Environmental Research 152 (2017) 503–513

Contents lists available at ScienceDirect

Environmental Research

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

Deleterious effects in reproduction and developmental immunity elicited by pulmonary iron oxide nanoparticles

Eun-Jung Park[a,*], Uiseok Jeong[b], Younghun Kim[b], Byoung-Seok Lee[c], Myung-Haing Cho[d], You-Seok Go[e]

[a] Myunggok Eye Research Institute, Konyang University, 685, Gasuwon-dong, Seo-Gu, Daejeon 302-718, South Korea
[b] Department of Chemical Engineering, Kwangwoon University, Seoul 139-701, South Korea
[c] Toxicologic Pathology Center, Korea Institute of Toxicology, Daejeon, South Korea
[d] College of Veterinary Medicine, Seoul National University, Seoul 151-742, South Korea
[e] Genome Application Division, Macrogen Inc., Seoul, South Korea

ARTICLE INFO

Keywords:
Iron oxide nanoparticles
Reproduction
Immunotoxicity
Mortality
Sex ratio

ABSTRACT

With the extensive application of iron oxide nanoparticles (FeNPs), attention about their potential risks to human health is also rapidly raising, particularly in sensitive subgroups such as pregnant women and babies. In this study, we a single instilled intratracheally FeNPs (1, 2, and 4 mg/kg) to the male and female parent mice, mated, then assessed reproductive toxicity according to the modified OECD TG 421. During the pre-mating period (14 days), two female parent mice died at 4 mg/kg dose, and the body weight gain dose-dependently decreased in male and female parent mice exposed to FeNPs. Additionally, iron accumulation and the enhanced expression of MHC class II molecules were observed in the ovary and the testis of parent mice exposed to the highest dose of FeNPs, and the total sex ratio (male/female) of the offspring mice increased in the groups exposed to FeNPs. Following, we a single instilled intratracheally to their offspring mice with the same doses and evaluated the immunotoxic response on day 28. The increased mortality and significant hematological- and biochemical- changes were observed in offspring mice exposed at 4 mg/kg dose, especially in female mice. More interestingly, balance of the immune response was shifted to a different direction in male and female offspring mice. Taken together, we conclude that the NOAEL for reproductive and developmental toxicity of FeNPs may be lower than 2 mg/kg, and that female mice may show more sensitive response to FeNPs exposure than male mice. Furthermore, we suggest that further studies are necessary to identify causes of both the alteration in sex ratio of offspring mice and different immune response in male and female offspring mice.

1. Introduction

Iron, a representative particulate material-bound heavy metal, has been suggested as an important cause that provokes the respiratory symptoms by forming reactive oxygen species (ROS) when we inhaled ambient particles (Aust et al., 2002; Jacobs et al., 2012; Wang et al., 2014). Meanwhile, iron oxide nanoparticles (FeNPs) have been widely studied with the great potential for revolutionizing applications, such as drug delivery, magnetic resonance imaging agents, soil and groundwater remediation, and as photocatalysts (Liu, 2006; Penn et al., 2003). Therefore, it is anticipated that the level in the environment and human exposure to FeNPs may notably increase over the coming decade, enhancing the potential risks to human health, particularly in sensitive subgroups such as pregnant women and babies.

Nanoparticles (NPs) can easily penetrate through biological membranes due to their small size (Chu et al., 2010; Guarnieri et al., 2014; Lee et al., 2013; Schädlich et al., 2012; Wang et al., 2013). NPs also have an increased surface area ratio to mass compared to the micro-sized particles of the same substance, thus their chemical/catalytic reactivity are markedly enhanced. For example, carboxyl-coated FeNPs (10, 20, 30, and 40 nm) is primarily distributed in the liver and the spleen, the smallest size (10 nm) penetrated more readily into the brain and the uterus than other sizes, and smaller FeNPs (10 and 20 nm) effectively altered the expression level of oxidative stress-, iron transport-, metabolism-, and apoptosis-related genes (Yang et al., 2015). In addition, growing evidences suggest that exposure to harmful environmental particles during pregnancy period can cause adverse health effects on the offspring (Liu et al., 2007; Srám et al., 1999; Yokota et al., 2013). Therefore, reproductive and developmental toxicity has been recently raised as an important issue among the concerns about the

* Corresponding author.
E-mail address: pejtoxic@hanmail.net (E.-J. Park).

http://dx.doi.org/10.1016/j.envres.2016.08.025
Received 23 May 2016; Received in revised form 11 July 2016; Accepted 23 August 2016
Available online 21 October 2016