Environmental Toxicology and Pharmacology 44 (2016) 25–29

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/etap

Review

Recent advances (2010–2015) in studies of cerium oxide nanoparticles' health effects

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ARTICLE INFO

Article history:
Received 4 November 2015
Received in revised form 29 March 2016
Accepted 5 April 2016
Available online 9 April 2016

Keywords:
Cerium oxide nanoparticles
Health effects
Antioxidant activity
Toxicity
Epidemiology studies

ABSTRACT

Cerium oxide nanoparticles, widespread applied in our life, have attracted much concern for their human health effects. However, most of the works addressing cerium oxide nanoparticles toxicity have only used in vitro models or in vivo intratracheal instillation methods. The toxicity studies have varied results and not all are conclusive. The information about risk assessments derived from epidemiology studies is severely lacking. The knowledge of occupational safety and health (OSH) for exposed workers is very little. Thus this review focuses on recent advances in studies of toxicokinetics, antioxidant activity and toxicity. Additionally, aim to extend previous health effects assessments of cerium oxide nanoparticles, we summarize the epidemiology studies of engineered cerium oxide nanoparticles used as automotive diesel fuel additive, aerosol particulate matter in air pollution, other industrial ultrafine and nanoparticles (e.g., fumes particles generated in welding and flame cutting processes).

Contents

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http://dx.doi.org/10.1016/j.etap.2016.04.004
1382-6689/

1. Introduction

Cerium is a rare-earth element in the lanthanide series of the periodic Table (Kyosseva, 2015). Cerium oxide nanoparticles have fluorite structure and the similar material properties of high melting point, irradiation tolerance and a blue shift in the ultraviolet absorption (Ye et al., 2011). They display strong electrostatic attraction, high oxygen affinity and potential redox (Samiee and Goharshadi, 2012).

Commercially, cerium oxide nanoparticles play an important role in instruments, high technology, cosmetic products and consumer products. They have been extensively used as polishing materials, absorbents, automobile exhaust catalysts. Additionally, they are good oxide ion conductors in solid oxide fuel cells, and often used as electrode materials for gas sensors (Dahle and Arai, 2015). As polishing materials, cerium oxide nanoparticles are mainly used in final polishing process of producing electronic screen products, average optics glass and silica glass (Bandyopadhyay et al., 2012). As absorbents, cerium oxide nanoparticles have good adsorptive properties. For example, they are often used to remove the heavy metal from aqueous systems for their variable morphologies (Hua et al., 2012). Predominantly, cerium oxide nanoparticles have been used as automotive diesel fuel additive-combustion catalyst, which can increase fuel combustion efficiency and decrease diesel soot emissions (Xie et al., 2012). Apart from above mentioned, the growing and projected applications of cerium oxide nanoparticles are the promising pharmacological treatment for oxidative stress-related diseases, such as neurodegenerative pathologies, autoimmune diseases, diabetes and cancers (Caputo et al., 2014).

Increasing application has led to urgent studies considering the potential health effects of cerium oxide nanoparticles. This review focuses on recent advances (2010–2015) in studies of cerium oxide nanoparticles' toxicokinetics, antioxidant activity and toxicity, including cytotoxicity, genotoxicity, respiratory toxicity, neurotoxicity and hepatic toxicity in vitro and in vivo. To extend previous health effects assessments of cerium oxide nanoparticles, this review intends to summarize the epidemiology studies on ultrafine particulate matter, automotive diesel fuel additive containing cerium oxide nanoparticles, airborne fumes particles generated in welding and flame cutting processes. In the current insufficient database, these integrated toxicological assessments may insight on the cerium oxide nanoparticles-associated human health effects.

2. The toxicokinetics studies

The toxicokinetics of cerium oxide nanoparticles are not completely understood. The main advance is the establishment of exposure system with flaming spray and particle deposition synthesis. This exposure system can combine the aerosolized production with its simultaneous particle deposition. Based on some classical particles toxicokinetics investigations in submerged cell cultures or air-liquid cultivated cell cultures, Raemy et al. used this novel exposure system to cultivate A549 lung cells containing cerium oxide nanoparticles deposition at air-liquid interface. The results show that these particles' uptake over 35% of total deposited quantified mass after 10 min exposure, over 60% after 30 min exposure, over 80% of cerium oxide nanoparticles could be detected intracellularly in the following an additional 24 h post-incubation (Raemy et al., 2011). These findings reveal that cerium oxide nanoparticles suspensions can penetrate cellular membrane.

3. The antioxidant activity studies

Many chemical, biological and radiological insults may promote the production of free radicals, which can activate apoptotic response and cell death. Cerium oxide nanoparticles have antioxidant properties of variable particle sizes, crystal structures and surface chemistries. By virtue of these properties, they have analogous activity of two key antioxidant enzymes, superoxide dismutase and catalase in many biological contexts (Rodea-Palomares et al., 2012). They can decrease those toxic insults by scavenging intracellular reactive oxygen species (ROS), prevent the ROS accumulation, thus to promote cell longevity, eventually (Caputo et al., 2014). Based on these excellent antioxidant activities, cerium oxide nanoparticles have been developed to pharmacological tools for the treatment of diseases associated with oxidative stress.

3.1. *Anticancer activity*

Cerium oxide nanoparticles have selective cancer cells cytotoxicity and low normal cells toxicity. They can induce some changes in intracellular redox status, stimulate the prooxidant activity and lead to cancer cell damages and death (Pesic et al., 2015). But in human aortic endothelial cells (HAECs), they cause very little inflammatory response, even at the highest dose (Rim et al., 2013).

3.2. *Anti-obesity*

Cerium oxide nanoparticles can reduce the mRNA transcription of genes involved in adipogenesis and hinder the triglycerides accumulation in 3T3-L1 pre-adipocytes. This result reveals the possible mechanism of a novel anti-obesity pharmaceutical formulation. However, more in vivo hypolipidemic activity investigation of cerium oxide nanoparticles should be conducted in the future (Rocca et al., 2015).

3.3. *Wound repair*

Water soluble cerium oxide nanoparticles can penetrate into wound tissue, reduce oxidative damage of cellular membranes and proteins, and thus accelerate the healing of full-thickness dermal wounds. The repair mechanism may relate to the proliferation and migration of fibroblasts, keratinocytes and vascular endothelial cells (VECs) (Chigurupati et al., 2013).

3.4. *Manipulation of neuronal growth and activity*

Polak and Shefi demonstrated that cerium oxide nanoparticles can manipulate the neuronal growth and activity. The possible mechanism may be closely related to the enhancing of neuronal differentiation, survival, direct growth and electrical activity regulation (Polak and Shefi, 2015). Lee et al. also found cerium oxide nanoparticles can induce chemical- and size-specific changes in the murine neuronal cell transcriptome (Lee et al., 2012). These findings suggest that cerium oxide nanoparticles may have potential applications in neurodegenerative pathologies.

4. The toxicity studies

Currently, a number of toxicity effects of cerium oxide nanoparticles were reported. Many of these studies used in vitro models or in vivo methods. Normal cells culture or healthy animals are the main medium tools for in vitro models. Intravenous or intraperitoneal injections, intratracheal instillation, ingestion as a food additive are the most selective methods of in vivo exposure. After entered into the body, cerium oxide nanoparticles can accumulate in various organs, including heart and lung, and cause