Journal of Trace Elements in Medicine and Biology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

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

Are iron oxide nanoparticles safe? Current knowledge and future perspectives

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ARTICLE INFO

Article history:
Received 29 February 2016
Received in revised form 29 March 2016
Accepted 30 March 2016

Keywords:
Iron oxide nanoparticles
In vivo studies
In vitro studies
Epidemiological studies
Toxicity

ABSTRACT

Due to their unique physicochemical properties, including superparamagnetism, iron oxide nanoparticles (ION) have a number of interesting applications, especially in the biomedical field, that make them one of the most fascinating nanomaterials. They are used as contrast agents for magnetic resonance imaging, in targeted drug delivery, and for induced hyperthermia cancer treatments. Together with these valuable uses, concerns regarding the onset of unexpected adverse health effects following exposure have been also raised. Nevertheless, despite the numerous ION purposes being explored, currently available information on their potential toxicity is still scarce and controversial data have been reported. Although ION have traditionally been considered as biocompatible – mainly on the basis of viability tests results – influence of nanoparticle surface coating, size, or dose, and of other experimental factors such as treatment time or cell type, has been demonstrated to be important for ION *in vitro* toxicity manifestation. *In vivo* studies have shown distribution of ION to different tissues and organs, including brain after passing the blood-brain barrier; nevertheless results from acute toxicity, genotoxicity, immunotoxicity, neurotoxicity and reproductive toxicity investigations in different animal models do not provide a clear overview on ION safety yet, and epidemiological studies are almost inexistent. Much work has still to be done to fully understand how these nanomaterials interact with cellular systems and what, if any, potential adverse health consequences can derive from ION exposure.

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http://dx.doi.org/10.1016/j.jtemb.2016.03.017
0946-672X/© 2016 Published by Elsevier GmbH.

1. Introduction

Nanotechnology is rapidly expanding. With the increased applications of nanotechnology products, especially for biomedical purposes, concerns regarding the onset of unexpected adverse health effects following exposure have been also raised. Understanding of toxicological profiles of engineered nanomaterials is necessary in order to ensure that these materials are safe for use and are developed responsibly, with optimization of benefits and minimization of risks. However, development and production of engineered nanomaterials are increasing faster than generation of toxicological information. This lack of information on possible adverse effects of nanomaterials has been taken into consideration by many organizations worldwide such as the US Environmental Protection Agency (EPA), the World Health Organization (WHO), the US National Institute for Occupational Safety and Health (NIOSH), the European Commission (EC) and the Organization for Economic Co-operation and Development (OECD). Official documents have been prepared by these organizations addressing the need of dedicated research on appropriate methodological assays for assessing engineered nanomaterials toxicity [1]. Consequently, starting in the early 2000s, concerns about the potential human and environmental health effects of nanomaterials were being expressed by many scientists, regulators, and non-governmental agencies. Indeed, as a proof of the growing interest on this topic, the number of scientific articles published on 'nanotoxicity' or 'nanotoxicology' increased progressively in the last decade (around 1700 so far, according to PubMed database); before 2005 it was almost negligible.

Among engineered nanomaterials magnetic nanoparticles – made of iron, cobalt, or nickel oxides – offer promising possibilities in biomedical field mainly due to their special physicochemical features, including their proven biocompatibility and their magnetic properties that allow them to be manipulated by an external magnetic field gradient [2]. Particularly, nanoparticles made of a ferro- or ferromagnetic material, *i.e.*, iron oxide nanoparticles (ION), can exhibit a unique form of magnetism called superparamagnetism, which appears when the ION size is below a critical value – depending on the material, but typically around 10–20 nm –, and when the temperature is above the so-called blocking temperature [3]. This superparamagnetic behaviour is highly useful in biomedicine for a number of applications mainly related to diagnosis, tumour imaging, imaging of the central nervous system for neurovascular, neurooncological or neuroinflammatory processes, and drug delivery [4,5]. Indeed, clinical use of several ION as contrast agents for imaging were already approved by the US Food and Drug Administration since 1996 (US FDA) [6–8]. Therefore, due to the current and promising biomedical uses of ION involving the direct contact with different tissues and organs, studies addressing their potential toxicity are especially relevant.

ION are usually made of a crystalline core and a surface coating for stabilizing the core properties and optionally for preventing the aggregation. The crystalline core of ION, made of ferri- (Fe^{3+}) or ferro- (Fe^{2+}) magnetic material, is generally synthesized through protocols with controlled precipitation of iron oxides in organic solution [9], or in aqueous solution by adding a base [10]. Among the eight iron oxides known, magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3) and hematite (α-Fe_2O_3) are the most commonly used due to their polymorphism involving temperature-induced phase transition; they have unique biochemical, magnetic, catalytic, and other properties which provide suitability for specific technical and biomedical applications [9]. Surface of commercially available nanoparticles is normally modified by coating with different materials in order to stabilize them, modify their biodistribution, and enhance their biocompatibility. This coating is applied by adding a stabilizing coating material [*e.g.*, citrate, dextran, carboxydextran, chitosan, pullulan, polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyethylenimine (PEI), polyethylene oxide (PEO), polysaccharide, albumin, lipids, etc.] to monocrystalline (uniform ION with close particle size distribution) or polycrystalline (with significant size variance) ION [11]. Furthermore, particle coating may be further modified, especially in case of medical uses, with fluorescent dyes for imaging [12,13], targeting molecules [13,14], drugs [15] or nucleic acids [16,17]. This great variety of coatings leads to many diverse types of ION with different potential action mechanisms and toxic patterns.

ION have been reported in many studies to be highly biocompatible nanomaterials with none or low toxicity which do not pose a serious threat to the organism [18–21]. Despite being considered as generally safe, potential ION toxicity cannot be completely discarded since results from studies on this regard are often contradictory and ION effects at particular levels, such as genetic or carcinogenic, have been poorly addressed. Also, their effects on whole organisms and, specially, human health risks related to occupational and environmental exposure to ION have been scarcely evaluated. On this basis, and in order to improve the knowledge in this field, the aim of this review was to compile the *in vitro*, *in vivo* and epidemiological studies on ION toxicity published to date. Thus, the results and conclusions from the main ION toxicology studies were analysed, providing a general view of the current information on ION safety available as well as highlighting the main gaps of knowledge in the field that must be further addressed.

2. *In vitro* studies

2.1. Cellular effects

Most studies analysing ION toxicity are focused on cytotoxic effects of these nanoparticles on cell cultures. A number of different cell lines and testing conditions have been assessed reporting ION cellular effects at different levels, mainly decrease in viability, ROS production, and iron ion release, but also apoptosis induction, cell cycle alterations, cell membrane disruptions, cytoskeleton modifications, etc. An exhaustive revision of the former works can be found in some previous papers [22,23]. Since then, several studies published addressing the potential ION cytotoxicity show in general none or low cytotoxic effects of these nanoparticles. For instance, no adverse cellular effects were found in primary rat cerebellar cortex astrocytes treated with PEI-coated ION (magnetite) [24], in cultured rat astrocytes treated with

Please cite this article in press as: V. Valdiglesias, et al., Are iron oxide nanoparticles safe? Current knowledge and future perspectives, J Trace Elem Med Biol (2016), http://dx.doi.org/10.1016/j.jtemb.2016.03.017