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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.

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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

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