Challenges and Future Perspectives of Nanotoxicology

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Abstract

Nanotoxicology is a branch of toxicology that is related to potential effects of nanoparticles of diameter less than 100 nm. Due to relatively small size, they are reported to enter through biological tissue barriers and cellular membranes leading to toxic effects. Release of nanoparticles on the target surface also induces high level of toxicity in target cells. The nanoparticles are usually cationic and

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are easily attracted to the anionic biological membrane, resulting in the destruction of the membrane and interaction with proteins, DNA, and enzymes of the host cell. The carcinogenicity of some multiwall carbon nanotubes and nanoparticles are also reported in recent researches. Various concerns about the usage of nanoparticles including systemic translocation, direct effects on the central nervous system, intestinal tract involvement, biocompatibility, deposition, and clearing are reported till date. In this book chapter, we will review the potent role of nanomaterials to confer their toxicity at cellular and subcellular levels. Efforts have been made to summarize the new aspects of interactions with other toxicants either by reducing or enhancing health risks and the potent negative effects associated with nanomaterial pollution.

Keywords
Nanotoxicology · Nanoparticles · Toxicants · Target cells

22.1 Introduction

Increasing demand for high-quality water fit for consumption calls for effective strategies to treat wastewater (Rajasulochana and Preethy 2016). The growing use of pesticides and heavy metals pollutes the water bodies (Ayangbenro and Babalola 2017). The use of nanoparticles can help to solve this problem and would address the consequences of pesticides and heavy metals present in water (Cicek and Nadaroglu 2015). However, despite the progress made, use of these emerging sustainable technologies has been limited, largely due to limitation of the material's properties, including cost (Lim 2017).

Nanoparticles possess useful characteristics such as direct band gap, high optical absorption coefficient, layered structure, and tunable band edges for optimized catalysis (Khan et al. 2017). Conversion of single-component nanomaterials to hybrid materials such as nanocomposites involves integration of synergistically different components in a controlled fashion (Camargo et al. 2009). Hybrid nanostructures have many advantages over single component nanomaterials such as multi-functionality, highly efficient charge separation at the interface and tunable band gap (Li et al. 2016). The use of nanoparticles for photocatalytic degradation will result in appreciable reduction in the pesticide amount in the water (Das et al. 2017). The combination of nanoparticles with bio-adsorbents to form nanocomposites is expected to show improved performance in terms of high efficiency of photo-induced charge separation and photostability (Hasija et al. 2019). The surface modification of the nanoparticles will facilitate the interaction of heavy metal ions with the particle's surface and hence would result in better adsorption and improved performance of the photocatalyst (Upadhyay et al. 2014). Use of hybrid nanostructures is also expected to be advantageous over the single-component and pure systems. Better performance in terms of material stability, efficiency, and cost is expected over the existing systems (Sanchez et al. 2011). Recent advancement in

nanotechnology industry has shown remarkable revolution over the last few decades, which progressively and hopefully will continue in future. Nanotechnology has shown significant contribution for the future of health science and medicine care (Fakruddin et al. 2012). In gene delivery, immunotherapy, and drug delivery systems, the ideal nanomaterials can achieve biocompatibility, high payload, low immunogenicity, efficient penetration and selective targeting to get timely arrival at tissues of interest (Singh and Lillard Jr 2009). Regular exponential growth in nanotechnology has led to consider new challenges to manage, predict, and understand the potential negative health effects followed by exposure (Setyawati et al. 2015). Different nanomaterials of different surface topographies, sizes, and compositions and various other properties need to be scrutinized to build the safety and efficacy for their use in human population (Jeevanandam et al. 2018). Nanotoxicology basically deals with the toxic nature of nanoparticles and elucidating their toxic effect on living systems (Taghavi et al. 2013). Most of the inert element becomes more active at nanoscale dimensions. Most of the nanoparticles are benign, and they may distribute throughout the body causing inflammation, oxidative stress, and other serious adverse effects (Buzea et al. 2007). High doses of nanoparticles represent realistic exposure and should be interpreted with caution which might result in toxico-kinetics and exposure assessment (Laux et al. 2018).

Multiwall carbon nanoparticles are discovered to cause asbestos-related serious health effects which prompted nanotoxicologists to cautiously check the release of nanoparticles at drug delivery sites (Yildirimer et al. 2011). Adverse effects of nanoparticles are evidenced in epidemiological, in vitro, and in vivo studies. However, data related to low dose exposures and chronic abnormalities still need to be explored (Gwinn and Vallyathan 2006). In most of the cases, these emerging engineered nanoparticles are directly linked to adverse health risks. New areas in toxicology includes the binding of nanoparticles with other contaminants either by reducing or enhancing various health issues and various adverse environmental effects related to nanomaterials pollution (Gupta and Xie 2018).

The purpose of this book chapter was to review the potential harmful effects of nanoparticles on the immune system with new approaches in nano-science. Efforts also have been made to scale up various biomarkers to monitor toxicity of nanoparticles at cell system.

22.2 Properties and Application of Nanomaterials

Nanomaterials exhibit various properties such as electronic, chemical, magnetic, optical, physical, thermal, and elastic properties. The nanoparticles find their application in a variety of fields such as medical field for drug delivery in vivo and in vitro, agriculture, and treatment of wastewater (Singh et al. 2019a, b; Kumar et al. 2019a, b), pesticide degradation (Singh et al. 2019c; Bhati et al. 2019; Kapoor et al. 2019), solar sensitizers, nanosensors, and photocatalysis because of their small size and physicochemical properties (size, shape, surface area, phase, and composition) (Sidhu et al. 2019; Kumar et al. 2019c).

Nanomaterials found their vast applications in different fields such as nanoscale carriers, nano-herbicides, nano-fertilizers, nano-pesticides, nanosensors, veterinary care, etc. (Kumar and Singh 2018a, b). Murphy (2008) and Tarafdar (2015) developed clay nanotubes (Halloysite) to reduce the concentration of pesticides by more than 70%, hence reducing its effectiveness impact on water streams. Panyam and Labhasetwar (2003) developed poly(D,L-lactide-*co*-glycolide) (PLGA) nanoparticles for localized/targeted delivery of different agents including peptides, plasmid DNA, and proteins.

Recently, a titanium-based nanomaterial was found to have numerous applications such as in water splitting and degradation of organic compounds and as solar sensitizers. Titanium dioxide (TiO_2) has various features such as polymorphs, low cost, good stability, environmentally friendly, and having good optical and electronic properties. Li et al. (2018) investigated that core–shell-structured TiO_2 composites show tunable optical and electrical properties, even new functions, which are originated from the unique core–shell structures. The small size of Fe_2O_3 nanoparticles, changes their magnetic properties from paramagnetic to ferromagnetic and superparamagnetic and are used as contrast agents in intravenously injectable *T*2 MRI (Lee et al. 2014). The effective photocatalyst derived from TiO_2 nanoparticles are also reported to enhance photocatalytic degradation of triazine pesticides such as atrazine (Yola et al. 2014). Chitosan-based zinc oxide nanoparticles (CZNP) are spherical in shape and are used in the treatment of cervical cancer cells (Wu and Zhang 2018). Gold nanoparticles (GNPs) along with TiO_2 nanoparticles are used for fabricating conformal nanocomposite (NC) films of TiO_2–Au (Chander et al. 2014). Yuan et al. (2010) investigated the synthesis of ZnO quantum dots (QDs) combined with chitosan (*N*-acetylglucosamine) for its effectiveness against tumor-targeted drug delivery. It was observed that stability of the ZnO quantum dots is dependent on chitosan due to its cationic charge and hydrophilicity. Qiu et al. (2014) have developed a composite having core shell structure of ZnO interlayer and magnetic Fe_3O_4 core. Based on its properties, it has been shown to be effective against targeted delivery of anticancer drugs.

22.3 Hazardous Effect of Nanomaterials

The nanomaterials have a small size, i.e., few nanometers, and possess high reactivity to interact with organisms. They pose potential human health and environmental hazards when released directly into the environment and gets interacted with water, air, and soil (Elsaesser and Howard 2012). When the dust and air pollution consist of ultrafine particles of size <100 nm, it indicates possible long-term hazardous effects of man-made nanoparticles on humans. They can enter via oral, pulmonary (lungs), nasal, intraocular, and various other routes. Nanomaterials are found in aquatic and terrestrial environments by runoff and eventually reach into the food chain and accumulate in the body and other metabolic pathways. They are somehow toxic to various species including invertebrates, algae, bacteria, crustaceans, nematodes, mammals, fishes, rats, etc. (Landa et al. 2012; Exbrayat et al. 2015). Warheit et al. (2008) assessed the hazardous effects of several fine or nanoparticle types such

as carbonyl iron, amorphous silica, crystalline silica, and nano zinc oxide in rats. They observed that silica nanoparticles sustain cytotoxic and inflammation effects.

Karimi et al. (2018) used colloidal nanoparticles of fumed silica (f-SiO_2), silica (c-SiO_2), alumina (Al_2O_3), and ceria (CeO_2) as corrode in chemical and mechanical planarization (CMP) processes. The CMP slurries of CeO_2 and Al_2O_3 reduced reproduction in *Daphnia magna* upon chronic exposure which have negative consequences to water bodies. Jeng & Swanson (2006) investigated the effect of metal oxide nanoparticles ZnO, Al_2O_3, Fe_3O_4, TiO_2, and CrO_3 on apoptosis, cellular morphology, membrane leakage of lactate dehydrogenase (LDH mitochondrial function), and permeability of the plasma membrane, out of which ZnO nanoparticles were highly toxic, Al_2O_3 nanoparticles were moderately toxic, and TiO_2 and Fe_3O_4 exhibited low toxicity. It also results in the decreased mitochondrial function in the cells treated with ZnO nanoparticles ranging from 50 to 100 μg/mL.

Ghodake et al. (2011) reported the phytotoxicity of zinc and cobalt oxide NPs by *Allium cepa* test using onion bulbs as an indicator organism to check their effects on cell morphology, root elongation, adsorption potential, and root morphology of a plant. Zinc oxide NPs accumulate in the chromosomal and cellular modules, thus causing phytotoxic damage. Landa et al. (2012) studied the effect of titanium dioxide (TiO_2) and zinc oxide (ZnO) nanoparticles using microarrays on gene expression in roots of *Arabidopsis thaliana*. ZnO nanoparticles elicit stress response in phenotype and gene expression of *A. thaliana*.

22.4 Effects of Nano-based Products on the Immune System

Any alteration in the properties of nanoparticles transforms them either to a valuable or hazardous product (Jeevanandam et al. 2018). The deposition of nanoparticles in the human system acts as a foreign material that led to the emergence of a new branch, i.e., nanotoxicology (Suh et al. 2009). This field aims to cross verify the negative and harmful effects of nanoparticles on the environment as well as on human health (Table 22.1) (Singh 2009). This will aid in understanding how these nanoparticles cross the different barriers and enter into the blood system as well as interact with other tissues. Moreover, it will provide an insight into how the aggregation of these nanoparticles affects the normal functioning of the organ and induce ailments like fibrosis, inflammation, etc. (Barua and Mitragotri 2014). Nanoparticles induce biological toxicity by various possible routes in the human body via endocytosis and penetration into cell membrane and through the cell membrane channel (Manke et al. 2013). Most of the nanoparticles produces oxygen radicals and induces apoptosis and mitochondrial perturbation followed by toxicity (Behzadi et al. 2017). Nanoparticles react with biological fluids and body proteins and results in the generation of oxidative stress (Dayem et al. 2017). Nanoparticles such as silver NPs (AgNPs), titanium dioxide (TiO_2), NPs, and gold NPs (AuNPs) result in various immune-related disorders in mononuclear phagocytic system cells of the spleen and liver (Giannakou et al. 2016). Most of the immune cells such as macrophages, dendritic cells, leukocytes, platelets, monocytes, etc. recognize and uptake nanoparticles

Table 22.1 Immunotoxic effects of various nanoparticles in vitro and in vivo testing

S. No.	Nanomaterials	Size	Adverse side effects	References
1.	C60 fullerene	0.7 nm (diameter)	No effects	Fujita et al. (2009)
2.	Carbon black	<100 nm	Exaggeration of arthrosclerosis and induction of C-reactive proteins MCP-1, IL-6, and CCL2	Niwa et al. (2008)
3.	Carbon black	14 nm	Induction of MHC class II and CD80 expression Significant expression of DEC205 and CD86	Koike et al. (2008)
4.	Carbon black	14 nm	ROS production	Kroll et al. (2011)
5.	Citrate-stabilized AuNPs	10 nm	Induction of NF-κB-regulated luciferase reporter	Sharma et al. (2013)
6.	Fe_2O_3		Induction of TH0 cytokine (IL-2), pro-inflammatory cytokines (IL-6, TNF-α, IL-1), TH1-type cytokine TGF-α (IL-12), and IgE and TH2-type cytokines (IL-4, IL-5)	Park et al. (2010a)
7.	Fe_2O_3		Cell viability decreases and ferritin expression increases IL-1α expression and lactate dehydrogenase activity	Zhong et al. (2010)
8.	Gold	13 nm	Inflammation in the liver, induction of apoptosis, and nanoparticles localization in Kupffer cells of liver and macrophages in spleen	Cho et al. (2009)
9.	Gold	2, 40 nm	Internalization by primary hippocampal neurons and microglial cells and upregulation of TLR-2, olfactory bulb, and IL-1α	Hutter et al. (2010)
10.	Gold	0.8–15 nm	Oxidative stress induction	Brandenberger et al. (2010)
11.	Latex nanomaterial	25, 50, and 100 nm	Induction of fibrinogen	Inoue et al. (2009)
12.	Multiwalled carbon nanotubes	10–30 nm (diameter) 30–50 (length)	Induction of fibrosis	Ryman-Rasmussen et al. (2009)
13.	Multiwalled carbon nanotubes	20–40 nm (diameter) 5–30 μm (length)	ROS generation, induction of inflammatory cytokines, and activation of NF-κB in BEAS-2B or A549 cells	Ye et al. (2009)
14.	Nonporous silica nanoparticles	15 nm	ROS production in rats	Chen et al. (2013)

(continued)

Table 22.1 (continued)

S. No.	Nanomaterials	Size	Adverse side effects	References
15.	Polystyrene	60 nm	Highly toxic to human endothelial cells, BEAS-2B cells, macrophages hepatoma cells, and microvascular endothelial cells	Xia et al. (2008a)
16.	Polystyrene	20, 500, and 1000 nm	Migration of dendritic cells	Manolova et al. (2008)
17.	Silica	70, 300, and 1000 nm	Induction of inflammatory cytokines and liver damage	Nishimori et al. (2009)
18.	Silica particles	12 nm	Induction in mRNA expressions of COX-2, IL-1, iNOS, TNF-α, and IL-6	Li et al. (2009)
19.	Silicon	–	No changes or effects in HaCaT keratinocytes	Park et al. (2010b)
20.	Single-walled carbon nanotubes	1–4 nm (diameter)	ROS meditation via neutrophil myeloperoxidase in humans	Kagan et al. (2010)
21.	Single-walled carbon nanotubes	1–2 nm (diameter) 20 nm–several μm (length)	ROS generation, induction of inflammatory cytokines, apoptosis-related genesis macrophages	Chou et al. (2008)
22.	Single-walled carbon nanotubes	800 nm length	Inhibits production of MCP-1, TNF-α, and IL-8, 6	Herzog et al. (2009)
23.	Single-walled carbon nanotubes	50–200 nm (length) 1–5 nm (diameter)	Accumulation of SWNT in the kidney and liver for several months	Schipper et al. (2008)
24.	TiO_2	0.02–0.03 μm	ROS induction	Müller et al. (2010)
25.	TiO_2	4–6 nm	Lung inflammation, systemic inflammation cardiac edema, and induction of monocytes	Nemmar et al. (2008)
26.	TiO_2	20 nm	–	Geiser et al. (2008)
27.	TiO_2	15, 50, and 100 nm	Release of histamine	Yanagisawa et al. (2009)
28.	TiO_2	Less than 100 nm	Necrosis apoptosis in macrophage cells	Morishige et al. (2010)
29.	TiO_2	7–10 nm	Inflammatory responses via IL-1beta pathway ROS, inflammasome, etc.	Schanen et al. (2013)
30.	Zinc oxide, cerium oxide	11 nm, 8 nm	Oxidative stress induction	Xia et al. (2008b)

when they are in the tissue or in circulation process (Lameijer et al. 2013). Immune cells uptake nanoparticles from the bloodstream by adsorption process through opsonization. They remain in the body for a long term and cause various exposures. They also enhance intense manifestations that cause several disorders such as activation of complement system and acute inflammation (Look et al. 2010). It also has adverse effects on innate and specific immune responses. Acute inflammation is induced by activation of NF-κB pathway which results in enhanced production of chemokines and cytokines (Liu et al. 2017). Innate immune system results in the generation of ROS after exposure to metal oxide particles. Further, ROS lead to alterations in DNA and proteins which further causes inflammatory damage (Fu et al. 2014).

Gold nanoparticles are reported to induce various immunomodulatory effects by secreting inflammatory cytokines (IL-8 and TNFα) which activate NF-κB pathway when THP1 cells were exposed to AuNPs coated with negatively charged poly(acrylic acid) (Deng et al. 2011). In a similar study, Sharma et al. (2013) also confirmed that when B-lymphocytes were exposed to AuNPs stabilized with citrate, it induces NF-κB pathway and structural changes in cellular function of cells are registered. Another example of immunomodulatory effects by single and multiwall carbon nanotubes on various cell types was also reported in which they induce unregulated antigen-presenting cell maturation (He et al. 2013). CNT is also testified to enhance ROS production which causes alterations in fibrosis in lungs of rats and neoplastic damage. They also increased high risk against cardiopulmonary diseases in lungs by generating pro-oxidant and pro-inflammatory milieu (Dong and Ma 2016).

22.5 Mechanism of Toxicity of Nanomaterials

Recent studies have revealed that reactivity of the nanoparticles triggers the formation of ROS (especially, hydroxyl radicals and superoxide radical anions) due to activation of oxidative enzymes leading to the formation of oxidative stress (Kim et al. 2015). There are various reasons for the initiation of oxidative stress, such as (1) nanoparticles have the property to trigger the ROS production as the cellular response, (2) transition metal-based nanoparticles serve as the catalyst during the formation of non-metal nanoparticles, (3) formation of reactive molecules on the surface of nanoparticles, and (4) induction or activation of redox groups on nanoparticles (Fu et al. 2014).

Moreover, particle size is also considered to be the factor responsible for cellular cytotoxicity. As small particles provide the large surface area, it increases the chances of the interaction of nanoparticles with cellular components like carbohydrates, fatty acids, nucleic acids, and proteins (Wang et al. 2017). Further, nanosized particles have additional benefits as it readily enters the cell and leads to cellular damage (Wang and Wang 2013). Apart from this, the surface charge of particle also contributes to cytotoxicity as it controls the cellular uptake of particles and interaction among the biomolecules and cell organelles. This phenomenon can be understood by the context that positively charged nanoparticles interact with DNA (negatively charged), resulting in DNA damage (Fröhlich 2012). Additionally, the shape of nanoparticles has been considered to affect the toxicity level (Sukhanova

et al. 2018). Although the TiO_2 (amorphous) is known to have surface defects, this serves as evidence that active site stimulates the ROS production (Cheng et al. 2018). Besides, Fe_2O_3 nanoparticles (rod-shaped) were found to trigger high cytotoxic responses in comparison to Fe_2O_3 nanoparticles (sphere-shaped) in macrophage cell lines of RAW 264.7 of murine (Lee et al. 2014). Hence, it has become essential to understand the cellular as well as the molecular mechanism of nanoparticle toxicity and their effect on the biological system to develop a safe and precise assay of engineered nanoparticles for risk evaluation.

22.6 Biomarkers to Monitor Nanotoxicology

The advent of nanoparticles has gained significant attention in short period of time due to its widespread functionality in different fields. But the biggest challenge remains the same, i.e., their effect on the biological system (Riehemann et al. 2009). The outmost reasons are their applicability of nanotechnology in different industries and increase in the number of nanomaterials for different purposes in industries, increasing their chances of interaction with our body (Dowling 2004). Nowadays, researchers are focusing on understanding the potent effects of these nanoparticles on cells and tissues on the basic route, which can be due to dermal penetration, ingestion, injection, or inhalation. Moreover, studies have also been conducted to discover biomarkers involved during bio-interfaces, facilitating in creating the biomarkers database to monitor nanotoxicity (Della Rocca et al. 2011).

Biomarkers are stated to be characteristic which measure as well as work as an indicator to assess the biological process, pharmacologic response, or pathogenic process. Hence, it can be anything which can measure the change in antigens, cytokine concentration, genes, and even proteins (Wagner and Atkinson Jr 2015). Because of a wide range of biomarkers, we are focusing on the two groups of biomarkers pro-oxidative and pro-inflammatory because the primary responses induced by toxic nanoparticles in various tissues and cells are oxidative stresses and inflammation (Khanna et al. 2015). The outcomes of these two responses are impairment of tissue function and cell damage. Therefore, these biomarkers can serve as primary detection tool to measure the effect of nanoparticles on health and can also be used for early detection of the adverse effects (Iavicoli et al. 2012).

Pro-inflammatory biomarkers are commonly used to assess the variation in responses due to inflammation and oxidative stress in particular organs like the cardiovascular, immune, and respiratory systems (Bergamaschi 2012). Inflammatory immunological biomarkers are used to define any change in the immune system on the introduction of nanomaterial in the biological system which elicits inflammation. In these antigens, antibodies, chemokines, cytokines, and phagocyte congregation are measured and interrelated with the inflammation response (Xu et al. 2016). These biomarkers are effective in diagnosis of various diseases, but during nanotoxicological studies, its efficacy decreases. Hence, extensive care is taken while identifying the cause of inflammatory response via nanoparticles (Gendelman et al. 2015). This supports and provides evidence as to why the immune system

synthesizes different types of antibodies, cytokines, and chemokines, after encountering with pathogen or external agent causing stress (Gamucci et al. 2014). The major advantage of nanoparticles is its size, which allows them to penetrate directly through the cell wall, accumulate protein on their surface, and even translocate themselves through blood–brain barrier (Sonvico et al. 2018). The mobile nature of nanoparticles and their ability to aggregate themselves in various tissues elicit the immune response and make correlation between the immune response and presence of nanoparticles, which form the basis of biomarker analysis (Dobrovolskaia et al. 2016). At this point of time, major researchers are focusing on determining the toxic dosage which triggers immune response and how to prevent the toxic exposure of nanoparticles. Till date, numerous biomolecules have been identified which play a key role in inflammation (Elsabahy and Wooley 2013).

Numerous studies have highlighted metal oxide nanoparticles like iron oxide (Fe_3O_4), as it elicits immunogenic response in cell and can be used for biomarker studies for assessing potential toxicity (Arias et al. 2018). Joo with his colleague (2013) investigated the adverse effect of Fe_3O_4 on rodents. The results obtained were quite similar with Srinivas et al. (2012), as there was an increase in level of pro-inflammatory cytokines such as transforming growth factor beta (TGF-β TNF-α), interleukin-1 (IL-1,2,4,6,12), and immunoglobulin-E (IgE) which can serve as the biomarker for detecting various ailments (Srinivas et al. 2012). Additionally, tissue damage and inflammation have also reported to increase the expression of few genes encoding for different proteins like tissue-inhibiting metalloproteinase, serum amyloid A (SAA), and heat shock protein. The gene SAA is usually expressed in the liver which elicits the synthesis of TNF-α IL-1 and IL-6 which are also produced as a response to metal oxide nanoparticles (Skovgaard et al. 2009). The discussed biomarkers have recorded to involve in various situation when cell experiences stress. Moreover, they are also reported to be produced by the body in response to cold (Buzea et al. 2007). Biomarkers also serve as parameter for analysis in experimental design and aid in interpreting the result of biomarker assessment. Hence, studies focusing on the assessment of nanomaterial only triggering the inflammatory response enable us to discover the true biomarkers of nanotoxicity (Oberdörster 2010).

On the other hand, pro-oxidative biomarkers are the ones having response to various metal oxide nanoparticles, generally by generating the ROS stress. Therefore, it is essential to observe the ROS level induced by interaction of nanoparticles as ROS generation has been linked with different cardiovascular and respiratory ailments like atherosclerosis, asthma exacerbation, thrombosis, and inflammation (Fu et al. 2014). CuO (copper oxide), TiO_2 (titanium oxide), ZnO (zinc oxide), and Fe_3O_4 (iron oxide) are the metal oxide nanoparticles which have shown to cause the overproduction of ROS, as they allow the propagation of free radicals on their surface during their interaction with enzymes, oligomers, and proteins (Karlsson et al. 2008). Due to distinctive electrical surface properties, these nanoparticles generate substantial amount of ROS, which can be used as nanotoxicity biomarker. These are the two important types of biomarkers that are employed for nanotoxicological assessment.

22.7 Conclusion

There cannot be a second opinion that nano-sized materials have widespread applications in various fields of science and technology. However, there are numerous reports that depict the side effects of the nanomaterials on biological systems and cellular levels. Although they are relatively small sized, yet they have an enormous effect on human life and ecosystem. The elevated use of nanotechnology poses a risk not only to consumers but also firsthand to the workers. Their physicochemical parameters in addition to production of toxic ions, generation of free radical species, and high surface charge ratio result in cytotoxicity by nanoparticles which may include quantum dots, gold and silver nanoparticles, titanium dioxides, CNTs, etc. Both in vivo and in vitro assays require a better knowledge of toxicity mechanism so as to avoid side effects and exploit the benefits that nanotechnology has to offer. The information will further help to formulate the measures able to reduce the potential hazards of nanomaterials. Nanomaterials causing oxidative stress could be replaced with nanomaterials that are relatively less harmful. Further proper administration of antioxidants and other therapies to the occupational workers should also be taken into consideration to check their immune-related disorders. Also, the incorporation of nanomaterials should be considered effectively because the method of incorporation of nanomaterials in a product strongly influences its release in the environment. Thus, knowledge of pathogenic mechanisms of the nanomaterials is very crucial.

References

Arias L, Pessan J, Vieira A, Lima T, Delbem A, Monteiro D (2018) Iron oxide nanoparticles for biomedical applications: a perspective on synthesis, drugs, antimicrobial activity, and toxicity. Antibiotics 7(2):46

Ayangbenro A, Babalola O (2017) A new strategy for heavy metal polluted environments: a review of microbial biosorbents. Int J Environ Res Public Health 14(1):94

Barua S, Mitragotri S (2014) Challenges associated with penetration of nanoparticles across cell and tissue barriers: a review of current status and future prospects. Nano Today 9(2):223–243

Behzadi S, Serpooshan V, Tao W, Hamaly MA, Alkawareek MY, Dreaden EC, Brown D, Alkilany AM, Farokhzad OC, Mahmoudi M (2017) Cellular uptake of nanoparticles: journey inside the cell. Chem Soc Rev 46(14):4218–4244

Bergamaschi E (2012) Human biomonitoring of engineered nanoparticles: an appraisal of critical issues and potential biomarkers. J Nanomater 2012:564121

Bhati S, Kumar V, Singh S, Singh J (2019) Synthesis, biological activities and docking studies of piperazine incorporated 1,3,4-oxadiazole derivatives. J Mol Struct 1191:197–205

Brandenberger C, Rothen-Rutishauser B, Mühlfeld C, Schmid O, Ferron GA, Maier KL, Gehr P, Lenz AG (2010) Effects and uptake of gold nanoparticles deposited at the air-liquid interface of a human epithelial airway model. Toxicol Appl Pharmacol 242:56–65

Buzea C, Pacheco II, Robbie K (2007) Nanomaterials and nanoparticles: sources and toxicity. Biointerphases 2(4):MR17–MR71

Camargo PH, Satyanarayana KG, Wypych F (2009) Nanocomposites: synthesis, structure, properties and new application opportunities. Mater Res 12(1):1–39

Chander N, Khan AF, Thouti E, Sardana SK, Chandrasekhar PS, Dutta V, Komarala VK (2014) Size and concentration effects of gold nanoparticles on optical and electrical properties of plasmonic dye sensitized solar cells. Sol Energy 109:11–23

Chen Q, Xue Y, Sun J (2013) Kupffer cell-mediated hepatic injury induced by silica nanoparticles *in vitro* and *in vivo*. Int J Nanomed 8:1129–1140

Cheng Y, Yang H, Yang Y, Huang J, Wu K, Chen Z, Wang X, Lin C, Lai Y (2018) Progress in TiO_2 nanotube coatings for biomedical applications: a review. J Mater Chem B 6(13):1862–1886

Cho WS, Kim S, Han BS, Son WC, Jeong J (2009) Comparison of gene expression profiles in mice liver following intravenous injection of 4 and 100 nm-sized PEG-coated gold nanoparticles. Toxicol Lett 191:96–102

Chou CC, Hsiao HY, Hong QS, Chen CH, Peng YW, Chen HW, Yang PC (2008) Single-walled carbon nanotubes can induce pulmonary injury in mouse model. Nano Lett 8:437–445

Cicek S, Nadaroglu H (2015) The use of nanotechnology in the agriculture. Adv Nano Res 3(4):207–223

Das R, Vecitis CD, Schulze A, Cao B, Ismail AF, Lu X, Chen J, Ramakrishna S (2017) Recent advances in nanomaterials for water protection and monitoring. Chem Soc Rev 46(22):6946–7020

Dayem AA, Hossain MK, Lee SB, Kim K, Saha SK, Yang GM, Choi HY, Cho SG (2017) The role of reactive oxygen species (ROS) in the biological activities of metallic nanoparticles. Int J Mol Sci 18(1):120

Della Rocca J, Liu D, Lin W (2011) Nanoscale metal–organic frameworks for biomedical imaging and drug delivery. Acc Chem Res 44(10):957–968

Deng ZJ, Liang M, Monteiro M, Toth I, Minchin RF (2011) Nanoparticle-induced unfolding of fibrinogen promotes Mac-1 receptor activation and inflammation. Nat Nanotechnol 6(1):39–44

Dobrovolskaia MA, Shurin M, Shvedova AA (2016) Current understanding of interactions between nanoparticles and the immune system. Toxicol Appl Pharmacol 299:78–89

Dong J, Ma Q (2016) Myofibroblasts and lung fibrosis induced by carbon nanotube exposure. Part Fibre Toxicol 1(13):1–22

Dowling AP (2004) Development of nanotechnologies. Mater Today 7(12):30–35

Elsabahy M, Wooley KL (2013) Cytokines as biomarkers of nanoparticle immunotoxicity. Chem Soc Rev 42(12):5552–5576

Elsaesser A, Howard CV (2012) Toxicology of nanoparticles. Adv Drug Deliv Rev 64:129–137

Exbrayat J, Moudilou EN, Lapied E (2015) Harmful effects of nanoparticles on animals. J Nanotechnol 2015:861092

Fakruddin M, Hossain Z, Afroz H (2012) Prospects and applications of nanobiotechnology: a medical perspective. J Nanobiotechnol 10(1):31

Fröhlich E (2012) The role of surface charge in cellular uptake and cytotoxicity of medical nanoparticles. Int J Nanomedicine 7:5577–5591

Fu PP, Xia Q, Hwang HM, Ray PC, Yu H (2014) Mechanisms of nanotoxicity: generation of reactive oxygen species. J Food Drug Anal 22(1):64–75

Fujita K, Morimoto Y, Ogami A, Myojyo T, Tanaka I, Shimada M, Wang WN, Endoh S, Uchida K, Nakazato T, Yamamoto K, Fukui H, Horie M, Yoshida Y, Iwahashi H, Nakanishi J (2009) Gene expression profiles in rat lung after inhalation exposure to C60 fullerene particles. Toxicol 258:47–55

Gamucci O, Bertero A, Gagliardi M, Bardi G (2014) Biomedical nanoparticles: overview of their surface immune-compatibility. Coatings 4(1):139–159

Geiser M, Casaulta M, Kupferschmid B, Schulz H, Semmler-Behnke M, Kreyling W (2008) The role of macrophages in the clearance of inhaled ultrafine titanium dioxide particles. Am J Respir Cell Mol Biol 38:371–376

Gendelman HE, Anantharam V, Bronich T, Ghaisas S, Jin H, Kanthasamy AG, Liu X, McMillan J, Mosley RL, Narasimhan B, Mallapragada SK (2015) Nanoneuromedicines for degenerative, inflammatory, and infectious nervous system diseases. Nanomed 11(3):751–767

Ghodake G, Seo YD, Lee DS (2011) Hazardous phytotoxic nature of cobalt and zinc oxide nanoparticles assessed using Allium cepa. J Hazard Mater 186:952–955

Giannakou C, Park MV, de Jong WH, van Loveren H, Vandebriel RJ, Geertsma RE (2016) A comparison of immunotoxic effects of nanomedicinal products with regulatory immunotoxicity testing requirements. Int J Nanomedicine 11:2935–2952

Gupta R, Xie H (2018) Nanoparticles in daily life: applications, toxicity and regulations. J Environ Pathol Toxicol Oncol 37(3):209–230
Gwinn MR, Vallyathan V (2006) Nanoparticles: health effects—pros and cons. Environ Health Perspect 114(12):1818–1825
Hasija V, Raizada P, Sudhaik A, Sharma K, Kumar A, Singh P, Jonnalagadda SB, Thakur VK (2019) Recent advances in noble metal free doped graphitic carbon nitride based nanohybrids for photocatalysis of organic contaminants in water: a review. Appl Mater Today 15:494–524
He H, Pham-Huy LA, Dramou P, Xiao D, Zuo P, Pham-Huy C (2013) Carbon nanotubes: applications in pharmacy and medicine. Biomed Res Int 2013:578290
Herzog E, Byrne HJ, Casey A, Davoren M, Lenz AG, Maier KL, Duschl A, Oostingh GJ (2009) SWCNT suppress inflammatory mediator responses in human lung epithelium in vitro. Toxicol Appl Pharmacol 234:378–339
Hutter E, Boridy S, Labrecque S, Lalancette-Hébert M, Kriz J, Winnik FM, Maysinger D (2010) Microglial response to gold nanoparticles. ACS Nano 4:2595–2606
Iavicoli I, Leso V, Bergamaschi A (2012) Toxicological effects of titanium dioxide nanoparticles: a review of in vivo studies. J Nanomater 2012:5
Inoue K, Takano H, Yanagisawa R, Koike E, Shimada A (2009) Size effects of latex nanomaterials on lung inflammation in mice. Toxicol Appl Pharmacol 234:68–76
Jeevanandam J, Barhoum A, Chan YS, Dufresne A, Danquah MK (2018) Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein J Nanotechnol 9(1):1050–1074
Jeng HA, Swanson J (2006) Toxicity of metal oxide nanoparticles in mammalian cells. J Environ Sci Health A 41(12):2699–2711
Joo J, Lee M, Bae S, An SS (2013) Blood biomarkers: from nanotoxicity to neurodegeneration. SPIE Newsroom
Kagan VE, Konduru NV, Feng W, Allen BL, Conroy J, Volkov Y, Vlasova II, Belikova NA, Yanamala N, Kapralov A, Tyurina YY, Shi J, Kisin ER, Murray AR, Franks J, Stolz D, Gou P, Klein-Seetharaman J, Fadeel B, Star A, Shvedova AA (2010) Carbon nanotubes degraded by neutrophil myeloperoxidase induce less pulmonary inflammation. Nat Nanotechnol 5:354–359
Kapoor D, Singh S, Kumar V, Romero R, Prasad R, Singh J (2019) Antioxidant enzymes regulation in plants in reference to reactive oxygen species (ROS) and reactive nitrogen species (RNS). Plant Gene 19:100182
Karimi S, Troeung M, Wang R, Draper R, Pantano P (2018) Acute and chronic toxicity of metal oxide nanoparticles in chemical mechanical planarization slurries with *Daphnia magna*. Environ Sci Nano 5(7):1670–1684
Karlsson HL, Cronholm P, Gustafsson J, Moller L (2008) Copper oxide nanoparticles are highly toxic: a comparison between metal oxide nanoparticles and carbon nanotubes. Chem Res Toxicol 21(9):1726–1732
Khan I, Saeed K, Khan I (2017) Nanoparticles: properties, applications and toxicities. Arab J Chem 12:908. https://doi.org/10.1016/j.arabjc.2017.05.011
Khanna P, Ong C, Bay B, Baeg G (2015) Nanotoxicity: an interplay of oxidative stress, inflammation and cell death. Nanomaterials 5(3):1163–1180
Kim KS, Lee D, Song CG, Kang PM (2015) Reactive oxygen species-activated nanomaterials as theranostic agents. Nanomed 10(17):2709–2723
Koike E, Takano H, Inoue KI, Yanagisawa R, Sakurai M, Aoyagi H, Shinohara R, Kobayashi T (2008) Pulmonary exposure to carbon black nanoparticles increases the number of antigen-presenting cells in murine lung. Int J Immunopathol Pharmacol 21:35–42
Kroll A, Dierker C, Rommel C, Hahn D, Wohlleben W, Schulze-Isfort C, Göbbert C, Voetz M, Hardinghaus F, Schnekenburger J (2011) Cytotoxicity screening of 23 engineered nanomaterials using a test matrix of ten cell lines and three different assays. Part Fibre Toxicol 8(1):9
Kumar V, Singh S (2018a) Kinetics of dechlorination of atrazine using tin (SnII) at neutral pH conditions. Appl Chem Eng. https://doi.org/10.63019/ace.v1i4
Kumar V, Singh S (2018b) Interactions of acephate, glyphosate, monocrotophos and phorate with bovine serum albumin. Indian J Pharm Sci 80(6):1151

Kumar V, Singh S, Srivastava B, Bhadouria R, Singh R (2019a) Green synthesis of silver nanoparticles using leaf extract of *Holoptelea integrifolia* and preliminary investigation of its antioxidant, anti-inflammatory, antidiabetic and antibacterial activities. J Environ Chem Eng 2019:103094

Kumar V, Singh S, Singh R (2019b) Phytochemical constituents of guggul gum and their biological qualities. Mini-Rev Org Chem 16. https://doi.org/10.2174/1570193X16666190129161757

Kumar V, Singh S, Singh A, Subhose V, Prakash O (2019c) Assessment of heavy metal ions, essential metal ions, and antioxidant properties of the most common herbal drugs in Indian Ayurvedic hospital: for ensuring quality assurance of certain Ayurvedic drugs. Biocatal Agric Biotechnol 18:101018

Lameijer MA, Tang J, Nahrendorf M, Beelen RH, Mulder WJ (2013) Monocytes and macrophages as nanomedicinal targets for improved diagnosis and treatment of disease. Expert Rev Mol Diagn 13(6):567–580

Landa P, Vankova R, Andrlova J, Hodek J, Marsik P, Storchova H, White JC, Vanek T (2012) Nanoparticle-specific changes in Arabidopsis thaliana gene expression after exposure to ZnO, TiO_2, and fullerene soot. J Hazard Mater 241:55–62

Laux P, Tentschert J, Riebeling C, Braeuning A, Creutzenberg O, Epp A, Fessard V, Haas KH, Haase A, Hund-Rinke K, Jakubowski N (2018) Nanomaterials: certain aspects of application, risk assessment and risk communication. Arch Toxicol 92(1):121–141

Lee JH, Ju JE, Kim BI, Pak PJ, Choi EK, Lee HS, Chung N (2014) Rod-shaped iron oxide nanoparticles are more toxic than sphere-shaped nanoparticles to murine macrophage cells. Environ Toxicol Chem 33(12):2759–2766

Li W, Elzatahry A, Aldhayan D, Zhao D (2018) Core–shell structured titanium dioxide nanomaterials for solar energy utilization. Chem Soc Rev 47(22):8203–8237

Li X, Hu Y, Jin Z, Jiang H, Wen J (2009) Silica-induced TNF-α and TGF-β 1 expression in RAW264. 7 cells are dependent on Src-ERK/AP-1 pathways. Toxicol Mech Methods 19(1):51–58

Li X, Zhu J, Wei B (2016) Hybrid nanostructures of metal/two-dimensional nanomaterials for plasmon-enhanced applications. Chem Soc Rev 45(11):3145–3187

Lim CT (2017) Nanofiber technology: current status and emerging developments. Prog Polym Sci 70:1–7

Liu Y, Hardie J, Zhang X, Rotello VM (2017) Effects of engineered nanoparticles on the innate immune system. Semin Immunol 34:25–32

Look M, Bandyopadhyay A, Blum JS, Fahmy TM (2010) Application of nanotechnologies for improved immune response against infectious diseases in the developing world. Adv Drug Deliv Rev 62(4–5):378–393

Manke A, Wang L, Rojanasakul Y (2013) Mechanisms of nanoparticle-induced oxidative stress and toxicity. Biomed Res Int 2013:942916

Manolova V, Flace A, Bauer M, Schwarz K, Saudan P, Bachmann MF (2008) Nanoparticles target distinct dendritic cell populations according to their size. Eur J Immunol 38(5):1404–1413

Morishige T, Yoshioka Y, Tanabe A, Yao X, Tsunoda S, Tsutsumi Y, Mukai Y, Okada N, Nakagawa S (2010) Titanium dioxide induces different levels of IL-1beta production dependent on its particle characteristics through caspase-1 activation mediated by reactive oxygen species and cathepsin B. Biochem Biophys Res Commun 392:160–165

Müller L, Riediker M, Wick P, Mohr M, Gehr P, Rothen-Rutishauser B (2010) Oxidative stress and inflammation response after nanoparticle exposure: differences between human lung cell monocultures and an advanced three-dimensional model of the human epithelial airways. J R Soc Interface 7(Suppl 1):S27–S40

Murphy K (2008) Nanotechnology: agriculture's next "industrial" revolution. Spring (Financial partner, yankee farm credit, ACA), Williston, pp 3–5

Nemmar A, Melghit K, Ali BH (2008) The acute proinflammatory and prothrombotic effects of pulmonary exposure to rutile TiO_2 nanorods in rats. Exp Biol Med (Maywood) 233:610–619

Nishimori H, Kondoh M, Isoda K, Tsunoda S, Tsutsumi Y, Yagi K (2009) Silica nanoparticles as hepatotoxicants. Eur J Pharm Biopharm 72:496–501

Niwa Y, Hiura Y, Sawamura H, Iwai N (2008) Inhalation exposure to carbon black induces inflammatory response in rats. Circ J 72:144–149

Oberdörster G (2010) Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. J Intern Med 267(1):89–105
Panyam J, Labhasetwar V (2003) Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Adv Drug Deliv Rev 55:329–347
Park EJ, Kim H, Kim Y, Yi J, Choi K, Park K (2010a) Inflammatory responses may be induced by a single intratracheal instillation of iron nanoparticles in mice. Toxicology 275(1–3):65–71
Park YH, Kim JN, Jeong SH, Choi JE, Lee SH, Choi BH, Lee JP, Sohn KH, Park KL, Kim MK, Son SW (2010b) Assessment of dermal toxicity of nanosilica using cultured keratinocytes, a human skin equivalent model and an in vivo model. Toxicol 267:178–181
Qiu H, Cui B, Li G, Yang J, Peng H, Wang Y, Li N, Gao R, Chang Z, Wang Y (2014) Novel Fe_3O_4@ ZnO@ $mSiO_2$ nanocarrier for targeted drug delivery and controllable release with microwave irradiation. J Phys Chem C 118(27):14929–14937
Rajasulochana P, Preethy V (2016) Comparison on efficiency of various techniques in treatment of waste and sewage water–a comprehensive review. Resour Efficient Technol 2(4):175–184
Riehemann K, Schneider SW, Luger TA, Godin B, Ferrari M, Fuchs H (2009) Nanomedicine—challenge and perspectives. Angew Chem Int Ed 48(5):872–897
Ryman-Rasmussen JP, Cesta MF, Brody AR, Shipley-Phillips JK, Everitt JI, Tewksbury EW, Moss OR, Wong BA, Dodd DE, Andersen ME, Bonner JC (2009) Inhaled carbon nanotubes reach the subpleural tissue in mice. Nat Nanotechnol 4:747–751
Sanchez C, Belleville P, Popall M, Nicole L (2011) Applications of advanced hybrid organic–inorganic nanomaterials: from laboratory to market. Chem Soc Rev 40(2):696–753
Schanen BC, Das S, Reilly CM, Warren WL, Self WT, Seal S, Drake DR III (2013) Immunomodulation and T helper TH1/TH2 response polarization by CeO_2 and TiO_2 nanoparticles. PLoS One 8(5):e62816
Schipper ML, Nakayama-Ratchford N, Davis CR, Kam NW, Chu P, Liu Z, Sun X, Dai H, Gambhir SS (2008) A pilot toxicology study of single-walled carbon nanotubes in a small sample of mice. Nat Nanotechnol 3(4):216–221
Setyawati MI, Tay CY, Docter D, Stauber RH, Leong DT (2015) Understanding and exploiting nanoparticles' intimacy with the blood vessel and blood. Chem Soc Rev 44(22):8174–8199
Sharma M, Salisbury RL, Maurer EI, Hussain SM, Sulentic CE (2013) Gold nanoparticles induce transcriptional activity of NF-κB in a B-lymphocyte cell line. Nanoscale 5(9):3747–3756
Sidhu GK, Singh S, Kumar V, Dhanjal DS, Datta S, Singh J (2019) Toxicity, monitoring and biodegradation of organophosphate pesticides: a review. Crit Rev Environ Sci Technol 49:1–53
Singh N (2009) Conference scene-nanotoxicology: health and environmental impacts. Nanomed 4(4):385–390
Singh R, Lillard JW Jr (2009) Nanoparticle-based targeted drug delivery. Exp Mol Pathol 86(3):215–223
Singh S, Kumar V, Singh J (2019a) Kinetic study of the biodegradation of glyphosate by indigenous soil bacterial isolates in presence of humic acid, Fe (III) and Cu (II) ions. J Environ Chem Eng 2019:103098
Singh S, Kumar V, Sidhu GK, Datta S, Dhanjal DS, Koul B, Singh J (2019b) Plant growth promoting rhizobacteria from heavy metal contaminated soil promote growth attributes of Pisum sativum L. Biocatal Agric Biotechnol 17:665–671
Singh S, Kumar V, Singh S, Singh J (2019c) Influence of humic acid, iron and copper on microbial degradation of fungicide Carbendazim. Biocatal Agric Biotechnol 2019:101196
Skovgaard K, Mortensen S, Boye M, Poulsen KT, Campbell FM, Eckersall PD, Heegaard PM (2009) Rapid and widely disseminated acute phase protein response after experimental bacterial infection of pigs. Vet Res 40(3):1–2
Sonvico F, Clementino A, Buttini F, Colombo G, Pescina S, Stanisçuaski Guterres S, Raffin Pohlmann A, Nicoli S (2018) Surface-modified nanocarriers for nose-to-brain delivery: from bioadhesion to targeting. Pharmaceutics 10(1):34
Srinivas A, Rao PJ, Selvam G, Goparaju A, Murthy BP, Reddy NP (2012) Oxidative stress and inflammatory responses of rat following acute inhalation exposure to iron oxide nanoparticles. Hum Exp Toxicol 31(11):1113–1131

Suh WH, Suslick KS, Stucky GD, Suh YH (2009) Nanotechnology, nanotoxicology, and neuroscience. Prog Neurobiol 87(3):133–170

Sukhanova A, Bozrova S, Sokolov P, Berestovoy M, Karaulov A, Nabiev I (2018) Dependence of nanoparticle toxicity on their physical and chemical properties. Nanoscale Res Lett 13(1):44

Taghavi SM, Momenpour M, Azarian M, Ahmadian M, Souri F, Taghavi SA, Sadeghain M, Karchani M (2013) Effects of nanoparticles on the environment and outdoor workplaces. Electron Physician 5(4):706–712

Tarafdar JC (2015) Nanoparticle production, characterization and its application to horticultural crops. Compendium of winter school on utilization of degraded land and soil through horticultural crops for improving agricultural productivity and environmental quality. NRCSS, Ajmer, India, pp 222–229

Upadhyay RK, Soin N, Roy SS (2014) Role of graphene/metal oxide composites as photocatalysts, adsorbents and disinfectants in water treatment: a review. RSC Adv 4(8):3823–3851

Wagner JA, Atkinson AJ Jr (2015) Measuring biomarker progress. Clin Pharmacol Ther 98(1):2–5

Wang EC, Wang AZ (2013) Nanoparticles and their applications in cell and molecular biology. Integr Biol 6(1):9–26

Wang L, Hu C, Shao L (2017) The antimicrobial activity of nanoparticles: present situation and prospects for the future. Int J Nanomed 12:1227–1249

Warheit DB, Sayes CM, Reed KL, Swain KA (2008) Health effects related to nanoparticle exposures. Environmental, health and safety considerations for assessing hazards and risks. Pharmacol Ther 120:35–42

Wu H, Zhang J (2018) Chitosan-based zinc oxide nanoparticle for enhanced anticancer effect in cervical cancer: a physicochemical and biological perspective. Saudi Pharm J 26:205–210

Xia T, Kovochich M, Liong M, Zink JI, Nel AE (2008a) Cationic polystyrene nanosphere toxicity depends on cell-specific endocytic and mitochondrial injury pathways. ACS Nano 2:85–96

Xia T, Kovochich M, Liong M, Mädler L, Gilbert B, Shi H, Yeh JI, Zink JI, Nel AE (2008b) Comparison of the mechanism of toxicity of zinc oxide and cerium oxide nanoparticles based on dissolution and oxidative stress properties. ACS Nano 2:2121–2134

Xu Y, Sherwood JA, Lackey KH, Qin Y, Bao Y (2016) The responses of immune cells to iron oxide nanoparticles. J Appl Toxicol 36(4):543–553

Yanagisawa R, Takano H, Inoue K, Koike E, Kamachi T, Sadakane K, Ichinose T (2009) Titanium dioxide nanoparticles aggravate atopic dermatitis-like skin lesions in NC/Nga mice. Exp Biol Med 234:314–322

Ye SF, Wu YH, Hou ZQ, Zhang QQ (2009) ROS and NF-kappaB are involved in upregulation of IL-8 in A549 cells exposed to multi-walled carbon nanotubes. Biochem Biophys Res Commun 379:643–648

Yildirimer L, Thanh NT, Loizidou M, Seifalian AM (2011) Toxicology and clinical potential of nanoparticles. Nano Today 6(6):585–607

Yola ML, Eren T, Atar N (2014) A novel efficient photocatalyst based on TiO_2 nanoparticles involved boron enrichment waste for photocatalytic degradation of atrazine. Chem Eng J 250:288–294

Yuan Q, Hein S, Misra RDK (2010) New generation of chitosan-encapsulated ZnO quantum dots loaded with drug: synthesis, characterization and *in vitro* drug delivery response. Acta Biomater 6:2732–2739

Zhong CY, Zhou YM, Smith KR, Kennedy IM, Chen CY, Aust AE, Pinkerton KE (2010) Oxidative injury in the lungs of neonatal rats following short-term exposure to ultrafine iron and soot particles. J Toxicol Environ Health A 73:837–847