Journal of Pharmaceutical and Health Sciences 2014;2(2), 109-114.

Short Review

JPHS

A Review of Toxicity of Some Conventional Nanomaterials

Safoura Soleymani[1], Hadi Zare-Zardini[2,3,*], Adel Ghorani Azam[1], Azam Hashemi[2], Leila Ebrahimi[4], Zahra Esfahanian[2], Farideh Zolfaghari[2]

[1] *Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran*

[2] *Department of Pediatric Hematology, Oncology and Genetics Research Center, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran*

[3] *Young Researchers and Elite Club, Yazd Branch, Islamic Azad University, Yazd, Iran*

[4] *Department of hematology, Iranian blood transfusion organization, Tehran, Iran*

Abstract

Increased production and use of nanomaterials has led to an ever growing exposure of living organisms to these substances. Limited knowledge about possible toxicity of nanomaterials and their potential to harm living creatures is becoming a serious concern. To address this problem, there is a need for development of diagnostic methods enabling effective determination of potential toxicity of nanomaterials. On the other hand, developing appropriate test methods is contingent on identifying cellular mechanism underlying toxicity of nanomaterials. This study reviews toxicity of some of the most widely used nanomaterials. According to the literature, Iron oxide nanoparticles can augment rate of cell death through oxidative stress and lipid peroxidation. Exposure to zinc oxide, gold and silver nanoparticles can result in cell death via mitochondrial dysfunction, expression of abnormal protein in cells, and altering the patterns of gene expression, respectively. Likewise, carbon nanotubes can lead to an increased rate of cell death through the reduction of membrane fluidity, thereby destroying cell membrane. Our literature review identified a lower toxic effect for nanotubes as compared with other nano-structures. Regarding the evident high toxicity of nanomaterials, caution must be exercised in irregular production and use of these substances in the industry. In addition, from the health and environmental standpoints, carbon nanotubes are the preferable nano-structures for development of nanotechnologies regarding their lower toxicity in comparison with other nanomaterials.

Keywords: Nano-materials, Nanoparticles, Toxicity, Cell Mortality

Corresponding author: H. Zare Zardini, Department of Pediatric Hematology, Oncology and Genetics Research Center, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.
Tel: : Tel: +98 3526528147 Fax: +98 3518229104
Email address: ha_za63@yahoo.com

Introduction

Nanomaterials (NMs) are usually classified into four structural categories including Tube NMs, Rod NMs, Wire NMs and Ball shapes (Spheres) NMs. In another category nanomaterials are classified into five categories of Metal NMs, Metal oxide NMs, Quantum dot NMs, Fullerenes NMs and Fibrous NMs (Aguilar, 2013, Sahoo et al., 2007, Singh et al., 2009).

Nanomaterials offer significant electrical, thermal, mechanical and visual advantages, which render them promising for commercial, medical and environmental applications. Among the most important commercial contexts of nanomaterials are electronics, computers, food, furniture, and health industries (Jeng and Swanson, 2006, Romig Jr et al., 2007, Singh et al, 2009).

Despite the broad application NMs, the growing production of nanomaterials has increased the exposure of living organisms to them (Hahn and Pauluhn, 2008, Jia, Li and Chen, 2005, Jones and Grainger, 2009, Muñoz and Costa, 2012). In the present study, the toxicity of several categories of some widely used nanomaterials is reviewed.

Review

Toxicity assessment methods

In vitro evaluation of the toxicity of nanomaterial is the most developed approach to investigate the safety of nanomaterials. In vitro studies can be classified into two categories of genomic and cellular toxicity investigation.

In vitro Evaluation of Cytotoxicity

There are three main methods used in study of the potential cytotoxicity of nanomaterials (Chen etal., 2011, Hu et al., 2010, Jones and Grainger, 2009):

Cell viability

- Determination of mitochondrial activity (Colorimetric MTT assay)
- Release of lactate dehydrogenase (LDH) after necrosis
- Annexin V and Propidium iodide (PI) staining for apoptotic and necrotic cells
- Determination of the collisions with lysosome through the neutral red absorption
- Determination of an apoptotic marker (Caspase 3)

Stress response

In order to determine stress responses, the concentration of ROS should be measured by 2, 7 di chloro-dihydroergotaminediacetate.

Inflammatory response

ELISA method is used to assess the production of inflammatory markers. Important inflammatory markers used in mice and humans studies include interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (Jones and Grainger, 2009, Seaton, Tran, Aitken and Donaldson, 2009).

In vitro Evaluation of Genotoxicity

The most common tests used to evaluate the NMs' genotoxicity include Aest test, Chromosome aberration test, Comet assay, Cytokinesis-blocked, Micronucleus assay, HPRT forward mutation assay, H2AX staining and DNA adduct hydroxyl deoxy guanosine (Jones and Grainger, 2009, Seaton Tran et al., 2009).

Mechanisms of toxicity of nanocompounds

While the application of NMs is already developed, mechanisms of their toxicity are not yet well understood. However, several investigations have shown that the physicochemical characteristics of the NMs can significantly impact their cellular uptake rate, thereby imposing undesirable physiological effects to the cells. Several risks have been identified for exposure of living organisms to NMs, including cell-environment interactions, fate and

transport of NMs, agglomeration and mobility in the permeable medium, accumulation (density) and changes in the redox potential (Melanie et al., 2006, Mélanie et al., 2008).
Evidence shows that NMs leave toxic effects on cells and their genetic content through different mechanisms. A summary of the relevant studies is summarized as following:

Iron oxide Nanoparticles

The effect of iron oxide NMs has been studied in a series of cells (Ban et al., 2012. Ying and Hwang, 2010). While iron oxide NMs have shown anti-cancer properties, they also have the potential to contribute to the development of cancer regarding their ionic nature. Studies on the spindle cells of connective tissue and pleomorphic cells of the sarcoma connective tissue in mice have proposed the following mechanisms for the cell destruction (Bhasin et al., 2002):

- Increased oxidative stress followed by lipid peroxidation, which can lead to direct damage of DNA and proteins.
- Excessive availability of iron pool in the cell, which can lead to dysfunction of cell.
- Increased level of hydroxyl radicals via the Fenton reaction (Bhasin et al., 2002).

Zinc oxide Nanoparticle

Several studies are conducted on the cytotoxic effects of NPs, especially on lung epithelial cells (Chang et al., 2011). The most important mechanism of NP-related cancer induction has been identified to be increased oxidative stress, thereby damage of macromolecules essential to the cells. On the other hand, while zinc oxide nanoparticles have shown advantageous properties in treatment of human colon cancer, their use in medical applications can lead to the following undesirable effects (Guo et al., 2013):

- Decrease in mitochondrial potential
- Increased production of superoxide
- Increased markers of apoptosis
- Cell death due to mitochondrial dysfunction (Heng et al., 2010, Moos et al., 2010).

Gold Nanoparticle

Study on human lung embryonic fibroblast cells, has identified important adverse effects for exposure to gold particles with the following mechanisms (Chuang et al., 2010, Soenen et al., 2012):

- Unspecific interactions between nitrogen bases of oligonucleotides
- Disruption of the hydrogen bonds formed between oligonucleotides (Li et al., 2007)

Silver Nanoparticle

Although antibacterial and antifungal properties of silver nanoparticles have found interesting medical applications, evidence indicates toxic effects for these NPs on stem cells and embryonic fibroblasts of rats (Ahamed et al., 2010, Grosse et al., 2013). Literature suggests the following mechanisms for the adverse effects of silver nanoparticles on the cells:

- Increased expression of p53 protein and phosphor-H2AX
- Decreased cell viability with respect to the time
- Lack of toxicity or changes in the production of glutathione
- Changes in the patterns of gene expression, in particular apoptotic and inflammatory genes (Ahamed et al., 2008).

Cobalt Nanoparticle

A study on the effects of Cobalt NPs on human peripheral blood leukocytes has identified the following mechanisms to be responsible for their toxicity of on cells (Colognato et al., 2008):

- An increase in DNA strand breakage at different dose levels of nanoparticle
- An extensive production of superoxide and hydroxyl radicals
- Increased percentage of comet tail and cytotoxicity
- Disruption in repairing DNA-binding proteins (enzyme), due to competition with mag-

nesium (Colognato et al., 2008).

Carbon Nanotubes

Use of carbon nanotubes (CNTs) has become popular in medicine regarding their antibacterial, antifungal and anticancer activities (Ji et al., 2010, Yang et al., 2011, Zare-Zardini et al., 2012, Zare-Zardini et al., 2013). Carbon nanotubes are also useful in development of novel drug delivery systems (DD system) (Chowdhury 2011, Elhissi et al., 2012, Prakash et al., 2011). Similar to other nanomaterials these compounds have the potential to leave a series of cell-specific toxic effects as well (Ghosh et al., 2011, Kayat et al., 2011, Zhao and Liu, 2012). It is evident that CNTs, in particular single-walled CNTs, can destroy the cells by reducing membrane fluidity or specific interactions with genetic material (Cheng et al., 2011, Davoren et al., 2007). While some useful biological effects of carbon nanotubes has been identified to be lower than other nanostructures they have reportedly the lowest toxic effects among almost all other nanomaterials (Cheng et al., 2011). It has been shown that implementing of functional groups on the surface of CNTs can improve their biological activities (Amiri et al., 2012, Zare-Zardini et al., 2012, Zare-Zardini et al., 2013).

Conclusion

The high toxicity of nanomaterials calls for caution in irregular production or use of them in the industry. Alongside with application of nanomaterial in industry and medicine, significant emphasis should be given to removal of waste nanomaterials from the environment. Our review of literature on toxicological aspects of nanomaterials identified carbon nanotubes as the safest nanostructures from toxicological aspects. Therefore, from the environmental standpoint carbon nanotubes are the preferable nanomaterials for future nanotechnology developments. Although biomedical application of carbon nanotubes is limited as compared with other nano-scale materials, this drawback can be alleviated by their conjugation with biological compounds including amino acids.

Acknowledgements

The authors would like to thank Young Researchers and Elite Club of the Islamic Azad University-Yazd Branch and Department of Pediatric Hematology, Oncology and Genetics Research Center, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran for their financial support of this study. Also, the authors thank Akhundzadeh, Ghanizadeh, Dehghani and Aminorroaya for their kind collaboration.

Conflict of Interest

The authors declare no conflict of interest.

References

Aguilar ZP. Chapter 2 - Types of Nanomaterials and Corresponding Methods of Synthesis. Nanomaterials for Medical Applications,(Zoraida A, ed.^eds.), p.^pp. 33-82. Elsevier. 2013.

Ahamed M, AlSalhi MS, Siddiqui MKJ. Silver nanoparticle applications and human health. Clinica Chimica Acta. 2010; 411: 1841-1848.

Ahamed M, Karns M, Goodson M, Rowe J, Hussain SM, Schlager JJ, Hong Y. DNA damage response to different surface chemistry of silver nanoparticles in mammalian cells. Toxicology and Applied Pharmacology. 2008; 233: 404-410.

Amiri A, Zare-Zardini H, Shanbedi M, Maghrebi M, Baniadam M, Tolueinia B. Efficient method for functionalization of carbon nanotubes by lysine and improved antimicrobial activity and water-dispersion. Materials Letters. 2012; 72: 153-156.

Auffan M, Decome L, Rose J, et al. In vitro interactions between DMSA-coated maghemite nanoparticles and human fibroblasts: A physicochemical and cyto-genotoxical study. Environmental Science and Technology. 2006; 40: 4367-4373.

Auffan M, Rose J, Proux O, et al. Enhanced adsorption of arsenic onto maghemites nanoparticles: As(III) as a probe of the surface structure and heterogeneity. Langmuir. 2008; 24: 3215-3222.

Ban M, Langonné I, Huguet N, Goutet M. Effect of submicron and nano-iron oxide particles on pulmonary immunity in mice. Toxicology Letters. 2012; 210: 267-275.

Bhasin G, Kauser H, Athar M. Iron augments stage-I and stage-II tumor promotion in murine skin. Cancer Letters. 2002; 183: 113-122.

Chang H, Ho C-C, Yang CS, Chang W-H, Tsai M-H, Tsai H-T, Lin P. Involvement of MyD88 in zinc oxide nanoparticle-induced lung inflammation. Experimental and Toxicologic Pathology. 2013; 65: 887-896.

Chen B, Liu Y, Song WM, Hayashi Y, Ding XC, Li WH. In Vitro Evaluation of Cytotoxicity and Oxidative Stress Induced by Multiwalled Carbon Nanotubes in Murine RAW 264.7 Macrophages and Human A549 Lung Cells. Biomedical and Environmental Sciences. 2011; 24: 593-601.

Cheng W-W, Lin Z-Q, Wei B-F, et al. Single-walled carbon nanotube induction of rat aortic endothelial cell apoptosis: Reactive oxygen species are involved in the mitochondrial pathway. The International Journal of Biochemistry, Cell Biology. 2011; 43: 564-572.

Chowdhury DF. Carbon Nanotube for Drug Delivery and Controlled Release. Comprehensive Biotechnology (Second Edition),(Editor-in-Chief: Murray M-Y, ed.^eds.), p.^pp. 643-655. Academic Press, Burlington. 2011.

Chuang S-M, Lee Y-H, Liang R-Y, et al. Extensive evaluations of the cytotoxic effects of gold nanoparticles. Biochimica et Biophysica Acta (BBA) - General Subjects.

Colognato R, Bonelli A, Ponti J, Farina M, Bergamaschi E, Sabbioni E, Migliore L. Comparative genotoxicity of cobalt nanoparticles and ions on human peripheral leukocytes in vitro. Mutagenesis. 2008; 23: 377-382.

Davoren M, Herzog E, Casey A, Cottineau B, Chambers G, Byrne HJ, Lyng FM. In vitro toxicity evaluation of single walled carbon nanotubes on human A549 lung cells. Toxicology in Vitro. 2007; 21: 438-448.

Elhissi A, Ahmed W, Dhanak VR, Subramani K. Chapter 20 - Carbon Nanotubes in Cancer Therapy and Drug Delivery. Emerging Nanotechnologies in Dentistry,ed.^eds.), p.^pp. 347-363. William Andrew Publishing, Boston. 2012.

Ghosh M, Chakraborty A, Bandyopadhyay M, Mukherjee A. Multi-walled carbon nanotubes (MWCNT): Induction of DNA damage in plant and mammalian cells. Journal of Hazardous Materials. 2011;197: 327-336.

Grosse S, Evje L, Syversen T. Silver nanoparticle-induced cytotoxicity in rat brain endothelial cell culture. Toxicology in Vitro. 2013; 27: 305-313.

Guo D, Bi H, Liu B, Wu Q, Wang D, Cui Y. Reactive oxygen species-induced cytotoxic effects of zinc oxide nanoparticles in rat retinal ganglion cells. Toxicology in Vitro. 2013; 27: 731-738.

Hahn A, Pauluhn J. Assessment of early acute lung injury in rats exposed to aerosols of 'Magic Nano' sealing sprays. Toxicology Letters 180, Supplement: S55. 2008.

Heng BC, Zhao X, Xiong S, Woei Ng K, Yin-Chiang Boey F, Say-Chye Loo J. Toxicity of zinc oxide (ZnO) nanoparticles on human bronchial epithelial cells (BEAS-2B) is accentuated by oxidative stress. Food and Chemical Toxicology. 2010; 48: 1762-1766.

Hu X, Cook S, Wang P, Hwang H-m, Liu X, Williams QL. In vitro evaluation of cytotoxicity of engineered carbon nanotubes in selected human cell lines. Science of The Total Environment. 2010;408: 1812-1817.

Jeng HA, Swanson J. Toxicity of Metal Oxide Nanoparticles in Mammalian Cells. Journal of Environmental Science and Health, Part A. 2006; 41: 2699-2711.

Ji S-r, Liu C, Zhang B, et al. Carbon nanotubes in cancer diagnosis and therapy. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer. 2010; 1806: 29-35.

Jia X, Li N, Chen J. A subchronic toxicity study of elemental Nano-Se in Sprague-Dawley rats. Life Sciences. 2005; 76: 1989-2003.

Jones CF, Grainger DW. In vitro assessments of nanomaterial toxicity. Advanced Drug Delivery Reviews. 2009; 61: 438-456.

Kayat J, Gajbhiye V, Tekade RK, Jain NK. Pulmo-

nary toxicity of carbon nanotubes: a systematic report. Nanomedicine: Nanotechnology, Biology and Medicine. 2011; 7: 40-49.

Li JJ, Zou L, Hartono D, Ong CN, Bay BH, Lanry Yung LY. Gold Nanoparticles Induce Oxidative Damage in Lung Fibroblasts In Vitro. Advanced Materials. 2008; 20: 138-142.

Moos PJ, Chung K, Woessner D, Honeggar M, Cutler NS, Veranth JM. ZnO particulate matter requires cell contact for toxicity in human colon cancer cells. Chemical research in toxicology. 2010; 23: 733-739.

Muñoz A, Costa M. Elucidating the mechanisms of nickel compound uptake: A review of particulate and nano-nickel endocytosis and toxicity. Toxicology and Applied Pharmacology. 2012; 260: 1-16.

Prakash S, Malhotra M, Shao W, Tomaro-Duchesneau C, Abbasi S. Polymeric nanohybrids and functionalized carbon nanotubes as drug delivery carriers for cancer therapy. Advanced Drug Delivery Reviews. 2011; 63: 1340-1351.

Romig Jr AD, Baker AB, Johannes J, et al. An introduction to nanotechnology policy: Opportunities and constraints for emerging and established economies. Technological Forecasting and Social Change, 2007; 74: 1634-1642.

Sahoo SK, Parveen S, Panda JJ. The present and future of nanotechnology in human health care. Nanomedicine: Nanotechnology, Biology and Medicine. 2007; 3: 20-31.

Seaton A, Tran L, Aitken R, Donaldson K. Nanoparticles, human health hazard and regulation. Journal of The Royal Society Interface. 2009.

Singh N, Manshian B, Jenkins GJS, et al. NanoGenotoxicology: The DNA damaging potential of engineered nanomaterials. Biomaterials. 2009; 30: 3891-3914.

Soenen SJ, Manshian B, Montenegro JM, et al. Cytotoxic Effects of Gold Nanoparticles: A Multiparametric Study. ACS Nano. 2012; 6: 5767-5783.

Yang F, Jin C, Yang D, et al. Magnetic functionalised carbon nanotubes as drug vehicles for cancer lymph node metastasis treatment. European Journal of Cancer. 2011; 47: 1873-1882.

Yang J, Pong B-K, Lee JY, Too H-P. Dissociation of double-stranded DNA by small metal nanoparticles. Journal of Inorganic Biochemistry. 2007; 101: 824-830.

Yang X, Liu X, Lu H, Zhang X, Ma L, Gao R, Zhang Y. Real-Time Investigation of Acute Toxicity of ZnO Nanoparticles on Human Lung Epithelia with Hopping Probe Ion Conductance Microscopy. Chemical Research in Toxicology. 2011; 25: 297-304.

Ying E, Hwang H-M. In vitro evaluation of the cytotoxicity of iron oxide nanoparticles with different coatings and different sizes in A3 human T lymphocytes. Science of The Total Environment. 2010; 408: 4475-4481.

Zare-Zardini H, Amiri A, Shanbedi M, Maghrebi M, Baniadam M. Enhanced antibacterial activity of amino acids-functionalized multi walled carbon nanotubes by a simple method. Colloids and Surfaces B: Biointerfaces. 2012; 92: 196-202.

Zare-Zardini H, Amiri A, Shanbedi M, Memarpoor-Yazdi M, Asoodeh A. Studying of antifungal activity of functionalized multiwalled carbon nanotubes by microwave-assisted technique. Surface and Interface Analysis. 2013; 45: 751-755.

Zhao X, Liu R. Recent progress and perspectives on the toxicity of carbon nanotubes at organism, organ, cell, and biomacromolecule levels. Environment International. 2012; 40: 244-255.