well (Nowack and Bucheli 2007). Susceptibility to toxicity for

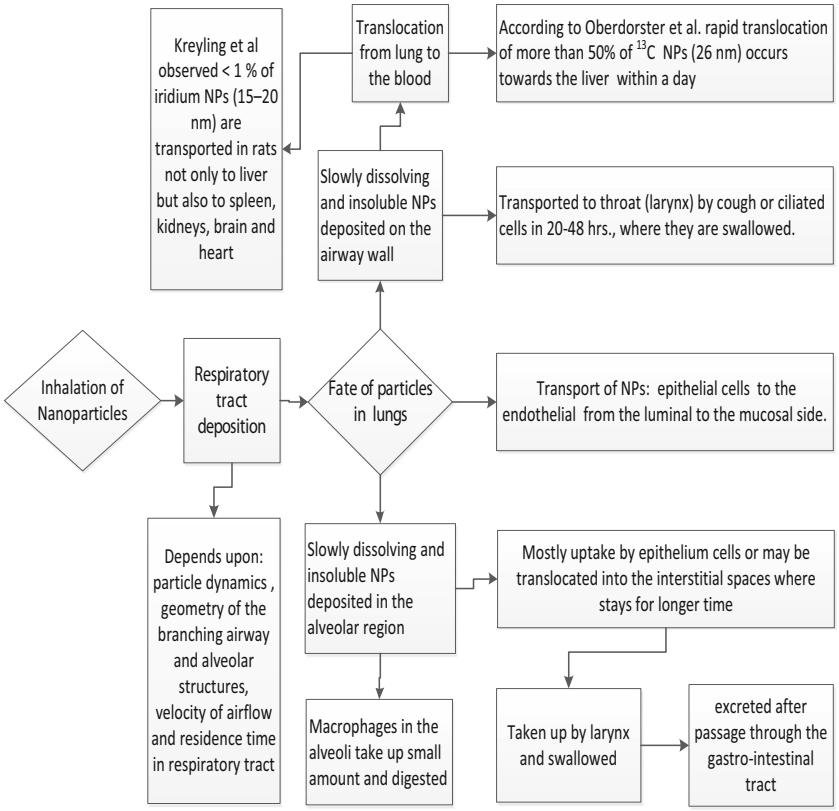

Fig. 3 Inhalation of nanoparticles and their transport and fate in lungs

aquatic animals varies from species to species (Griffitt et al. 2008). Determining exact concentration of the NPs in aquatic environment is still challenging. The engineered NPs are highly toxic and selective pathway mechanism exists for the fish and rodents (Tjälve and Henriksson 1999). Along the particle size which provides a large surface area to volume ratio, the biocompatibility of the NPs with organism also depends on the surface charge and its chemical reactivity (Oberdörster 2004). The particle size and later on biodegradation of the particles may have hazardous biological effects on aquatic organisms. The small particles due to large surface area could generate oxygen-reactive species which are very harmful and cause serious damage to proteins, DNA, and membranes (Reijnders 2006; Brown et al. 2001). The NPs may enter into the aquatic animals through gills and ingestion (Oberdörster et al. 2008).

When algal species, dolphins, and zebrafish were exposed to the ENPs of nickel, copper, silver, and aluminum, results revealed that silver and copper NPs had hazardous effects on all the tested organisms (Griffitt et al. 2008). A high degree of homology is possessed by the zebrafish with the human genome, so it is chosen for study of risk assessment of NPs (Bar-Ilan et al. 2009). No toxicity observed when embryos of zebrafish were exposed to silica NPs (Fent et al. 2010) but AgNPs were found extremely lethal (Bar-Ilan et al. 2009). Deleterious effects could be induced by the AgNPs on the aquatic life. Liver tissue analysis of the zebrafish after exposure to AgNps indicated a number of cellular changes including apoptotic changes and disruption of hepatic cells. In addition to this, the total glutathione level and malondialdhyde which is byproduct of cellular lipid peroxidation was increased. DNA damage was also induced by the AgNPs treatment (Choi et al. 2010). Photosynthetic yield of the *Chalmydomonas reinhardtii* is affected by the Ag NPs. Short-term exposure of the zebrafish to TiO_2 NPs has very little toxic effect while long-term exposure led to serious damage of different organs. The gills, liver, brain, and growth rate affected due to long-time exposure (Chen et al. 2011). About 29.5 % reduction in the zebrafish eggs' was observed after exposure of 13 days to TiO_2 NPs (Wang et al. 2011). TiO_2 NPs transferred through food chain from daphnia to zebra fish which is a high tropical level organism (Zhu et al. 2010b). Acute and chronic toxicity observed in *D. magna* when exposed for short and long time respectively with the TiO_2 NPs. Furthermore, high mortality and low growth rates were observed due to reproductive problems induced by TiO_2 NPs (Wiench et al. 2009) (Zhu et al. 2010a). *D. magna*, hyalella azteca, and marine harpaticoid copepod were exposed to the water soluble fullerene to assay the toxic effects. After 21 days of exposure, daphnia showed a significant delay in molting and offspring production (Oberdörster et al. 2006). TiO_2 NPs caused a considerable decrease in the activity of the Na^+-K^+-ATPase in intestine and gills of the rainbow trout. Enzyme activity also decreased in the brain. Minor fatty

changes observed in the liver (Federici et al. 2007). ZnO is toxic to algae in bulk form as well as in small particle form while CuO and TiO_2 NPs are much more dangerous for algae (Aruoja et al. 2009).

NPs are toxic for the aquatic life, although severity depends upon the number of factors like size, type of NP, charge, and the species which is being exposed. Some organs are more affected than the others in same species. Transfer of NPs through food chain is a serious issue. More studies are required to assess the damage of various NPs to the aquatic life in details. Figure 4 shows the schematic description of exposure pathways, uptake by aquatic organisms, and hazard identification of NPs in aquatic environment.

Effects on soil environment

It is highly important to study interactions between ENPs and the soil environment to find the fate and effects. Recent literature which deals with fate and effects of ENPs on the soil environment is presented below to highlight their impact on soil but it is admitted that every toxicity study on interaction of soil and NPs deals with different aspects which makes correlation a tedious job.

Enzyme activity in soil can be measured to predict anthropogenic effects on the soil environment. Soils are enriched with a variety of microbes. AgNPs showed very oblivious toxic effects to enzyme activities at very low concentrations (Peyrot et al. 2014). AgNPs also showed concentration-dependent effect on the growth rate and population of *Lumbricus rubellus* earthworms. Exposure to high concentrations of AgNPs for a longer period of time may deplete population growth to zero. These particles also affect immune cells of earthworms (Van der Ploeg et al. 2014). AgNPs showed toxicity to soil bacteria *Bacillus cereus* and *Pseudomonas stutzeri* and bactericidal effects were observed at concentration of 5 mg/L for an exposure period of 48 h (Fajardo et al. 2014). Similarly, ZnO NPs showed adverse effects on the fertility of earth worms and their uptake was higher than bulk ZnO and $ZnCl_2$ (García-Gómez et al. 2014). ZnO NPs and $ZnCl_2$ salt showed same chronic toxic effects on growth, fertility, and accumulation in *D. magna* (Adam et al. 2014). Cesium NPs were found to affect denitrification kinetics in soil samples and this denitrification process showed dependence on particle size, concentration, and species being tested (Dahle and Arai 2014). A study was designed to estimate toxicity of three different-sized CeO NPs in terms of reproduction, accumulation, survival, and histopathological effects on earthworm *Eisenia fetida*. Studies revealed that long-term exposure can induce histopathological changes in *Eisenia fetida* (Lahive et al. 2014). A recent article can be found on description of fate and bioavailability of NPs in soil environment (Cornelis et al. 2014).

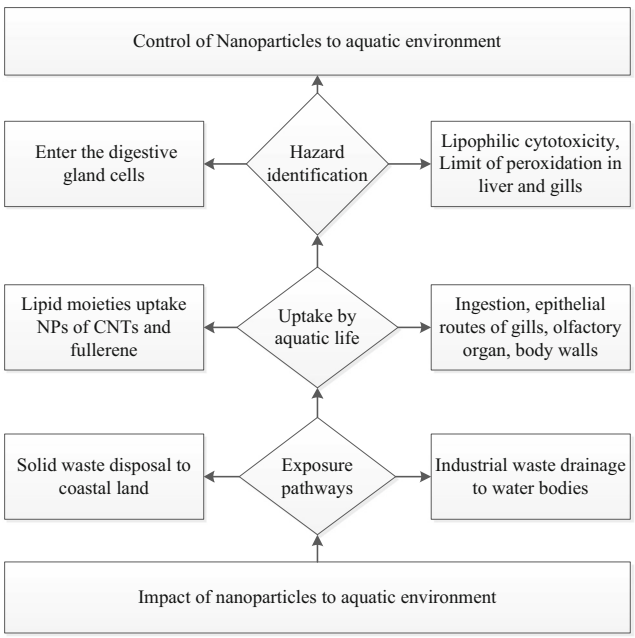

Fig. 4 Exposure and toxicity of nanoparticles to aquatic environment

Control of exposure to nanoparticles

Control of working environment and personal safety

Nanotechnology deals with the form of matter that appears in the size range of 100 nm or less. This technology has produced a new generation of materials and devices. The creation of a large number and variety of new materials and products has raised the issue of safety for producers, consumers, and environment. NPs can harm individuals, workers, and the environment because of their potential as irritants, haptens, reactive materials, and interactive substances (Nel et al. 2006). People working on aluminum smelters are exposed to high amounts of ultrafine particles and NPs generated as result of milling. Such processes can produce detectable concentrations of NPs in work place (Debia et al. 2013). Disposal of NPs presents another challenge and precautions must be taken while disposing off NPs containing materials.

The most important parameters in controlling occupational exposure of NPs to the workers are proper understanding of hazardous substances and use of safety equipment. Consideration of toxic limits for these particles needs more and comprehensive studies, because presently existing literature is not sufficient to address this issue. However, some general strategies can be adopted to get control of exposure to NPs. One study was carried out to assess the airborne NPs during the preparation of nanocomposites and results revealed that exposure to NPs is dependent on air flow, ventilation, feeder type, method of feeding, and properties and nature of

particles itself (Tsai et al. 2012). Another study suggests that levels of TiO_2 and carbon black NPs can be reduced to acceptable limits by use of ventilation system combined with N95 respirator protection (Ling et al. 2011). Usage of local ventilation system within the working equipment and general ventilation system can be helpful in reducing the airborne particles. Complete enclosure of releasing source can also reduce exposure. Similarly, decrease in number of workers and development of automated manufacturing systems can reduce amount of exposure. Use of safety equipment like gloves, masks, and complete covering of body parts can significantly reduce extent of exposure. Regular cleaning of working place, walls, equipment, and other accessories is also a way to reduce exposure to NPs. Eating and drinking must be avoided within in the working place in order to avoid inhalation of such toxic particles. Studies suggest that handling of NPs in glove box helps in preventing exposure to them (Debia et al. 2013). In addition to all precautionary measures, medical testing of occupational workers must be done on regular basis.

Inhalation can be avoided by achieving proper control of laboratory environment. Due to extremely small size of NPs compared to other materials, they have very high penetrating ability. Therefore, systems must be installed for their ventilation from working places like many advance laboratories have systems which effectively manage gases and aerosols in the laboratory environment. Use of filters in the laboratory can be helpful. These filters should be able to clean the environment of the working place before the next session. Personal safety equipment can reduce or stop inhalation of NPs. Similarly, reduction in working period for dealing with such material can be helpful. Such kind of strategies can also be adopted to avoid dermal and ingestion exposure.

Instruments and strategies for measurement of NPs exposure

The devices used for measurement of airborne NPs work on different principles and employ different types of detectors. Size-resolved and time-resolved devices work on the principle of optical properties or electrical mobility measurements. Such devices consider all the particles spherically equivalent which is not the actual case at work places and measurements are somehow biased (Kuhlbusch et al. 2011). Optical particle sizer (OPS) is based on measurement of scattered light from the particles. One mandatory condition for optical detectors is that, the size of particle should not be smaller than half of the wavelength of the light. Such detectors are thus not capable of measuring the particles with size less than 200 nm and they are also susceptible to erroneous size measurements. This limitation, however, can be overcome by use of condensation particle counter (CPC) where the particles are condensed by the use of a fluid like water or alcohol to a size which can be easily detected by optical light. CPC can cover a range of 2.5 nm to 10 μm.

Scanning mobility particle sizer (SPMS) works based on electrical mobility of the particles. Particles are charged and then passed through a differential mobility analyzer where they are exposed to different voltages in a programmed manner. Particles are separated according to their electrical mobility and hence counted. Electrical mobility has a direct relationship with charge to size ratio. For particles with same charge, electrical mobility will be higher for the smaller ones. SMPS uses time resolutions in the range of 3–5 min but in real, size distributions of NPs may change at a time scale of few seconds. Thus the devices with lesser time resolutions can accomplish the task of measuring fast changes in size distributions. Fast mobility particle sizer (FMPS) provides resolution of 1 s and can measure particles in range of 5.6–560 nm. Like SMPS, FMPS measurements are also based on electrical mobility. Such fast devices are being used in toxicology assessment studies, indoor air monitoring, and environmental research. Experiments were performed to compare the performance of condensation particle counter-based SMPS and FMPS devices for finding particle number concentrations using ambient as well as lab produced particles and results indicated that concentrations were extensively higher in case of FMPS (Jeong and Evans 2009) . Although FMPS provides faster size distribution measurements and higher results in terms of particle number concentrations but some reports indicate that it underestimates the particle size (Lee et al. 2013).

Electrical low-pressure impactor (ELPI) has much faster response with resolution of 0.1 s and covers a wide particle range 6 nm–10 μm. Particles are charged and entered into cascade of low-pressure where they are collected according to their aerodynamic diameter at different impactor stages and a real time response is produced by highly sensitive electrical detectors. Produced electrical signal represents particle concentration and size. It fits best for unstable concentrations or size distributions. Main applications include engine exhaust measurement, outdoor, and indoor air quality monitoring, and combustion resulted particles. The main limitation arises from the fact that particles are further deagglomerated when enter into an area of low pressure through a small orifice (Stahlmecke et al. 2009). This can change the active surface area of a huge fraction of particles which may lead to error in measurement. Moreover, diffusion charger-based equipment is also used to measure surface area concentration of particles with size less than 1,000 nm.

In addition to real-time instruments which measure particle number concentration, some instruments can measure mass of NPs in real time. The aerosol particle mass analyzer (APMA) measures the particles according to their mass to charge ratio and such measurements are not dependent on particle size or shape. Tapered element oscillating microbalance (TEOM) also serves the same job.

In offline methods, NPs are collected on filter samplers and then analyzed by morphological or chemical analysis. Variety of filter media can be used for sampling but sometimes it is dictated by analytical method. Poly carbonate or silicon wafers are used for scanning electron microscopy (SEM) or transmission electron microscopy (TEM). Tedious sample preparation, withstanding of samples at high vacuum conditions, expensive equipment, and need for expert personnel, limits the use of SEM and TEM in exposure and control studies.

Thermal precipitator is very efficient sampler for the particles having size less than 10 μm. It employs a hot wire or sphere in between two plates. Particles passing between heated element and cooler surface will deposit on the cooler surface and then can be analyzed by any microscopic technique (Azong-Wara et al. 2009). Applications of thermal precipitator are limited due to low flow rates and sampling capacities.

Despite of all advancement in online and offline measurement and sampling techniques for exposure and control of NPs, there is lack of correlation criteria for comparison among methods and specific type of nanoparticles. A detailed review article on exposure of NPs at work places and their measurement can be consulted for more details on instruments and devices (Kuhlbusch et al. 2011).

Regulatory measures

Other than natural sources NPs emission from anthropogenic sources can be sub categorized into two parts. Intentionally produced engineered NPs such as nanotubes, nanowires, nanofibers, and unintentionally produced NPs such as from combustion sources, vehicles exhaust, and mechanical workshops (Wu et al. 2008). The main source of human exposure to such NPs is inhalation of polluted air (Kumar et al. 2011b). Although there are certain environmental protection regulations and air quality standards such as, Clean Air Act, European Union Directive (2008/50/EC) on ambient air quality, and cleaner air for Europe. These regulations include restrictions based on the amount of particulate emission to the ambient environment. However, these current regulations on the particulate materials are based on mass concentration and they cannot be applied to NPs. The reason of inapplicability is that NPs possess different characteristics and toxicity as compared to ultra-fine size of NPs which can penetrate and deposit inside lungs (Kumar et al. 2010).

There is a need to determine new threshold values and criteria for evaluation of NPs and their characteristics. The further regulations on the emission of NPs should also take the number concentration of the NPs into consideration (Heal et al. 2012; Nowack et al. 2014). The identification of size range of atmospheric NPs on number concentration is important. For instance particles less than 300 nm have been found to be over 99 % of total particle number concentration and particles less than 100 nm contribute about 80 % of the total particles in the urban environment (Kumar et al. 2011b). The particle number varies with location and time. More studies on number concentration of NPs in ambient environment can be found in references (Wehner and Wiedensohler 2003; Charron and Harrison 2003; Wu et al. 2008; Kumar et al. 2011b, 2013). Similarly, significant number of particles around 1 nm and less than 1 nm are expected to be in higher number concentration but the accurate measurement is more challenging for much smaller NPs such as below 20 nm.

The specific legislations about NPs are Euro 5 and Euro 6 vehicle emission standards. These regulations are of their first kind to control NPs emissions of solid particles bigger than 23 nm. The lower cut-off set by these standards allows more than 30 % of the smallest NPs to be excluded (Heal et al. 2012). Future regulatory frame work needs to consider the smaller range of particles as well. Recent advances in nanotechnology integrated products will more likely lead to an increased level of ENPs such as nanotubes, nanowires, nanofibers, and their counterparts into the ambient environment. So far, indoor emissions of these NPs such as inside research laboratories and commercial units are dealt with high priority. However, the ambient emissions of such ENPs are not being taken into strict considerations as a whole. The main reason for this is that the current knowledge database about their characteristics is insufficient to influence a regulatory frame work. A strong emphasis is required on developing innovative methods for detection and measurement of NPs in the environment. Regulatory measures for ENPs also require their accurate physicochemical characterizations and exposure-response functions.

The US Environmental Protection Agency (USEPA) is dealing nanomaterials under Toxic Substances Control act (TSCA). The agency has reviewed number of nanoscale materials under TSCA such as single and multiwall carbon nanotubes, silica, and aluminum NPs for prolonged inhalation. USEPA is also developing a rule named "Significant New Use Rule (SNUR)" to ensure regulatory review of nanoscale materials. Manufacturers who intend to prepare new nanoscale material from the substances listed under TSCA are required to take permission at least 90 days before preparation. Under the "Information gathering rule" the manufacturers of nanoscale material should provide information about the production volume, method of synthesis, available data on safety and health exposure of the material. Certain nanomaterials are selected to be tested for safety and environmental health (http://www.epa.gov/oppt/nano/). However, such a database which can provide information on the safe limits of exposure to different kind of NPs is highly desired. Environment Canada (EC) (http://www.ec.gc.ca/) assesses NPs under the Canadian Environmental Protection Act (CEPA) (1999). Under this act, the new substances being

prepared in Canada or imported to Canada must go through risk assessment studies. Currently, Canada lacks any specific nomenclature for nanomaterials. Substances listed on the Domestic Substance List (DSL) whose nanoscale forms do not have unique structures or molecular arrangements are considered "existing". The nanoscale form of a substance on the DSL is considered a "new" substance if it has unique structures or molecular arrangements. Similarly, the European commission is regulating the engineered nanoparticles under Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) as ordinary chemical substances (Morimoto and Kobayashi 2010; Kumar et al. 2011b). European Union (EU) has developed a new regulation about classification, labeling, and packaging of new materials. International organizations such as the International Organization for Standardization (ISO) and the Organization for Economic Cooperation and Development (OECD) are gearing up for nanotechnology concerned issues. The ISO is currently working on developing standards for terminology, nomenclature, metrology, and instrumentation regarding testing and science-based health and safety practices of nanomaterials. Similarly, Working Party on Manufactured Nanomaterials (WPMN) established by OECD is also working on variety of projects related to environmental health and safety research database, exposure measurements, cooperation of environmentally sustainable use of nanotechnology and testing guide lines for ENPs. More details can be found on the OECD website (http://www.oecd.org/env/ehs/nanosafety/). US National Institute for Occupational Safety and Health (NIOSH) has issued detailed guidelines regarding the personal safety, exposure assessment, potential health concerns, and precautionary measures for the people dealing with NPs at workplaces. Details of these guidelines can be found at (http://www.cdc.gov/niosh/docs/2009-125/pdfs/2009-125.pdf)

Toxicological studies of nanoparticles: recent status, weaknesses, and future challenges

More ENPs enter into the environment as a result of advancements in field of nanotechnology. The risk associated with NPs entering into the environment, their transport mechanism, fate in the environment, and effects on living organisms need to be assessed in following areas.

1. Effective measurement of NPs emission to environment
2. NPs concentration detection in the environment
3. Behavior of NPs in the environment
4. Life cycle assessment of NPs in environment
5. Toxicity assessment to human being and environment
6. Impact of toxicity assessment to ecosystem

Human and environmental exposure to airborne anthropogenic NPs has increased enormously over the last few decades mainly due to unintentional combustion processes and intentional advancement in nanotechnology development and applications (Pipal et al. 2014). Research on fate of environmental NPs is being focused due to many reasons. These NPs in environment act as precursor to form larger particles which strongly affect the atmospheric chemistry, global climatic changes, visibility, global and regional transportations of biological species and pollutants. The presence of NPs in air may critically influence the human health and increase the impact associated with other environmental pollutants. In addition to that NPs affect the chemistry of atmosphere in terms of composition and reactivity which leads to formation of agglomerates, coating of layers, and larger soot particles. The presence of active sites on NP surface may affect the phase transition of particles (Pipal et al. 2014).

The most important fields to be focused include post production life cycle assessment of NPs in terms of entrance mechanism and pathways in the environment, and toxicological effects to ecosystem (Garner and Keller 2014). Most prominent processes occurring during the transport and fate of NPs in environment includes deposition, aggregation, dissolution, chemical transformation, oxidation, surface coating, and interaction with organic matters and colloids (Arvidsson and SMBASMH 2011; Quik et al. 2011; Praetorius et al. 2012; Levard et al. 2012). Because of antimicrobial properties, increasing concentration of metal-based NPs in pesticides, aerosol sprays, toothbrush, toothpaste, filters, creams, washing machines etc. has also increased the concern of environmental regulations (Dos Santos et al. 2014).

Recent studies indicate diffusive and indirect release of NPs to environment estimated around 8,300 metric ton annually around the globe (Keller and Lazareva 2014). Still, exact measurement of concentration of released NPs is difficult to estimate. Direct implication of NPs to environment may result from intentional and unintentional degradation of products, industrial, and wastewater treatment effluent and sludge, pesticides, and combustion (Maurer-Jones et al. 2013). With release of NPs to environment their size is increased as result of condensation of particles by nucleation of organic and inorganic vapors, deposition, coagulation, agglomeration, and reaction with biomolecules (Meesters et al. 2013).

Transformation of NPs into degraded products in environment occurs through oxidation and photocatalysis (Tiwari and Marr 2010). These transformations of NPs make their properties critical to understand such as their fate, transport, and toxicological effects (Kumar et al. 2011a; Meesters et al. 2013). It is difficult to predict the deposition time and agglomeration rate of specific NPs due to lack of proper instruments and complex characteristics of NPs in atmosphere; however, estimates shows that 1/36th of NPs remain in lower atmosphere while others settle down. But some conflict exists

regarding persistence of NPs in environment for a longer period of time (Gottschalk et al. 2010; Quik et al. 2014).

Different studies are conducted to assess the transport and ultimate fate of ENPs during production process and release to indoor and outdoor environment (Bello et al. 2008; Curwin and Bertke 2011; Lee et al. 2012). The particle concentration in range of 10 nm to 1 μm were found to be stable in the environment for long time but majority of particles were found to be agglomerated (Brouwer 2010; Curwin and Bertke 2011). The removal of these suspended NPs occurs through either wet or dry deposition. Dry deposition occurs mainly by diffusion and inertial impact depending on size and rate of agglomeration of particles (Friedlander and Pui 2004). Wet deposition removal takes place by particles precipitation through nucleation by rain drops and aerosol coagulation (Jacobson 2003; Laakso 2003). Atmospheric conditions also affect the particle behavior and hence the fate in the environment.

Translocation of suspended toxic NPs occurs to different local and global environment along with bio-molecular species by climatic and air movement along the globe especially to urban population affecting human beings, agricultural forms, and food chain. The deposited NPs become part of water bodies including drinking water sources, irrigation system, and more importantly the marine environment which ultimately becomes part of human food. More comprehensive study is needed to explore the toxicity of NPs life cycle to environment (Sánchez et al. 2011; Gottschalk and Nowack 2011; Love et al. 2012; Sharifi et al. 2012; Praetorius et al. 2012; Etheridge et al. 2013).

Research in this area is widely dispersed and scattered and it is very tedious job to draw any straight forward conclusions. Different toxicity assays have been tried for different NPs where mechanism of their action is looked from different perspectives. Moreover, differences in preparation methods of NPs have made it difficult for any possible comparisons among their toxicity studies. NPs are being tested against various cell lines and animals but still their direct effect on human health is scarce. Under these circumstances, it is suggested that some standard protocols must be developed to evaluate toxicity of ENPs.

A recent opinion is published which draws attention of researchers to study interaction of NPs and soil. The effects of NPs on soil composition, soil macro organisms, microbes, and their interaction with soil pollutants can reveal some unexpected harms (Bakshi et al. 2014).

We think that the knowledge on exposure to nanoparticles, methods to assess exposure and consequences to human health is still limited. NPs are replacing materials in paints (Al-Kattan et al. 2014), textiles (Vílchez-Maldonado et al. 2014), and spraying (Losert et al. 2014) but their exposure and after effects to human and environment are less known.

Conclusion

NPs are finding widespread applications in consumer products because of their unique properties. But there is sufficient evidence that they induce toxicity to higher organisms including human and wildlife. Cellular uptake of these particles may induce cytotoxicity by generation of reactive oxygen species. Cytotoxicity and genotoxicity of NPs is mainly focused by many researchers. Unique characteristics of NPs which increase their applications in domestic and industrial processes, also contribute to enhance their toxicity. Toxicity of NPs is affected by their intrinsic properties such as size, shape, nature, surface chemistry, charge, medium of synthesis, storage time, aggregation, stability, mobility, and reactivity. Dermal contact, inhalation, and digestion are three main routes of exposure of NPs to human and wild life. Dermal exposure occurs through intentional and unintentional means. Antimicrobial NPs-based cosmetics are directly applied on the skin and it is most prominent mean of intentional exposure. Although skin is an effective barrier against particle penetrations but sweat glands and follicles provide a route for penetration. Inhalation provides a route to lungs from where these particles translocate into different organs. But the subject of translocation from lungs to other organs is highly conflicting and debated. NPs in food products and drugs are ingested directly and enter into gastrointestinal tract and interact with lymphatic cell tissues. These digested particles are excreted depending on their nature but in case of their blockage in gastrointestinal tract, they may lead to death. Environmental conditions are important in determining toxicity of engineered nanoparticles. Control of exposure to NPs can be achieved by getting control of engineering equipment and working place. Use of personal safety equipment and regular medical checkup may save from risks of exposure.

Research in area of NPs toxicity is very scattered and different toxicity assays have been tried for different kind of NPs. Decisive conclusions cannot be drawn based on available literature. Standard methods must be developed to explore toxicity of all kind of NPs.

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