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Review Article

# Oxidative DNA Damage from Nanoparticle Exposure and Its Application to Workers' Health: A Literature Review

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ABSTRACT

The use of nanoparticles (NPs) in industry is increasing, bringing with it a number of adverse health effects on workers. Like other chemical carcinogens, NPs can cause cancer via oxidative DNA damage. Of all the molecules vulnerable to oxidative modification by NPs, DNA has received the greatest attention, and biomarkers of exposure and effect are nearing validation. This review concentrates on studies published between 2000 and 2012 that attempted to detect oxidative DNA damage in humans, laboratory animals, and cell lines. It is important to review these studies to improve the current understanding of the oxidative DNA damage caused by NP exposure in the workplace. In addition to examining studies on oxidative damage, this review briefly describes NPs, giving some examples of their adverse effects, and reviews occupational exposure assessments and approaches to minimizing exposure (e.g., personal protective equipment and engineering controls such as fume hoods). Current recommendations to minimize exposure are largely based on common sense, analogy to ultrafine material toxicity, and general health and safety recommendations.



## 1. Introduction

In recent decades, advances in nanotechnology engineering have given rise to the rapid development of many novel applications for nanoparticles (NPs) in various industries. Few studies, however, have been conducted to evaluate the health and safety implications of the introduction of these NPs into the workplace. The main concerns that NPs create in the workplace are the adverse effects of acute or chronic exposure. The lung is one of the main routes of entry for NPs into the body, making it a likely site for NP accumulation. Once NPs enter the interstitial air spaces, they are quickly taken up by alveolar cells and are likely to induce toxic effects [1]. Thus, the need to create hazard identification and risk management strategies for these new products is of increasing importance.

Owing to the extremely small size of the NPs being used in industry, there is a concern that they may interact directly with macromolecules such as DNA. Objects on the nano scale take on novel properties and functions that differ markedly from those seen in their corresponding bulk counterparts, primarily because of their small sizes and large surface areas. Studies have revealed that the same properties that make NPs so unique could also be responsible for their potential toxicity [2].

Nanotechnology involves a wide range of physical and chemical properties, and many NPs are so dramatically new that they have highly unpredictable qualities. Employees involved in the development, production, and use of these new NPs are already exposed to unclear levels of toxicity. Occupational exposure to NPs could be associated with an increased risk of various cancers, as has been the case with occupational exposure to some metals. Although the exact mechanisms are not yet studied, there is accumulating evidence that reactive oxygen species (ROS) play important roles in the carcinogenetic effects of metals [3]. Oxidative stress-based biomarkers have been essential to comprehend how oxidative stress may be mediating the toxic effects of occupational exposure to many known carcinogenic substances.

There have been numerous studies demonstrating the induction of ROS following exposure to NPs. Both *in vivo* and *in vitro* studies have consistently found that NPs have biological effects on the

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respiratory system, including the generation of oxidative stress, the induction of emphysema and proinflammatory status, and damage to DNA. Improved knowledge of such biological effects is needed to guide preventive strategies for the workplace [4].

This review concentrates on studies published between 2010 and 2013 that attempted to detect oxidative DNA damage indicated by the presence of 8-oxo-7-hydrodeoxyguanosine (8-oxodG) in humans, laboratory animals, and cell lines. Reviewing these studies will help improve the current understanding of the potential oxidative DNA damages associated with exposure to NPs in the workplace. This improved understanding will help establish safe and healthy working environments in industries that use NPs.

## 2. Materials and methods

In this extensive literature review, relevant articles in the fields of toxicology (including *in vitro* and *in vivo* studies), industrial hygiene, and epidemiology were found using PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Google Scholar (http://scholar.google.com), and ScienceDirect (www.sciencedirect.com). Keywords were used to locate relevant articles, and the following is an example of a typical search: nanoparticle AND toxicology AND worker OR environment OR occupation AND health OR industry.

These searches yielded more than 300 articles, which were further reviewed for occupational or environmental content. At the end of this selection process, 121 articles were deemed relevant to this review, and they were examined with a particular emphasis on three topics: molecular and cellular toxicology, animal and human epidemiology, and impacts of workers' environmental and occupational exposure. The prospects of industries that depend on NPs and the significance of preventive health and safety measures in these industries were also discussed.

## 3. Results

The increasing utilization of NPs in electronics and biomedicine demands an assessment of the risks associated with deliberate or accidental exposure to these substances, with metal-based NPs being the most important. Since the physical chemical properties such as the length and aspect ratio of NPs are linked to their genotoxicity, small NPs can induce primary DNA lesions at very low concentrations and this DNA damage is exclusively induced by oxidative stress. Particles with higher aspect ratios exhibited weaker genotoxicity wherein oxidative stress was a minor factor, and other mechanisms were likely involved [5]. When cells are exposed to NPs, they may undergo repairable oxidative stress and DNA damage or be induced into apoptosis, either of which may cause the cells to alter their proliferation, differentiation, or cell-to-cell signaling [6].

Studies in animal models indicate that silicate, titanium dioxide ($TiO_2$), buckminsterfullerene ($C_{60}$), carbon nanotubes, and particles produced by the combustion of wood or diesel oil produce elevated levels of lipid peroxidation products and oxidatively damaged DNA. Further, biomonitoring studies in humans have shown links between exposure to air pollution and oxidative damage to DNA. These results indicate that oxidative stress and elevated levels of oxidatively altered biomolecules are important intermediates that may be useful markers for characterizing the potential hazards of NP exposure [7].

### 3.1. Metals

Although metallic NPs are widely used, the long-term fate of NPs in biological environments is not well understood. Once metallic NPs in particular have entered cells, they might not induce DNA damage themselves but instead corrode over time, releasing metallic ions that could induce genotoxicity. Thus, long-term genotoxic responses to NPs may involve effects that are significantly different from those seen in short-term exposure datasets; further research is required to resolve these uncertainties.

#### 3.1.1. Gold nanoparticles

Gold nanoparticles (AuNPs) have been utilized in imaging, biosensing, gene and drug delivery, and cancer diagnostics and therapy, owing to their unique optical properties and biocompatibility [8]. Although the safety of using AuNPs is of growing concern, most studies have focused on these particles' characteristics, including their physical dimensions, surface chemistry, and shape. AuNPs can catalyze the rapid decomposition of hydrogen peroxide ($H_2O_2$), which is accompanied by the formation of hydroxyl radicals at lower and oxygen at higher pH levels. Further, AuNPs efficiently catalyze superoxide ($O_2^-$) decomposition, acting as catalase mimetics by mimicking superoxide dismutases (SODs). Because ROS are biologically relevant products continuously generated in cells, these results, obtained under conditions resembling different biological microenvironments, may provide insights for evaluating AuNP-associated risks [9]. Studies of the effects of 10-day exposure in an *in vitro* model with BALB/c 3T3 fibroblast cells show that AuNPs, although they are not themselves severe cytotoxicants, are likely to induce DNA damage through an indirect mechanism triggered by oxidative stress [10].

In a study on cytosolic and mitochondrial glutathione (GSH) depletion in HL7702 cells following exposure to 8-nm AuNPs, $H_2O_2$ generation increased significantly following the depletion of mitochondrial GSH, and the sequence of mitochondrial signaling events induced apoptosis [11]. Exposure to 1.9-nm AuNPs induced a range of cell line-specific responses, including decreased clonogenic survival, increased apoptosis, and induction of DNA damage possibly mediated through the production of ROS [12]. In rat brains, exposure to 1.9-nm AuNPs was accompanied by an increase in 8-hydroxy-2′-deoxyguanosine (8-OHdG), caspase-3, and heat shock protein 70, all of which could lead to DNA damage and cell death. This level of exposure also caused the generation of interferon gamma, which may lead to inflammation, DNA damage, or cell death [13]. These results suggest that AuNP exposure can induce oxidative stress-mediated genomic instability [14].

In another study, different-sized AuNPs were instilled once into the lungs of male Wistar rats, but there were no relevant clinical or histopathological findings; a Comet assay showed no increased DNA damage in the lung cells, and the micronucleus (MN) rate in the bone marrow cells was not adversely affected [15]. In another study, however, severe hepatic cell damage, acute inflammation, increased apoptosis and ROS production were observed in the livers of AuNP-injected mice on a methionine and choline-deficient diet, whereas these liver injuries were attenuated in mice fed a normal chow diet. It was suggested that AuNPs create toxicity in a stressed liver environment by stimulating the inflammatory response and accelerating stress-induced apoptosis [16]. Although AuNP induced genotoxicity is controversial, the expression of genes involved in DNA repair, detoxification processes, apoptosis, mitochondrial metabolism, and oxidative stress was also modulated in response to AuNP contamination [17].

#### 3.1.2. Silver nanoparticles

In a recent study, cell death and DNA damage induced by silver nanoparticles (AgNPs) were prevented by Tiron and dimethyl thiourea, which scavenge superoxide anions ($O_2^-$) and $H_2O_2$, respectively, demonstrating the role of ROS in AgNP-induced cell death and DNA damage [18]. In another study, 200-nm AgNPs appeared to cause a concentration-dependent increase in DNA strand breaks in NT2 human testicular embryonic carcinoma cells. Although in another study no significant induction of DNA damage in AgNP-treated

mouse lymphoma cells was observed in the standard Comet assay, the AgNP treatments induced a dose-responsive increase in oxidative DNA damage in an enzyme-modified Comet assay in which oxidative lesion-specific endonucleases were added. These AgNPs were taken up by cells, decreasing cell viability in a dose- and time-dependent manner at 6.25–100 μg/mL dosage levels, and decreasing the activities of SODs and GSH peroxides. Levels of malondialdehyde, a lipid peroxidation end product, were also increased in the AgNP-exposed cells [19]. In another study, AgNPs reduced cell viability, as demonstrated by the formation of apoptotic bodies, sub-G1 hypo-diploid cells, and DNA fragmentation. From all of these studies, it could suggest that AgNPs cause cytotoxicity by oxidative stress-induced apoptosis and damage to cellular components [20].

Researchers have also shown that AgNPs impair mitochondrial function, mainly owing to altered mitochondrial membrane permeability, which results in an uncoupling effect on the oxidative phosphorylation system [21]. In L929 fibroblasts, but not in RAW 264.7 macrophages, 20-nm AgNPs were shown to be more cytotoxic than silver (Ag) ions in L929 fibroblasts but not in RAW264.7 macrophages. Collectively, these results indicate that the effects of AgNPs on different toxicities may be a consequence of their ability to inflict cell damage. In addition, the tendency of Ag to induce greater cell damage when in the NP form than when in the ion form is cell type- and size-dependent [22]. AgNP cytotoxicity was also shown to depend on NP size and dosage in human lung fibroblast cells [23].

Although the potential for AgNPs to damage mitochondria and cells was shown to be mediated by their production of Ag ions. One study showed that neither the presence of AgNPs nor Ag ions caused cell leakage or membrane damage [24]. However, in another study, Ag ions significantly inhibited the removal of phosphorus (P) by creating an increase in ROS production that in turn decreased the presence of enzymes related to P removal [25]. Yet another study established that AgNP exposure can lead to DNA damage and chromosomal aberrations, it is raising concerns about the safety of AgNPs [26]. Actually the research claims that intravenously administered low doses of small AgNPs have a toxic effect on germ cells, change sperm counts, and may have a genotoxic effect [27].

Some studies assessed the toxicity of AgNP in fish. In one study, male medakas (*Oryzias latipes*) were exposed to two doses (1 and 25 μg/L) of either silver nitrate ($AgNO_3$) or AgNPs for 28 days. The fish exposed to AgNPs experienced increased metal detoxification, and oxidative and inflammatory stresses [28]. In a study using rainbow trout (*Oncorhynchus mykiss*), the bioavailability of hepatic Ag was higher for fish exposed to dissolved Ag than to AgNP. The AgNP produced inflammation in trout, whereas Ag disturbed the protein stability and redox status in the liver [29].

Low-dose (3 mg/kg) and high-dose (30 mg/kg) AgNP were given to rats in another study for 14 days. The rats treated with AgNP showed significantly increased ROS in their hippocampal homogenate, and this increase may have been responsible for the rats' impaired hippocampal function [30].

In research on gene expression using an oxidative stress and antioxidant defense polymerase chain reaction array, the expressions of 17 of the 59 genes on the arrays were altered in cells treated with AgNPs. These genes are involved in producing ROS, antioxidants, and oxygen transporters, and in oxidative stress responses and DNA repair. It was also suggested that 5-nm AgNPs are mutagenic in mouse lymphoma cells owing to the induction of oxidative stress [31].

The cytotoxicity of AgNPs is decreased by antioxidants. The level of bulky DNA adducts induced by AgNPs has not only been correlated with the level of cellular ROS, but is also inhibited by antioxidant pretreatment, suggesting AgNPs mediate ROS-induced genotoxicity. The balances between anti-ROS responses and DNA damage, chromosome instability, and mitosis inhibition might play important roles in AgNP-induced toxicity [32].

### 3.2. Metal oxides

#### 3.2.1. Titanium dioxide nanoparticles

Studies have tested a range of titanium dioxide nanoparticle ($TiO_2$NP) forms with different sizes and crystalline structures in an array of mammalian cell lines. The primary factor that appears to be critical to the genotoxicity of $TiO_2$NPs is its crystalline structure; anatase $TiO_2$NPs generally induce DNA strand breaks and chromosomal damage, whereas rutile $TiO_2$NPs are largely nongenotoxic *in vitro* [33]. Only a small number of studies have directly compared the genotoxicity of rutile and anatase $TiO_2$NPs, and have reported that the rutile NPs are larger than the anatase NPs investigated [34]. In one study comparing pure anatase- to anatase- and rutile-containing samples of $TiO_2$NPs, only the samples containing both anatase and rutile $TiO_2$NPs induced significant lactate dehydrogenase (LDH) leakage or mild DNA damage (assessed using an Fpg Comet assay) [35].

An increased level of DNA oxidation lesions detected in Cos-1 and TK6 cells indicates that the leading mechanism by which $TiO_2$NPs trigger genotoxicity is most likely oxidative stress [36]. ROS-mediated oxidative stress, the activation of p53, Bax, caspase-3, and oxidative DNA damage were shown in another study to be involved in the mechanistic pathways of $TiO_2$NP-induced apoptosis in HEK-293 cells [37]. A study in which human amnion epithelial (WISH) cells were exposed to $TiO_2$NPs (10 μg/mL), the cells exhibited significant reduction in the catalase activity and GSH levels (46.3% and 34.6%, respectively; $p < 0.05$). Treated cells showed a 1.87-fold increase in intracellular ROS generation and a 7.3% ($p < 0.01$) increase in G2/M cell cycle arrest. These cells also showed a formation of DNA double-strand breaks with a 14.6-fold ($p < 0.05$) increase in the Olive tail moment value at 20 μg/mL concentration. These results show that such NPs have the potential to induce cytotoxicity and genotoxicity in cultured WISH cells [38]. In another study, $TiO_2$NPs alone did not induce significant DNA and chromosome damage in human embryo L-02 hepatocytes, but a mixture of $TiO_2$NPs and bisphenol A increased toxicity by increasing oxidative stress, DNA double-strand breaks, and micronuclei formation [39]. In one study Chinese hamster ovary cells appeared to adapt to chronic exposure to $TiO_2$NPs and to detoxify excess ROS, possibly through the upregulation of SOD and by reducing particle uptake [40]. In human hepatoma (HepG2) cells, anatase $TiO_2$NPs (<25 nm) caused a persistent increase in DNA strand breaks (Comet assay) and oxidized purines (Fpg-Comet assay), whereas rutile $TiO_2$NPs (>100 nm) did not. Both types of $TiO_2$NPs transiently upregulated the mRNA expression of protein 53 (p53), downregulated DNA damage-responsive genes (MDM2, GADD45a, p21), and provided additional evidence that $TiO_2$NPs are genotoxic [33]. $TiO_2$NPs alone (0.01–1 μg/mL) increased the levels of oxidative stress and oxidative DNA adducts (8-OHdG), but they did not induce DNA breaks or chromosome damage on human embryo L-02 hepatocytes. The addition of trace amounts of $TiO_2$NPs and trace amounts of p,p′-dichlorodiphenyltrichloroethane (p,p′-DDT) synergistically enhanced genotoxicity by increasing oxidative stress, oxidative DNA adducts, DNA breaks, and chromosome damage in L-02 cells. Low concentrations of $TiO_2$NPs and p,p′-DDT increased the oxidative stress by means of ROS formation and lipid oxidation [41]. In human epidermal cells (A431), $TiO_2$NPs elicited a significant ($p < 0.05$) reduction in GSH levels (15.76%) with a concomitant increase in lipid hydroperoxide levels (60.51%; $p < 0.05$) and ROS generation (49.2%; $p < 0.05$) after 6 hours of exposure. It was demonstrated that $TiO_2$NPs have only mild cytotoxic potential, but they induce ROS and oxidative stress leading to oxidative DNA damage and MN formation [42]. $TiO_2$ microparticles ($TiO_2$MPs, 160 nm) induced DNA damage and micronuclei in bone marrow cells, whereas $TiO_2$NPs (33 nm) induced DNA damage in

bone marrow and liver cells. The mitotic index in the forestomach and colon epithelia, the frequency of spermatids with two and more nuclei, and apoptosis in the testis were increased by either $TiO_2$MPs and $TiO_2$NPs, whereas apoptosis in the forestomach was increased only by $TiO_2$NPs [43].

One study revealed that $TiO_2$NPs induce significant ($p < 0.05$) oxidative DNA damage (Fpg-Comet assay) even at 1 μg/mL concentration. A corresponding increase in MN frequency was also observed. This effect could be attributed to the reduced GSH levels and the concomitant increase in lipid peroxidation and ROS generation. This study systematically showed that $TiO_2$NPs induce DNA damage and cause apoptosis in HepG2 cells even at very low concentrations [44].

The chronic toxicity of $TiO_2$NPs was later assessed in nematodes using a modified chronic toxicity assay system. Chronic toxicities of large-sized (60 nm and 90 nm) and small-sized $TiO_2$NPs in the μg/L range were detected, and the latter may have been due to the induction of oxidative stress [45]. In another study, mice that inhaled $TiO_2$NPs (anatase and brookite; 0.8, 7.2, or 28.5 mg/m$^3$) for 5 days showed a dose-dependent deposition of titanium (Ti) in their lung tissue. No increase in DNA damage was observed in lung epithelial cells, and no induction of micronuclei was detected in blood polychromatic erythrocytes. A clear pulmonary neutrophilia was, however, present at a dosage of 28.5 mg/m$^3$ [46].

#### 3.2.2. Zinc oxide nanoparticles

The effects of exposure to zinc oxide NPs (ZnONPs) on cellular morphology, mitochondrial function (MTT assay), and oxidative stress markers (malondialdehyde, GSH, and SOD) were assessed in human hepatocyte and embryonic kidney cells. The results demonstrated that ZnONPs lead to cellular morphological modifications, mitochondrial dysfunction, reduced levels of SOD, depleted GSH, and oxidative DNA damage [47]. In HepG2 cells exposed to 14–20 μg/mL ZnONPs for 12 hours, ROS triggered a decrease in mitochondrial membrane potential and an increase in the ratio of Bax/Bcl-2, leading to a mitochondria-mediated pathway involved in apoptosis [48]. ZnONPs were also found to induce caspase-3 activity, DNA fragmentation, ROS generation, and oxidative stress in these cells. ZnONPs were shown to selectively induce apoptosis in cancer cells, an effect that is likely mediated by ROS in the p53 pathway, through which most of the anticancer drugs trigger apoptosis [49]. Another study showed that core-shell nanostructures exhibited less oxidative stress toward A549 cells than did their corresponding ZnO and $TiO_2$ physical mixtures [50].

Mice exposed to 50 and 300 mg/kg doses of ZnONPs orally for 14 days showed elevated alanine aminotransferase and aspartate aminotransferase serum levels and hepatic accumulation of NPs, with subsequent pathological lesions. ZnONPs also induced oxidative stress in the liver and kidneys of the mice as indicated by an increase in lactoperoxidase [51]. ZnOPs (nanorods) were also found to induce cytotoxicity, ROS generation, oxidative stress, and activities of caspase-3 and caspase-9 in a dose- and time-dependent manner. These nanorods also induced apoptosis in A549 cells through ROS and oxidative stress in the p53, survivin, bax/bcl-2 and caspase pathways [52]. ZnONPs caused the most dramatic changes in Arabidopsis gene expression. These effects were the most toxic, and they upregulated most stress-related genes [53].

#### 3.2.3. Iron oxide nanoparticles

High doses of iron oxide NPs ($Fe_3O_4$NPs) generate an oxidative assault and it could be used as a treatment for cancer through the Fenton reaction, which can both cause and cure cancer [54]. However, doubts exist over the prudence of using $Fe_3O_4$NPs in human beings, as investigations of exposure to these NPs have turned up biomarkers for ROS, GSH, malondialdehyde, DNA-protein crosslinks, and 8-OHdG in hepatic and renal tissues, and injury to tissues and oxidative damage to cells at the molecular level were found [55]. The redox state of iron, a subtle though important physicochemical feature of ultrafine superparamagnetic iron oxide NPs, dramatically modifies the cellular uptake of these NPs and influences their induction of DNA damage [56]. $Fe_3O_4$NPs are phagocytized by monocytes to provoke oxidative stress responses [57]. An investigation reported that $Fe_3O_4$NPs, synthesized selectively, induced autophagy in cancer cells (A549). Although other studies have indicated that further investigation is needed into the safety of using $Fe_3O_4$NPs in humans, such selective destruction of cancerous cells is an encouraging potential of their application [58].

### 3.3. Silica nanoparticles

Exposure to silicon carbide NPs (SiCNPs) has been shown to cause ROS production, GSH depletion, and the inactivation of some antioxidant enzymes (GSH reductase and SOD, but not catalase), and an alkaline Comet assay has revealed that SiCNPs are genotoxic [59]. Silica is one of the metal oxide NPs most rigorously studied for genotoxic responses *in vitro*, but the resulting evidence is conflicting. For example, 34-nm silica NPs (SiNPs) induced positive genotoxic responses in 3T3 mouse fibroblasts [60], but this result was contradicted in a study on A549 lung carcinoma cells. However, it appears that the conflict is because of the choice of genotoxicity test; all studies utilizing the Comet assay demonstrated no significant DNA damage, whereas studies utilizing an MN assay reported a genotoxic response [61].

Increases in intracellular ROS levels, DNA damage, and apoptosis were also observed in HaCaT cells exposed to silicon dioxide NPs ($SiO_2$NPs). The cytotoxicity and DNA damage in these HaCaT cells resulting from exposure to $SiO_2$NPs has been shown to be concentration- and size-dependent, and these effects are closely correlated to increased oxidative stress [62]. There were no detectable changes in nitric oxide generation or 8-OHdG formation in cells treated with amorphous SiNPs or NPs plus lipopolysaccharide (LPS), indicating a low effect on oxidative DNA damage. These results demonstrated that LPS may enhance the oxidative stress (and therefore the cytotoxicity) created by these amorphous SiNPs [63]. When HepG2 cells were treated with different concentrations of SiNPs for 3 hours and 24 hours, the mitochondrion was the major organelle associated with SiNP cytotoxicity [64]. $SiO_2$NP exposure has also caused cell line-dependent, intracellular oxidative stress. This exposure led to the induction of antioxidant defenses in both A549 and MeT-5A cells. A549 cells exhibited high basal antioxidant defense protein expression compared to MeT-5A cells, and it was displayed resilience to oxidant-induced damage caused by $SiO_2$NPs [65]. $SiO_2$NPs and silver-doped $SiO_2$NPs have also been shown to induce an endoplasmic reticulum stress response. These NPs were not necessarily associated with CYP1A induction and induced oxidative stress [66].

### 3.4. Quantum dots

Quantum dots (QDs), as novel bioimaging and drug delivery agents, are generally introduced into the vascular system by injection, and directly exposed to vascular endothelial cells. In flow cytometric and immunofluorescence research, 10 μg/mL CdTe QDs elicited significant oxidative stress [67].

It was shown that after a 12-hour treatment, QDs at 1, 10, and 50 μg/mL levels induced the formation of yH2AX foci, that the indicative of dose-dependent DNA damage. Moreover, QD treatment clearly induced the generation of ROS. With *N*-acetyl-cysteine pretreatment, the ROS scavenger was shown to be capable of inhibiting the induction of ROS and formed the yH2AX foci. These

results indicate that ROS generation may be involved in QD induced DNA damage [68]. In research using lysosomal buffer systems and proliferation-restricted cells, intracellular QDs were found to localize in endosomes, generating ROS, interfering with cell cytoskeletons, and leaching free cadmium ($Cd^{2+}$) ions, resulting in increased toxicity and impeded QD fluorescence [69].

After 2 days of oral administration in mice, a high dose of cobalt doped mercaptoacetic acid (MAA)-QDs was significantly able to induce DNA damage, MN and DNA adduct (8-OHdG) generation. However, these effects were observed with both the undoped MAA-QDs (2,000 mg/kg) and doped MAA-QDs (1,000 and 2,000 mg/kg) after 7 days. This means that high doses of either pure MAA-QDs or cobalt-doped MAA-QDs have the potential to cause indirect *in vivo* genetic damage [70].

### 3.5. Carbon nanoparticles

With both bone marrow and liver from rats, the exposure to carbon nanotubes (CNTs) was shown to induce ROS release, necrosis, chromosomal aberrations, ultrastructural damage, and apoptosis, but did not cause an inflammatory response [71]. With human endothelial cells, multiwall carbon nanotubes (MWCNTs) were capable of causing DNA damage, indicated by the formation of gH2AX foci. It also affected cellular redox status, e.g., by increasing intracellular ROS and malondialdehyde levels, as well as by altering SOD activity and GSH peroxidase levels [72]. Most investigations into the effects of CNTs have highlighted the importance of oxidative stress-mediated DNA damage [73]. Numerous *in vitro* and *in vivo* studies have shown that CNTs and catalytic materials that arise during the production of CNTs may induce oxidative stress, pulmonary inflammation, apoptosis in different types of cells, and cytotoxic effects on the lungs [74].

In a study comparing MWCNTs with hydroxyl modified MWCNTs (MWCNT-OH), a significant LDH release was found only in association with regular MWCNTs, whereas a significant apoptosis induction was found in association with 10 μg/mL MWCNT-OH. A concentration-dependent increase of direct DNA damage, significant at 40 μg/mL MWCNTs and beginning at 5 μg/mL MWCNT-OH, was also detected. Oxidative DNA damage was not observed for either CNT [75]. Although aggregated diamond nanorods (ADNRs), or nanodiamonds, have led to mildly increased expression of DNA repair proteins (p53 and MOGG-1) in embryonic stem cells, their surface chemistry appeared to be important to this effect, as oxidized ADNRs caused more DNA damage than unmodified ADNRs [76]. Single-walled CNTs (SWCNTs) have been shown to have an adverse effect on protoplasts and leaves through oxidative stress, leading to some apoptosis [77]. SWCNT effects in human gingival fibroblasts have never been employed in either genetic toxicology or carcinogenesis research fields. A standard Comet assay is more sensitive than a cytokinesis-block MN test for the genotoxic monitoring of SWCNTs [78]. In the cell line Caco-2, carboxylic acid-functionalized SWCNTs (COOH-SWCNT) have been shown to induce oxidative stress responses; after exposure to >50 μg/mL COOH-SWCNT, lipid peroxidation and ROS increased, and at high concentrations, antioxidant enzyme and GSH levels were altered [79]. Other research has suggested that SWCNTs may induce oxidative stress to the nervous system *in vivo*, causing diseases related to cellular injury in neuronal cells (e.g., neurodegenerative disorders) and demonstrating the necessity of further *in vivo* research [80].

Other studies of the effects of MWCNTs include one that assessed their influences on red spinach. Cell damage was detected 15 days after the exposure to MWCNTs, and again, oxidative stress seems to be the key element responsible for the toxicity [81]. Another study showed that MWCNTs affect lung cancer biomarkers in mouse lungs, offering a potential means of monitoring the health of workers exposed to MWCNTs [82]. Such workers could be exposed to CNTs either accidentally by coming in contact with aerosol forms during production, or as a result of biomedical use.

#### 3.5.1. Fullerenes

A combination of $C_{60}$ and fluoranthene has been shown to increase DNA breaks and GSH levels. In a study on the tissues of marine mussels, however, no formation of DNA adducts was observed after exposure to $C_{60}$ and fluoranthene [83]. In another study, exposure to hydroxylated fullerene NPs reduced both the reproduction rate and the body growth of the nematode *Caenorhabditis elegans*. Adult *C. elegans* experienced apoptosis as a result of this exposure, but this toxicity was not dependent on oxidative stress [84].

The $C_{60}$ derivative DF-1 protected both cell types (human lymphocytes and rat intestinal crypt cells) against radiation-induced DNA damage, as measured by the inhibition of MN formation. DF-1 also reduced the levels of ROS in the crypt cells, which suggested that DF-1 provides powerful protection against several deleterious cellular consequences of irradiation in mammalian systems, including oxidative stress, DNA damage, and cell death [85].

### 3.6. Others

It was found that poly-lactic-co-glycolic acid-polyethylene oxide copolymer NPs were not cytotoxic and did not induce DNA strand breaks or oxidative DNA lesions. These results suggest that aneugenicity and clastogenicity may be considered important biomarkers when assessing the genotoxic potential of polymeric NPs [86]. Using three isolates of recombinant luminescent *Escherichia coli*, copper oxide NPs (CuONPs) were shown to induce the formation of $O_2^-$, $H_2O_2$, and single-stranded DNA at very low levels (0.1 mg Cu/L). The dissolution of CuONPs was a key factor triggering the ROS and DNA damage responses in *E. coli* [87]. CuONPs (15 mg/L) also induced mitochondrial depolarization, possibly mediated by ROS generation. Intracellular CuONPs first generate ROS, which subsequently induces the expression of p38 and p53, ultimately causing DNA damage (Comet assay). Dissolved copper ($Cu^{2+}$) ions contributed less than half of the total toxicity including ROS generation and DNA damage [88]. It was discovered that CuONPs possess a genotoxic potential in A549 cells, which may be mediated through oxidative stress [89]. Exposure to CuONPs in another study increased the production of ROS and RNS [90]. Different toxic mechanisms appeared to be involved in the resulting oxidative stress, depending on the form of copper (Cu) involved. Enzyme activities, except for CAT inhibition observed after CuONP exposure, remained unchanged or increased after exposure. Both CuO and $Cu^{2+}$ also induced lipid peroxidation despite different antioxidant efficiencies [91].

The utility of chitosan NPs with an *in vitro* model of acrolein-mediated cell injury using PC-12 cells was evaluated. The particles significantly reduced damage to membrane integrity, secondary oxidative stress, and lipid peroxidation [92]. In another study, 50 and 100 nm zeolite NPs were tested for A549 cells. Parameters for cytotoxicity, oxidative stress, and genotoxicity were studied, and both sizes of these NPs were found to be noncytotoxic, but could cause cellular damage [93]. Owing to the widespread industrial use of NPs, inhalation is the primary source of exposure to nickel NPs (NiNPs), which have been shown to reduce mitochondrial function and induced LDH leakage and oxidative stress in a dose- and time-dependent manner. Another study showed that NiNPs are significantly toxic in human lung epithelial A549 cells, and this toxicity is likely to be mediated through oxidative stress [94].

The ability of exposure to cerium dioxide NPs ($CeO_2$NPs) via inhalation to cause lung toxicity has been evaluated, and the results show that acute exposure via inhalation caused cytotoxicity via oxidative stress, which in turn led to chronic inflammation [95]. The neuroprotective effects of $CeO_2$NPs were investigated as well, and were found to be caused by a modest reduction in ROS. These findings suggest that the scavenging of peroxynitrite may be an important mechanism by which $CeO_2$NPs mitigate ischemic brain injury. Therefore, $CeO_2$NPs may be useful for therapeutic interventions to reduce oxidative and nitrosative damage after a stroke [96]. Research also demonstrated that $CeO_2$NPs can act as antioxidants to protect cells against oxidative damage [97].

In other research, type-II alveolar epithelial cells were exposed to manganese (III) oxide NPs ($Mn_3O_4$NPs) and manganese (Mn) salt. $Mn_3O_4$NPs led to intracellular oxidative stress, but Mn salt did not. Intracellular manganese contents were higher upon exposure to $Mn_3O_4$NPs [98].

In summary, the major findings related to DNA damage due to exposure to NPs and the tools used to assess these damages, are shown in Table 1.

### 3.7. Uptake and acting mechanisms of NPs

Inconsistencies in the cellular mechanisms involved in NP uptake and action are found in the literature, making it difficult to draw conclusions of these toxicological findings. One possible toxicity mechanism that has been proposed involves the disruption of the mitochondrial respiratory chain (demonstrated with AgNPs), which leads to the production of ROS and the interruption of adenosine triphosphate synthesis, which in turn causes DNA damage. The role of Nrf2 signaling in AgNP toxicity is increased by Nrf2 blockade, and Nrf2-dependent HO-1 induction protects cells from AgNP toxicity. PI3K and p38MAPK cascades are involved in Nrf2/HO-1 induction [99]. In human blood monocytes, both 5 nm and 28-nm AgNPs in one study induced inflammasome formation and subsequent caspase-1 activation. The exposure to AgNPs caused a leakage of cathepsins from lysosomes and an efflux of intracellular potassium ions ($K^+$). These two events induced $O_2^-$ production within mitochondrial membranes, leading to inflammasome formation. The 5-nm AgNPs produced more $H_2O_2$ and were more cytotoxic than the 28-nm AgNPs, suggesting that the balance between $O_2^-$ and $H_2O_2$ governs cell fate, death, and activation [100].

When more detailed transcriptional information on the toxic mechanism of AgNP and $TiO_2$NPs was identified, a better understanding of the mode of action of metal and metal oxide NPs began to develop. Both NPs were found to cause oxidative stress, cell membrane and transportation damage, and genotoxicity, and DNA damage. Although $TiO_2$NPs induced the DNA repair via the SOS response, AgNPs seemed to induce DNA repair via a pathway [101]. $TiO_2$NPs elicited a significant ($p < 0.05$) reduction in GSH (15.76%) with a concomitant increase in lipid hydroperoxide (60.51%; $p < 0.05$) and ROS generation (49.2%; $p < 0.05$) after 6 hours of exposure, leading to the conclusion that the resulting oxidative DNA damage and MN formation are probable mechanisms for $TiO_2$NP genotoxicity [42]. Since the effect of $TiO_2$NPs on hippocampal apoptosis or its molecular mechanism is not known, this was investigated for 60 days. $TiO_2$NPs in another study significantly

**Table 1**
Findings related to DNA damage from nanoparticle exposure

| NPs | | | *In vitro/in vivo* | Assays | Findings | Reference |
|---|---|---|---|---|---|---|
| Carbon-based naomaterials | $C_{60}$ | $C_{60}$ | *In vitro* and *in vivo* | ROS | $C_{60}$ has the capacity to generate singlet oxygen that induces lipid peroxidation of linoleate which leads to oxidative DNA damage. | [115] |
| | | Aqu/n$C_{60}$ and EthOH/n$C_{60}$ | *In vivo* (PBL) | Comet assay | Aqu/n$C_{60}$ suspensions elicited higher genotoxic response than EthOH/n$C_{60}$ at the same dose. | [116] |
| | | $C_{60}$ | *In vitro* FE1-Mutatrade mark-Mouse lung epithelial cells | Comet assay | Non-cytotoxic concentrations did not result in increased levels of strand breaks. | [117] |
| | CNTs | SWCNTs | *In vitro* FE1-Mutatrade mark-Mouse lung epithelial cells | Comet assay | Concentrations below cytotoxicity did not result in increased levels of strand breaks. | [117] |
| | | | *In vitro* lung fibroblast V79 cells | Comet assay | Some significance was detected. | [117] |
| | | MWCNTs | *In vitro* mouse embryonic stem cells | Double strand break repair protein assay | Cellular apoptosis and activation of p53, and increased mutation frequency. | [118] |
| | Other | Nanodiamonds | *In vitro* embryonic stem cells | Expression of DNA repair proteins | Oxidized nanodiamonds induced more DNA damage than the pristine/raw forms, showing the surface chemistry specific genotoxicity. | [119] |
| Metallic nanoparticles | Au NPs | Au NP | *In vitro* human fetal lung fibroblast cell line (MRC-5) | HPLC to measure 8-OHdG | Significant oxidative DNA damage; DNA repair genes downregulated (cyclin C, Hus1, BRCAI/BRCC1). | [119] |
| Metal oxides | $TiO_2$ | 10x40 nm <25 nm <5 μm | *In vitro* human bronchial epithelial BEAS 2B cells | Comet assay | Uncoated nanosized anatase $TiO_2$ and fine rutile $TiO_2$ are more efficient than $SiO_2$-coated nanosized rutile $TiO_2$ in inducing DNA damage. | [33] |
| | | <25 nm | *In vivo* PBL | Comet assay | Dose-dependent increase in ROS generation. | [120] |
| | Zinc oxide | 40–70 nm | *In vitro* and *in vivo* PBL human sperm cells | Comet assay | Dose-dependent increase in DNA damage. | [47] |
| | $SiO_2$ | 6.57, 8.2 and 196.52 nm | *In vitro* human lymphoblastoid cells | Comet assay | No increase in comet tail detected. | [121] |

Note. From "Genotoxicity and cancer" by Fadeel B, Pietroiusti A, Shvedova AA (eds), Genotoxicity and cancer. 1st ed. Adverse effects of engineered nanomaterials: exposure, toxicology, and impact on human health. San Diego: Academic Press; 2012. p. 248–52. Copyright 2012, Adapted with permission.
8-OHdG, 8-hydroxy-2′-deoxyguanosine; AuNPs, gold nanoparticles; C60, buckminsterfullerene; CNTs, carbon nanotubes; HPLC, High-performance liquid chromatography; MWCNTs, multiwall CNTs; NPs, nanoparticles; PBL, peripheral blood lymphocytes; ROS, reactive oxygen species; SWCNTs, single-walled CNTs.

activated caspase-3 and -9, inhibited Bcl-2, and increased levels of Bax and cytochrome c. $TiO_2$NPs also induced an accumulation of ROS in the hippocampi of mice, suggesting that $TiO_2$NP-induced apoptosis in the hippocampi of mice may result from an intrinsic pathway [102].

Further studies indicated that the effects of $SiO_2$NPs are not mediated by oxidative stress but by interference with the MAPK/ERK1/2 and the Nrf2/ARE signaling pathways. Investigations into DNA integrity upon exposure to $SiO_2$NPs revealed no substantial oxidative DNA damage [103]. SiNPs were also modulated apoptosis markers at both mRNA and protein levels [104]. Although the inhalation of NPs has been shown to cause pulmonary damage, $SiO_2$NPs can also be deposited in target organs where they exert potentially toxic effects. An analysis of oxidative stress based on the tests of ROS production (using dihydroethidium) or lipid peroxidation (using malondialdehyde) clearly demonstrated the involvement of oxidative stress in the toxicity of 20 nm $SiO_2$NPs [105].

NPs with a more reactive surface may generate inflammation more readily. There is some evidence *in vitro* that NPs can gain access to the nucleus and genetic material if specifically designed to do so by surface modification. Such NPs can cause genetic aberrations by a primary mechanism in addition to the inflammation mediated mechanism [106]. In addition, the activities of caspase-3 and caspase-9 enzymes were also significantly higher in cells exposed to NPs. It was shown that NPs induced apoptosis in A549 cells through ROS generation and oxidative stress via p53, survivin, bax/bcl-2, and caspase pathways [107].

Thus, they have the potential to induce oxidative DNA damage not only through corrosion, leading to the release of metal ions, but also as a result of chronic inflammatory responses. This damage can invoke various cellular responses such as cell cycle arrest, apoptosis, and importantly, DNA repair. If, however, repair fails to occur during or before the replication of the damaged DNA, mutagenic and therefore carcinogenic consequences may result. Long-term exposure to inhaled NPs can induce oxidative stress and inflammation, not only in the lung but also in the cardiovascular system [108].

## 4. Discussion

### 4.1. Oxidative stress from NPs

The generation of ROS and oxidative injury is thought to play a significant role in many of the observed biological responses to NPs. The size, surface area, and surface chemistry (e.g., reactive groups) of particular NPs are thought to play a role in the generation of ROS. In addition to their damaging effects on cellular proteins, lipids, and DNA, an increased level of ROS triggers the cell to respond by inducing proinflammatory signaling cascades, ultimately inducing apoptosis. Additionally, NPs may induce or aggravate inflammatory and allergic responses by directly influencing immune-related cell populations in the lung [109]. After lung exposure, NPs recruit neutrophilic granulocytes to the lung, and some end up in lung macrophages [110]. Persistent oxidative stress and inflammation in lungs and brain tissue after exposure to NPs are thought to be the underlying cause for lung fibrosis and neurodegenerative diseases, respectively [111]. The ability of NPs to generate oxidative stress has formed the basis of their hypothetical structure—toxicity relationship. Redox-sensitive transcription factors, such as NF-kB, are important to the inflammatory effects that follow particle deposition. When these transcription factors are activated, they lead to the transcription of proinflammatory genes, which in turn leads to the production of cytokines, chemokines, and adhesion molecules. Although for NPs, this structure—toxicity relationship has some support, other studies have failed to show a clear relationship between the intrinsic free radical-generating activity of NPs and their ability to cause inflammation in the lungs [112].

### 4.2. Application of NPs to workers' health

Occupational exposure limits are critical for protection against airborne exposure to chemicals in the workplace. At present, however, there is an inadequate level of awareness and scientific understanding of their toxicity to create a knowledgeable system of limiting occupational exposure to NPs. Better understanding of the potential biological effects of NPs will be required in order to implement appropriate preventive measures in the workplace. A vital area governing regulatory risk assessment (RA) is genotoxicology as DNA damage can initiate and promote carcinogenesis. Recently, considerable attention has been given to the toxicity of NPs, but the importance of their genotoxic potential on workers' health has been largely overlooked.

In this review, we summarized recent data on the hazards of NPs, with particular emphasis on the toxic effects demonstrated by *in vitro* and *in vivo* studies. In the literature, there is increasing evidence to suggest that NPs are potentially hazardous to humans and that strict industrial hygiene measures should be taken to limit exposure during their manipulation. New approaches are urgently needed to evaluate potential hazards posed by NP exposure. At present, gene expression profiling provides information on the potential modes of action of NPs and their human relevance, and tools have recently become available for pathway-based quantitative RA. Recent work has identified ways that these methods may be used to promote workers' health and safety, which was an important step toward ultimately recognizing significant biomarkers to gauge health risks in the workplace. As our knowledge of molecular pathways and dose-response characteristics and their relevance to occupational disease continues to grow, it is anticipated that biomarkers will become increasingly useful in assessing chemical toxicities and in human health RA [113]. With significant advancements in genetics, proteomics, cellular and molecular biology, and biochemical engineering, separate safe exposure limits for microparticles and NPs may be set [114].

Despite the great promise that NPs show, especially for future industrial and biomedical applications, few studies have examined the human body's reaction to NP exposure. Likewise, few studies have explored the possible reactions that uncontrolled uptake of NPs could have on workers' health. As NPs are a diverse group of molecules and have different properties and effects, even sometimes in the same materials and standard sizes, this task will be complex. Overall, industrial hygiene controls worker exposure by comparing pollutant concentrations in the breathing zone of the worker with a limited value (TLV). To perform this type of evaluation is necessary to define an index of exposure adequately, and the measure of this index is representative of what the worker is breathing. Awareness of the levels of particles which can cause health effects is necessary.

### 4.3. Conclusions

The main factors that determine the toxicological effects of NPs in the body are the characteristics of the exposure (e.g., penetration route, duration, and concentration) and of the exposed organism (e.g., individual susceptibility, activity at time of exposure, and the particular route the NPs follow in the body), and the intrinsic toxicity of NPs.

Although much more research is urgently needed to investigate the risks of NP exposure in the workplace, some studies have already found elevated levels of lung cancer among workers

exposed to certain NPs, such as particles emitted by diesel engines or welding fumes. Moreover, epidemiological studies have begun to show a relationship, in the general population, between particulate air pollution and increased morbidity and mortality due to respiratory and cardiovascular diseases.

This review briefly describes NPs, their application, the major routes of human exposure, and some examples of their uptake and adverse effects. Although little has been reported on occupational exposure assessment and approaches to minimizing exposure and health hazards associated with NPs, there are a few measures currently in use, including and personal protective equipment and engineering controls such as fume hoods. Given the present lack of relevant information, current recommendations to minimize exposure and hazards are largely based on common sense, analogy to ultrafine material toxicity, and general health and safety recommendations for establishing and maintaining a safe working environment.

## Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

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## References

[1] Li JJ, Muralikrishnan S, Ng CT, Yung LY, Bay BH. Nanoparticle-induced pulmonary toxicity. Exp Biol Med (Maywood) 2010;235:1025–33.
[2] Arora S, Rajwade JM, Paknikar KM. Nanotoxicology and in vitro studies: the need of the hour. Toxicol Appl Pharmacol 2012;258:151–65.
[3] Lee JC, Son YO, Pratheeshkumar P, Shi X. Oxidative stress and metal carcinogenesis. Free Radic Biol Med 2012;53:742–57.
[4] Kuhlbusch TA, Asbach C, Fissan H, Göhler D, Stintz M. Nanoparticle exposure at nanotechnology workplaces: a review. Part Fibre Toxicol 2011;8:22.
[5] Liu W, Chaurand P, Di Giorgio C, De Méo M, Thill A, Auffan M, Masion A, Borschneck D, Chaspoul F, Gallice P, Botta A, Bottero JY, Rose J. Influence of the length of imogolite-like nanotubes on their cytotoxicity and genotoxicity toward human dermal cells. Chem Res Toxicol 2012;25:2513–22.
[6] Eustaquio T, Leary JF. Single-cell nanotoxicity assays of superparamagnetic iron oxide nanoparticles. Methods Mol Biol 2012;926:69–85.
[7] Møller P, Jacobsen NR, Folkmann JK, Danielsen PH, Mikkelsen L, Hemmingsen JG, Vesterdal LK, Forchhammer L, Wallin H, Loft S. Role of oxidative damage in toxicity of particulates. Free Radic Res 2010;44:1–46.
[8] Wang L, Liu Y, Li W, Jiang X, Ji Y, Wu X, Xu L, Qiu Y, Zhao K, Wei T, Li Y, Zhao Y, Chen C. Selective targeting of gold nanorods at the mitochondria of cancer cells: implications for cancer therapy. Nano Lett 2011;11:772–80.
[9] He W, Zhou YT, Wamer WG, Hu X, Wu X, Zheng Z, Boudreau MD, Yin JJ. Intrinsic catalytic activity of Au nanoparticles with respect to hydrogen peroxide decomposition and superoxide scavenging. Biomaterials 2013;34:765–73.
[10] Di Guglielmo C, De Lapuente J, Porredon C, Ramos-López D, Sendra J, Borràs M. In vitro safety toxicology data for evaluation of gold nanoparticles chronic cytotoxicity, genotoxicity and uptake. J Nanosci Nanotechnol 2012;12:6185–91.
[11] Gao W, Xu K, Ji L, Tang B. Effect of gold nanoparticles on glutathione depletion-induced hydrogen peroxide generation and apoptosis in HL7702 cells. Toxicol Lett 2011;205:86–95.
[12] Butterworth KT, Coulter JA, Jain S, Forker J, McMahon SJ, Schettino G, Prise KM, Currell FJ, Hirst DG. Evaluation of cytotoxicity and radiation enhancement using 1.9 nm gold particles: potential application for cancer therapy. Nanotechnology 2010;21:295101.
[13] Siddiqi NJ, Abdelhalim MA, El-Ansary AK, Alhomida AS, Ong WY. Identification of potential biomarkers of gold nanoparticle toxicity in rat brains. J Neuroinflammation 2012;12:123.
[14] Li JJ, Lo SL, Ng CT, Gurung RL, Hartono D, Hande MP, Ong CN, Bay BH, Yung LY. Genomic instability of gold nanoparticle treated human lung fibroblast cells. Biomaterials 2011;23:5515–23.
[15] Schulz M, Ma-Hock L, Brill S, Strauss V, Treumann S, Gröters S, van Ravenzwaay B, Landsiedel R. Investigation on the genotoxicity of different sizes of gold nanoparticles administered to the lungs of rats. Mutat Res 2012;745:51–7.
[16] Hwang JH, Kim SJ, Kim YH, Noh JR, Gang GT, Chung BH, Song NW, Lee CH. Susceptibility to gold nanoparticle-induced hepatotoxicity is enhanced in a mouse model of nonalcoholic steatohepatitis. Toxicology 2012;294:27–35.
[17] Geffroy B, Ladhar C, Cambier S, Treguer-Delapierre M, Brèthes D, Bourdineaud JP. Impact of dietary gold nanoparticles in zebrafish at very low contamination pressure: the role of size, concentration and exposure time. Nanotoxicology 2012;6:144–60.
[18] Panda KK, Achary VM, Krishnaveni R, Padhi BK, Sarangi SN, Sahu SN, Panda BB. In vitro biosynthesis and genotoxicity bioassay of silver nanoparticles using plants. Toxicol In Vitro 2011;25:1097–105.
[19] Song XL, Li B, Xu K, Liu J, Ju W, Wang J, Liu XD, Li J, Qi YF. Cytotoxicity of water-soluble mPEG-SH-coated silver nanoparticles in HL-7702 cells. Cell Biol Toxicol 2012;28:225–37.
[20] Piao MJ, Kang KA, Lee IK, Kim HS, Kim S, Choi JY, Choi J, Hyun JW. Silver nanoparticles induce oxidative cell damage in human liver cells through inhibition of reduced glutathione and induction of mitochondria-involved apoptosis. Toxicol Lett 2011;201:92–100.
[21] Teodoro JS, Simões AM, Duarte FV, Rolo AP, Murdoch RC, Hussain SM, Palmeira CM. Assessment of the toxicity of silver nanoparticles in vitro: A mitochondrial perspective. Toxicol In Vitro 2011;25:664–70.
[22] Park MV, Neigh AM, Vermeulen JP, de la Fonteyne LJ, Verharen HW, Briedé JJ, van Loveren H, de Jong WH. The effect of particle size on the cytotoxicity, inflammation, developmental toxicity and genotoxicity of silver nanoparticles. Biomaterials 2011;32:9810–7.
[23] Li L, Sun J, Li X, Zhang Y, Wang Z, Wang C, Dai J, Wang Q. Controllable synthesis of monodispersed silver nanoparticles as standards for quantitative assessment of their cytotoxicity. Biomaterials 2012;33:1714–21.
[24] Singh RP, Ramarao P. Cellular uptake, intracellular trafficking and cytotoxicity of silver nanoparticles. Toxicol Lett 2012;213:249–59.
[25] Chen Y, Chen H, Zheng X, Mu H. The impacts of silver nanoparticles and silver ions on wastewater biological phosphorous removal and the mechanisms. J Hazard Mater 2012;239–240:88–94.
[26] Ghosh M, Manivannan J, Sinha S, Chakraborty A, Mallick SK, Bandyopadhyay M, Mukherjee A. In vitro and in vivo genotoxicity of silver nanoparticles. Mutat Res 2012;749:60–9.
[27] Gromadzka-Ostrowska J, Dziendzikowska K, Lankoff A, Dobrzyñska M, Instanes C, Brunborg G, Gajowik A, Radzikowska J, Wojewódzka M, Kruszewski M. Silver nanoparticles effects on epididymal sperm in rats. Toxicol Lett 2012;214:251–8.
[28] Pham CH, Yi J, Gu MB. Biomarker gene response in male medaka (*Oryzias latipes*) chronically exposed to silver nanoparticle. Ecotoxicol Environ Saf 2012;78:239–45.
[29] Gagné F, André C, Skirrow R, Gélinas M, Auclair J, van Aggelen G, Turcotte P, Gagnon C. Toxicity of silver nanoparticles to rainbow trout: A toxicogenomic approach. Chemosphere 2012;89:615–22.
[30] Liu Y, Guan W, Ren G, Yang Z. The possible mechanism of silver nanoparticle impact on hippocampal synaptic plasticity and spatial cognition in rats. Toxicol Lett 2012;209:227–31.
[31] Mei N, Zhang Y, Chen Y, Guo X, Ding W, Ali SF, Biris AS, Rice P, Moore MM, Chen T. Silver nanoparticle-induced mutations and oxidative stress in mouse lymphoma cells. Environ Mol Mutagen 2012;53:409–19.
[32] Kim JS, Sung JH, Ji JH, Song KS, Lee JH, Kang CS, Yu IJ. In vivo genotoxicity of silver nanoparticles after 90-day silver nanoparticle inhalation exposure. Saf Health Work 2011;2:34–8.
[33] Petković J, Zegura B, Stevanović M, Drnovšek N, Uskoković D, Novak S, Filipić M. DNA damage and alterations in expression of DNA damage responsive genes induced by $TiO_2$ nanoparticles in human hepatoma HepG2 cells. Nanotoxicology 2011;5:341–53.
[34] Xu J, Sagawa Y, Futakuchi M, Fukamachi K, Alexander DB, Furukawa F, Ikarashi Y, Uchino T, Nishimura T, Morita A, Suzui M, Tsuda H. Lack of promoting effect of titanium dioxide particles on ultraviolet B-initiated skin carcinogenesis in rats. Food Chem Toxicol 2011;49:1298–302.
[35] Gerloff K, Fenoglio I, Carella E, Kolling J, Albrecht C, Boots AW, Förster I, Schins RP. Distinctive toxicity of $TiO_2$ rutile/anatase mixed phase nanoparticles on Caco-2 cells. Chem Res Toxicol 2012;25:646–55.
[36] Magdolenova Z, Bilanièová D, Pojana G, Fjellsbø LM, Hudecova A, Hasplova K, Marcomini A, Dusinska M. Impact of agglomeration and different dispersions of titanium dioxide nanoparticles on the human related in vitro cytotoxicity and genotoxicity. J Environ Monitor 2012;14:455–64.
[37] Meena R, Rani M, Pal R, Rajamani P. Nano-$TiO_2$-induced apoptosis by oxidative stress-mediated DNA damage and activation of p53 in human embryonic kidney cells. Appl Biochem Biotechnol 2012;167:791–808.
[38] Saquib Q, Al-Khedhairy AA, Siddiqui MA, Abou-Tarboush FM, Azam A, Musarrat J. Titanium dioxide nanoparticles induced cytotoxicity, oxidative stress and DNA damage in human amnion epithelial (WISH) cells. Toxicol In Vitro 2012;26:351–61.
[39] Zheng D, Wang N, Wang X, Tang Y, Zhu L, Huang Z, Tang H, Shi Y, Wu Y, Zhang M, Lu B. Effects of the interaction of TiO2 nanoparticles with bisphenol A on their physicochemical properties and in vitro toxicity. J Hazard Mater 2012;199–200:426–32.
[40] Wang S, Hunter LA, Arslan Z, Wilkerson MG, Wickliffe JK. Chronic exposure to nanosized, anatase titanium dioxide is not cyto- or genotoxic to Chinese hamster ovary cells. Environ Mol Mutagen 2011;52:614–22.

[41] Shi Y, Zhang JH, Jiang M, Zhu LH, Tan HQ, Lu B. Synergistic genotoxicity caused by low concentration of titanium dioxide nanoparticles and p, p′-DDT in human hepatocytes. Environ Mol Mutagen 2010;51:192–204.
[42] Shukla RK, Sharma V, Pandey AK, Singh S, Sultana S, Dhawan A. ROS mediated genotoxicity induced by titanium dioxide nanoparticles in human epidermal cells. Toxicol In Vitro 2011;25:231–41.
[43] Sycheva LP, Zhurkov VS, Iurchenko VV, Daugel-Dauge NO, Kovalenko MA, Krivtsova EK, Durnev AD. Investigation of genotoxic and cytotoxic effects of micro- and nanosized titanium dioxide in six organs of mice in vivo. Mutat Res 2011;726:8–14.
[44] Shukla RK, Kumar A, Gurbani D, Pandey AK, Singh S, Dhawan A. $TiO_2$ nanoparticles induce oxidative DNA damage and apoptosis in human liver cells. Nanotoxicology 2013;7:48–60.
[45] Wu Q, Wang W, Li Y, Li Y, Ye B, Tang M, Wang D. Small sizes of $TiO_2$-NPs exhibit adverse effects at predicted environmental relevant concentrations on nematodes in a modified chronic toxicity assay system. J Hazard Mater 2012;243:161–8.
[46] Lindberg HK, Falck GC, Catalán J, Koivisto AJ, Suhonen S, Järventaus H, Rossi EM, Nykäsenoja H, Peltonen Y, Moreno C, Alenius H, Tuomi T, Savolainen KM, Norppa H. Genotoxicity of inhaled nanosized $TiO_2$ in mice. Mutat Res 2012;745:58–64.
[47] Guan R, Kang T, Lu F, Zhang Z, Shen H, Liu M. Cytotoxicity, oxidative stress, and genotoxicity in human hepatocyte and embryonic kidney cells exposed to ZnO nanoparticles. Nanoscale Res Lett 2012;7:602.
[48] Sharma V, Anderson D, Dhawan A. Zinc oxide nanoparticles induce oxidative DNA damage and ROS-triggered mitochondria mediated apoptosis in human liver cells (HepG2). Apoptosis 2012;17:852–70.
[49] Akhtar MJ, Ahamed M, Kumar S, Khan MM, Ahmad J, Alrokayan SA. Zinc oxide nanoparticles selectively induce apoptosis in human cancer cells through reactive oxygen species. Int J Nanomedicine 2012;7:845–57.
[50] Hsiao IL, Huang YJ. Titanium oxide shell coatings decrease the cytotoxicity of ZnO nanoparticles. Chem Res Toxicol 2011;24:303–13.
[51] Sharma V, Singh P, Pandey AK, Dhawan A. Induction of oxidative stress, DNA damage and apoptosis in mouse liver after sub-acute oral exposure to zinc oxide nanoparticles. Mutat Res 2012;745:84–91.
[52] Ahamed M, Akhtar MJ, Raja M, Ahmad I, Siddiqui MK, AlSalhi MS, Alrokayan SA. ZnO nanorod-induced apoptosis in human alveolar adenocarcinoma cells via p53, survivin and bax/bcl-2 pathways: role of oxidative stress. Nanomedicine 2011;7:904–13.
[53] Landa P, Vankova R, Andrlova J, Hodek J, Marsik P, Storchova H, White JC, Vanek T. Nanoparticle-specific changes in Arabidopsis thaliana gene expression after exposure to ZnO, TiO2, and fullerene soot. J Hazard Mater 2012;241–2:55–62.
[54] Foy SP, Labhasetwar V. Oh the irony: iron as a cancer cause or cure? Biomaterials 2011;32:9155–8.
[55] Ma P, Luo Q, Chen J, Gan Y, Du J, Ding S, Xi Z, Yang X. Intraperitoneal injection of magnetic $Fe_3O_4$-nanoparticle induces hepatic and renal tissue injury via oxidative stress in mice. Int J Nanomedicine 2012;7:4809–18.
[56] Singh N, Jenkins GJ, Nelson BC, Marquis BJ, Maffeis TG, Brown AP, Williams PM, Wright CJ, Doak SH. The role of iron redox state in the genotoxicity of ultrafine superparamagnetic iron oxide nanoparticles. Biomaterials 2012;33:163–70.
[57] Zhu MT, Wang B, Wang Y, Yuan L, Wang HJ, Wang M, Ouyang H, Chai ZF, Feng WY, Zhao YL. Endothelial dysfunction and inflammation induced by iron oxide nanoparticle exposure: risk factors for early atherosclerosis. Toxicol Lett 2011;203:162–71.
[58] Khan MI, Mohammad A, Patil G, Naqvi SA, Chauhan LK, Ahmad I. Induction of ROS, mitochondrial damage and autophagy in lung epithelial cancer cells by iron oxide nanoparticles. Biomaterials 2012;33:1477–88.
[59] Barillet S, Jugan ML, Laye M, Leconte Y, Herlin-Boime N, Reynaud C, Carrière M. In vitro evaluation of SiC nanoparticles impact on A549 pulmonary cells: cyto-, genotoxicity and oxidative stress. Toxicol Lett 2010;198:324–30.
[60] Park MV, Verharen HW, Zwart E, Hernandez LG, van Benthem J, Elsaesser A, Barnes C, McKerr G, Howard CV, Salvati A, Lynch I, Dawson KA, de Jong WH. Genotoxicity evaluation of amorphous silica nanoparticles of different sizes using the micronucleus and the plasmid lacZ gene mutation assay. Nanotoxicology 2011;5:168–81.
[61] Gonzalez L, Thomassen LC, Plas G, Rabolli V, Napierska D, Decordier I, Roelants M, Hoet PH, Kirschhock CE, Martens JA, Lison D, Kirsch-Volders M. Exploring the aneugenic and clastogenic potential in the nanosize range: A549 human lung carcinoma cells and amorphous monodisperse silica nanoparticles as models. Nanotoxicology 2010;4:382–95.
[62] Gong C, Tao G, Yang L, Liu J, He H, Zhuang Z. The role of reactive oxygen species in silicon dioxide nanoparticle-induced cytotoxicity and DNA damage in HaCaT cells. Mol Biol Rep 2012;39:4915–25.
[63] Shi Y, Yadav S, Wang F, Wang H. Endotoxin promotes adverse effects of amorphous silica nanoparticles on lung epithelial cells in vitro. J Toxicol Environ Health A 2010;73:748–56.
[64] Sun L, Li Y, Liu X, Jin M, Zhang L, Du Z, Guo C, Huang P, Sun Z. Cytotoxicity and mitochondrial damage caused by silica nanoparticles. Toxicol In Vitro 2011;25:1619–29.
[65] Berg JM, Romoser AA, Figueroa DE, Spencer West C, Sayes CM. Comparative cytological responses of lung epithelial and pleural mesothelial cells following in vitro exposure to nanoscale SiO2. Toxicol In Vitro 2013;27:24–33.
[66] Christen V, Fent K. Silica nanoparticles and silver-doped silica nanoparticles induce endoplasmatic reticulum stress response and alter cytochrome P4501A activity. Chemosphere 2012;87:423–34.
[67] Yan M, Zhang Y, Xu K, Fu T, Qin H, Zheng X. An in vitro study of vascular endothelial toxicity of CdTe quantum dots. Toxicology 2011;282:94–103.
[68] Wang L, Zhang J, Zheng Y, Yang J, Zhang Q, Zhu X. Bioeffects of CdTe quantum dots on human umbilical vein endothelial cells. J Nanosci Nanotechnol 2010;10:8591–6.
[69] Soenen SJ, Demeester J, De Smedt SC, Braeckmans K. The cytotoxic effects of polymer-coated quantum dots and restrictions for live cell applications. Biomaterials 2012;33:4882–8.
[70] Khalil WK, Girgis E, Emam AN, Mohamed MB, Rao KV. Genotoxicity evaluation of nanomaterials: DNA damage, micronuclei, and 8-hydroxy-2-deoxyguanosine induced by magnetic doped CdSe quantum dots in male mice. Chem Res Toxicol 2011;24:640–65.
[71] Di Giorgio ML, Di Bucchianico S, Ragnelli AM, Aimola P, Santucci S, Poma A. Effects of single and multi walled carbon nanotubes on macrophages: cyto and genotoxicity and electron microscopy. Mutat Res 2011;722:20–31.
[72] Guo YY, Zhang J, Zheng YF, Yang J, Zhu XQ. Cytotoxic and genotoxic effects of multi-wall carbon nanotubes on human umbilical vein endothelial cells in vitro. Mutat Res 2011;721:184–91.
[73] Ahn KH, Kim SM, Yu IJ. Multi-walled carbon nanotube (MWCNT) dispersion and aerosolization with hot water atomization without addition of any surfactant. Saf Health Work 2011;2:65–9.
[74] Kayat J, Gajbhiye V, Tekade RK, Jain NK. Pulmonary toxicity of carbon nanotubes: a systematic report. Nanomedicine 2011;7:40–9.
[75] Ursini CL, Cavallo D, Fresegna AM, Ciervo A, Maiello R, Buresti G, Casciardi S, Tombolini F, Bellucci S, Iavicoli S. Comparative cyto-genotoxicity assessment of functionalized and pristine multiwalled carbon nanotubes on human lung epithelial cells. Toxicol In Vitro 2012;26:831–40.
[76] Xing Y, Xiong W, Zhu L, Osawa E, Hussin S, Dai L. DNA damage in embryonic stem cells caused by nanodiamonds. ACS Nano 2011;5:2376–84.
[77] Shen CX, Zhang QF, Li J, Bi FC, Yao N. Induction of programmed cell death in Arabidopsis and rice by single-wall carbon nanotubes. Am J Bot 2010;97:1602–9.
[78] Cicchetti R, Divizia M, Valentini F, Argentin G. Effects of single-wall carbon nanotubes in human cells of the oral cavity: geno-cytotoxic risk. Toxicol In Vitro 2011;25:1811–9.
[79] Pichardo S, Gutiérrez-Praena D, Puerto M, Sánchez E, Grilo A, Cameán AM, Jos A. Oxidative stress responses to carboxylic acid functionalized single wall carbon nanotubes on the human intestinal cell line Caco-2. Toxicol In Vitro 2012;26:672–7.
[80] Wang J, Sun P, Bao Y, Liu J, An L. Cytotoxicity of single-walled carbon nanotubes on PC12 cells. Toxicol In Vitro 2011;25:242–50.
[81] Begum P, Fugetsu B. Phytotoxicity of multi-walled carbon nanotubes on red spinach (*Amaranthus tricolor* L) and the role of ascorbic acid as an antioxidant. J Hazard Mater 2012;243:212–22.
[82] Pacurari M, Qian Y, Porter DW, Wolfarth M, Wan Y, Luo D, Ding M, Castranova V, Guo NL. Multi-walled carbon nanotube-induced gene expression in the mouse lung: association with lung pathology. Toxicol Appl Pharmacol 2011;255:18–31.
[83] Al-Subiai SN, Arlt VM, Frickers PE, Readman JW, Stolpe B, Lead JR, Moody AJ, Jha AN. Merging nano-genotoxicology with eco-genotoxicology: an integrated approach to determine interactive genotoxic and sub-lethal toxic effects of C(60) fullerenes and fluoranthene in marine mussels, *Mytilus* sp. Mutat Res 2012;745:92–103.
[84] Cha YJ, Lee J, Choi SS. Apoptosis-mediated in vivo toxicity of hydroxylated fullerene nanoparticles in soil nematode *Caenorhabditis elegans*. Chemosphere 2012;87:49–54.
[85] Theriot CA, Casey RC, Moore VC, Mitchell L, Reynolds JO, Burgoyne M, Partha R, Huff JL, Conyers JL, Jeevarajan A, Wu H. Dendro[C(60)]fullerene DF-1 provides radioprotection to radiosensitive mammalian cells. Radiat Environ Biophys 2010;49:437–45.
[86] Kazimirova A, Magdolenova Z, Barancokova M, Staruchova M, Volkovova K, Dusinska M. Genotoxicity testing of PLGA-PEO nanoparticles in TK6 cells by the comet assay and the cytokinesis-block micronucleus assay. Mutat Res 2012;748:42–7.
[87] Bondarenko O, Ivask A, Käkinen A, Kahru A. Sub-toxic effects of CuO nanoparticles on bacteria: kinetics, role of Cu ions and possible mechanisms of action. Environ Pollut 2012;169:81–9.
[88] Wang Z, Li N, Zhao J, White JC, Qu P, Xing B. CuO nanoparticle interaction with human epithelial cells: cellular uptake, location, export, and genotoxicity. Chem Res Toxicol 2012;25:1512–21.
[89] Ahamed M, Siddiqui MA, Akhtar MJ, Ahmad I, Pant AB, Alhadlaq HA. Genotoxic potential of copper oxide nanoparticles in human lung epithelial cells. Biochem Biophys Res Commun 2010;396:578–83.
[90] Sarkar A, Das J, Manna P, Sil PC. Nano-copper induces oxidative stress and apoptosis in kidney via both extrinsic and intrinsic pathways. Toxicology 2011;290:208–17.
[91] Gomes T, Pereira CG, Cardoso C, Pinheiro JP, Cancio I, Bebianno MJ. Accumulation and toxicity of copper oxide nanoparticles in the digestive gland of *Mytilus galloprovincialis*. Aquat Toxicol 2012;118–9:72–9.
[92] Cho Y, Shi R, Ben Borgens R. Chitosan nanoparticle-based neuronal membrane sealing and neuroprotection following acrolein-induced cell injury. J Biol Eng 2010;4:2.

[93] Bhattacharya K, Naha PC, Naydenova I, Mintova S, Byrne HJ. Reactive oxygen species mediated DNA damage in human lung alveolar epithelial (A549) cells from exposure to non-cytotoxic MFI-type zeolite nanoparticles. Toxicol Lett 2012;215:151–60.
[94] Ahamed M. Toxic response of nickel nanoparticles in human lung epithelial A549 cells. Toxicol In Vitro 2011;25:930–6.
[95] Srinivas A, Rao PJ, Selvam G, Murthy PB, Reddy PN. Acute inhalation toxicity of cerium oxide nanoparticles in rats. Toxicol Lett 2011;205:105–15.
[96] Estevez AY, Pritchard S, Harper K, Aston JW, Lynch A, Lucky JJ, Ludington JS, Chatani P, Mosenthal WP, Leiter JC, Andreescu S, Erlichman JS. Neuroprotective mechanisms of cerium oxide nanoparticles in a mouse hippocampal brain slice model of ischemia. Free Radic Biol Med 2011;51:1155–63.
[97] Lee TL, Raitano JM, Rennert OM, Chan SW, Chan WY. Accessing the genomic effects of naked nanoceria in murine neuronal cells. Nanomedicine 2012;8:599–608.
[98] Frick R, Müller-Edenborn B, Schlicker A, Rothen-Rutishauser B, Raemy DO, Günther D, Hattendorf B, Stark W, Beck-Schimmer B. Comparison of manganese oxide nanoparticles and manganese sulfate with regard to oxidative stress, uptake and apoptosis in alveolar epithelial cells. Toxicol Lett 2011;205:163–72.
[99] Kang SJ, Ryoo IG, Lee YJ, Kwak MK. Role of the Nrf2-heme oxygenase-1 pathway in silver nanoparticle-mediated cytotoxicity. Toxicol Appl Pharmacol 2012;258:89–98.
[100] Yang EJ, Kim S, Kim JS, Choi IH. Inflammasome formation and IL-1b release by human blood monocytes in response to silver nanoparticles. Biomaterials 2012;33:6858–67.
[101] Gou N, Onnis-Hayden A, Gu AZ. Mechanistic toxicity assessment of nanomaterials by whole-cell-array stress genes expression analysis. Environ Sci Technol 2010;44:5964–70.
[102] Hu R, Zheng L, Zhang T, Gao G, Cui Y, Cheng Z, Cheng J, Hong M, Tang M, Hong F. Molecular mechanism of hippocampal apoptosis of mice following exposure to titanium dioxide nanoparticles. J Hazard Mater 2011;191:32–40.
[103] Gehrke H, Frühmesser A, Pelka J, Esselen M, Hecht LL, Blank H, Schuchmann HP, Gerthsen D, Marquardt C, Diabaté S, Weiss C, Marko D. In vitro toxicity of amorphous silica nanoparticles in human colon carcinoma cells. Nanotoxicology 2013;7:274–93.
[104] Ahmad J, Ahamed M, Akhtar MJ, Alrokayan SA, Siddiqui MA, Musarrat J, Al-Khedhairy AA. Apoptosis induction by silica nanoparticles mediated through reactive oxygen species in human liver cell line HepG2. Toxicol Appl Pharmacol 2012;259:160–8.
[105] Passagne I, Morille M, Rousset M, Pujalté I, L'azou B. Implication of oxidative stress in size-dependent toxicity of silica nanoparticles in kidney cells. Toxicology 2012;299:112–24.
[106] Donaldson K, Poland CA. Inhaled nanoparticles and lung cancer – what we can learn from conventional particle toxicology. Swiss Med Wkly 2012;142:w13547.
[107] Ahamed M, Akhtar MJ, Siddiqui MA, Ahmad J, Musarrat J, Al-Khedhairy AA, AlSalhi MS, Alrokayan SA. Oxidative stress mediated apoptosis induced by nickel ferrite nanoparticles in cultured A549 cells. Toxicology 2011;283:101–8.
[108] Kang GS, Gillespie PA, Gunnison A, Moreira AL, Tchou-Wong KM, Chen LC. Long-term inhalation exposure to nickel nanoparticles exacerbated atherosclerosis in a susceptible mouse model. Environ Health Perspect 2011;119:176–81.
[109] Inoue K, Takano H. Aggravating impact of nanoparticles on immune-mediated pulmonary inflammation. Sci World J 2011;11:382–90.
[110] Gosens I, Post JA, de la Fonteyne LJ, Jansen EH, Geus JW, Cassee FR, de Jong WH. Impact of agglomeration state of nano- and submicron sized gold particles on pulmonary inflammation. Part Fibre Toxicol 2011;7:37.
[111] Kim EA, Park J, Kim KH, Lee N, Kim DS, Kang SK. Outbreak of sudden cardiac deaths in a tire manufacturing facility: can it be caused by nanoparticles? Saf Health Work 2012;3:58–66.
[112] Rushton EK, Jiang J, Leonard SS, Eberly S, Castranova V, Biswas P, Elder A, Han X, Gelein R, Finkelstein J, Oberdörster G. Concept of assessing nanoparticle hazards considering nanoparticle dosemetric and chemical/biological response metrics. J Toxicol Environ Health 2010;73:445–61.
[113] Kuempel ED, Geraci CL, Schulte PA. Risk assessment and risk management of nanomaterials in the workplace: translating research to practice. Ann Occup Hyg 2012;56:491–505.
[114] Ahmad I, Khan MI, Patil G, Chauhan LK. Evaluation of cytotoxic, genotoxic and inflammatory responses of micro- and nano-particles of granite on human lung fibroblast cell IMR-90. Toxicol Lett 2012;208:300–7.
[115] Markovic Z, Trajkovic V. Biomedical potential of the reactive oxygen species generation and quenching by fullerenes (C60). Biomaterials 2008;29:3561–73.
[116] Dhawan A, Taurozzi JS, Pandey AK, Shan W, Miller SM, Hashsham SA, Tarabara VV. Stable colloidal dispersions of C60 fullerenes in water: evidence for genotoxicity. Environ Sci Technol 2006;40:7394–401.
[117] Jacobsen NR, Pojana G, White P, Møller P, Cohn CA, Korsholm KS, Vogel U, Marcomini A, Loft S, Wallin H. Genotoxicity, cytotoxicity, and reactive oxygen species induced by single-walled carbon nanotubes and C(60) fullerenes in the FE1-Mutatrade markMouse lung epithelial cells. Environ Mol Mutagen 2008;49:476–87.
[118] Zhu L, Chang DW, Dai L, Hong Y. DNA damage induced by multiwalled carbon nanotubes in mouse embryonic stem cells. Nano Lett 2007;7:3592–7.
[119] Brooks RA, Jones E, Storer A, Rushton N. Biological evaluation of carbon fibre-reinforced polybutyleneterephtahalate (CFRPBT) employed in a novel acetabular cup. Biomaterials 2004;25:3429–38.
[120] Wang JJ, Sanderson BJ, Wang H. Cytotoxicity and genotoxicity of ultrafine crystalline $SiO_2$ particulate in cultured human lymphoblastoid cells. Environ Mol Mutagen 2007;48:151–7.
[121] Auffan M, Rose J, Orsiere T, Demeo M, Thill A, Zeyons O, Proux O, Masion A, Chaurand P, Spalla O, Botta A, Wiesner MR, Bottero JY. $CeO_2$ nanoparticles induce DNA damage towards human dermal fibroblasts in vitro. Nanotoxicology 2009;3:161–71.