Applications, Challenges and Development of Nanomaterials and Nanotechnology

Ling Zhang*
Zhejiang Shuren University, No.8 Shuren Street, Hangzhou 310015, China.
zhlzju@163.com*

(Received on 27th June 2019, accepted in revised form 20th May 2020)

Summary: Nanomaterials and nanotechnology have been rapidly developed and widely applied in antimicrobial, biosensors, nanomedicine, nano-electronic technology, reinforcement, water treatment, and so on. However, there are also many problems and challenges during using and developing nanomaterials and nanotechnology. Are they secure enough for the health of human beings? Do they cause the environmental pollution? And how can we sustainably develop nanomaterial and nanotechnology? In this review, we introduced the applications, potential threats and hazards, and development and prospect of nanomaterial and nanotechnology.

Keywords: Nanomaterial; Nanotechnology; Nanomedicine; Nanotoxicity; Environment pollution

Introduction

The development of materials science has greatly improved the quality of daily life of human beings. Each of us uses materials almost all the time, and materials play a vital role in aspects of food, clothing, housing and transportation. Other than the innovation of traditional process technology and equipment, the development of new materials often leads to great development in the high-tech field. Among them, nanomaterial is at the forefront of research and is highly regarded by academics and industry. It is undoubtedly the jewel in the field of materials science. In the 1960s, the Nobel Prize-winning quantum physicist Feynman predicted that if we had some control over the arrangement of objects on a small scale, we would be able to make objects with a lot of exotic characteristics, and we would see the performance of the material produces a rich variety of changes. The current nanomaterial is that material he said. Gleiter first proposed the concept of nanomaterials in 1981. Nanomaterial refers to a material having a crystalline or amorphous particulate structure on a nanometer scale. Nanomaterials include nanoparticles, nanowires, nanomembranes, and nanoblocks of the material in the nanoscale range in three dimensions. The specificity of the size and structure of nanomaterials makes them possess special properties not found in many traditional materials. For example, conductive copper does not conduct electricity to a certain nanometer limit. The originally insulated silicon dioxide became semiconductor at a certain nanometer limit. These special phenomena attribute to the particular features of nanomaterials, such as nanosize, large specific surface areas and high surface energy [1, 2].

Nanotechnology involves many disciplines, including physics, chemistry, materials science, information science, energy science, medicine, biology and advanced manufacturing, etc., is a highly cross discipline, also represents the fusion of frontier science and high technology. It aims to take advantage of the special physicochemical properties of nanoscale materials to produce products that meet the needs of industrial practice, thus facilitating people's lives. Vapour phase techniques: aerosol based processes, atomic or molecular condensation, arc discharge generation, laser ablation process, plasma process, chemical vapor deposition; liquid phase techniques: sol-gel method, solvothermal method, sonochemical method; solid phase techniques: milling/ mechanochemical processing have been used for large-scale synthesis of nanomaterials [3]. X-rays, focused ion beams and electron beams will be used for nanolithography. The use of radiation has proved to be an essential technique in the fabrication of nanostructures with high resolution [4]. To meet the increasing demand for nanotechnology-enabled products, innovative integration of complementary technologies into novel process chains and their implementation in new manufacturing platforms will bring new development of nanotechnology [5]. Nowadays, nanotechnology has been widely used in biomedicine, mechanical equipment, environmental protection and other fields, and has promoted the overall development of these industries [6, 7].

From the perspective of appearance time, the first kind of nanomaterials is carbon-related materials, produced by evaporating graphite. Carbon nanotubes have a cylindrical structure with a aspect ratio of 132 000 000:1. Besides, its excellent mechanical properties and thermal conductivities make it the proper addictive for many structure materials. Carbon nanotubes have a solid density as low as 1.3 to 1.4

*To whom all correspondence should be addressed.

g/cm3 and a specific strength of up to 48,000 kN·m·kg-1. The potential applications of carbon nanotubes are quite inspiring, they can be used to manufacture the next generation of energy storage devices, high-performance catalysis, biomedical devices and implants. Although the properties of carbon nanotubes are powerful, the application is still limited due to the complicated synthesis, high cost and potential health risk.

The second kind of nanomaterials is zero-valent metals and metal oxides. For example, zero-valent nano-iron can reduce and decompose organochlorine pesticides and polychlorinated biphenyls, which can be used to remediate water and soil [8]. Titanium dioxide nanoparticles have self-cleaning effect. And the sunscreen which is close to our daily life just depends on the zinc oxide particles which have superior UV blocking properties. However, there are lots of worries about the safety of nanoparticle in the sunscreen. Nanoparticles have large surface volume ratio, strong reactivity or catalysis, so they are potential hazards for the environmental and huamn health. Zinc oxide nanoparticles will not be absorbed by blood in vivo, but it is still not known whether cosmetics and sunscreen containing nanoparticles will endanger health [9].

The third kind of nanomaterials is semiconductor nanocrystals, also called quantum dots (QDs). Quantum dots are very small, only a few nanometers and their optical and electronic properties are significantly different from those of large particles. Quantum dots have high extinction coefficient and special optical applications. Quantum dots emit a certain frequency of light when they are electrified or illuminated. The frequency of light can be controlled by changing the size, shape and composition of quantum dots. Quantum dots are highly controllable and can be used in transistors, solar cells, quantum computing and medical imaging. However, quantum dots are potentially harmful to human health and environmental safety. Animal experiment has been demonstrated the toxicity of cadmium containing particles. Many studies have used cell culture models to study the cytotoxicity of quantum dots. It has been proved that after quantum dots are exposed to ultraviolet radiation or air oxidation, free cadmium ions were released from CdSe QDs, and resulted in cell death.

The fourth kind of nanomaterials is polymer-based nanomaterial. Dendrimer is one kind of polymer, taking dendrimer for an example of polymer-based nanomaterial [10]. Dendrimers are usually monodispersed compounds with highly symmetrical spherical structures. The properties of dendrimers are mainly determined by their surface functional groups. Surface functional groups with charges or other hydrophilic groups can increase the water solubility of dendrimers. Dye molecules, affinity ligands, targeting components and pharmaceutically active compounds could be chemically conjugated to the dendrimer surface, so as to use as detecting agents or nanodrugs.

Nanomaterial and nanotechnology have been widely applied in antimicrobial, biosensors, nanomedicine, nano-electronic technology, reinforcement, water treatment, and so on. However, there are also many problems and challenges during using and developing nanomaterials. Increasing the production of nanomaterials, the release of nanomaterials in the environment and impact on ecological health are urgent problems to be solved. We should strengthen the research on the nanotoxicology mechanism and safety assessment techniques. And understanding the relationship between biosafety and nanomaterial is essential for the sustainable development. The following mainly introduces the applications, potential threats and hazards, and development and prospect of nanomaterial and nanotechnology.

Applications of nanomaterial and nanotechnology

Antimicrobial

Nanoparticles, such as silver and zinc oxide, can interact with cells in a unique way, thus promoting the transfer of nanoparticles into the cell. Nano-sized zinc oxide has a wide range of antimicrobial activities, and can interact with bacterial surface or bacterial interior, showing a unique bactericidal mechanism. Zinc oxide is a semiconductor catalyst. When a photon with a certain energy exceeding the semiconductor band gap, valence band holes rob the hydroxyl electrons in the surrounding environment. The hydroxyl group becomes a free radical which acts as a strong oxidant to kill the bacteria and the virus [11].

Silver nanoparticles were reduced and stabilized by catechol-conjugated chitosan (CSS), which showed excellent stability in aqueous solution with narrow diameter distribution. The CSS-silver nanoparticles have the characteristics of chitosan and silver nanoparticles. They have low cytotoxicity but good antimicrobial activity. When the concentration of CSS-silve nanoparticles is very low, it can kill

Escherichia coli and Staphylococcus aureus, and the low concentration will not damage HepG2 cells, which has a great application prospect in the prevention of microbial infections. Interestingly, the toxicity of CSS- silver nanoparticles to Gram-negative Escherichia coli (E.coli) was higher than that to Gram-positive Staphylococcus aureus (S.aureus) [12]. Leakage of the cytoplasm of bacteria resulted to kill Gram-positive bacteria, and changes of the permeability of the membrane resulted to kill Gram-negative bacteria. Structural differences in cell walls of Gram-positive bacteria lead to different antimicrobial mechanisms. The cell walls of Gram-positive bacteria are thicker and less affected by CSS-silve nanoparticles. However, the interaction between Gram-negative bacteria and CSS-silve nanoparticles is strong, and they are more likely to be killed [13]. A novel silver-loaded chitosan antimicrobial sponge was prepared by a simple method. Silver nanoparticles were introduced into chitosan matrix through the chemical interactions between catechol of CSS-silve and amino groups of chitosan. Silver nanoparticles were well dispersed in chitosan sponge. Catechol binds nano-silver to chitosan matrix, which greatly prolongs the release time of silver from 1 day to at least 4 days. The long-term release of silver made the chitosan-based composite sponge possess long-term antimicrobial properties. It completely inhibited the growth of bacteria within 3 days and could meet the requirements of wound healing [14].

Biosensors

Biological materials, such as antibody, enzyme and antigen, were fixed as a component on a medical microbial sensor surface. Microorganism specifically combining to the sensor surface generates an electrical signal for detection, thereby achieving the quantitative test of the presence or absence of a particular microorganism [15]. Nano-metal materials have broad applications for microbial sensors, which are highly conductive and can strengthen sensor electrodes and biological reaction centers. The electron transfer process increases the rate of chemical reactions, further enhances the sensitivity of the sensor. Therefore, such biosensors could be put into the human body by injection, and functionlized as a carrier or a probe to capture more detailed information in the patient's body, so that the doctor can perform diagnosis and treatment. Using carbon nanotubes as a substrate material, and Ag_2S nanospheres as a load to fabricate Au nanoparticles-labeled antibody biosensor, which has higher corresponding current and lower detection limit than the conventional detection method, and the detection limit is 4×102 cfu/mL [16].

Nanomedicine

Cancer is one of the most important cause of deaths worldwide today [17]. The poor water solubility, non-specific biological distribution and lower therapeutic effect of cancer chemotherapeutic drugs greatly limit their clinical applications, and the novel nano-drug delivery system can overcome these shortcomings. Drugs combined with nanocarriers to obtain controllable release with improved targeting ability, and enhanced their loading efficiency [18, 19]. Up to date, about 50 nanodrugs have been approved by the Food and Drug Administration for various diseases [20]. Nanodrug has great potential in curing diseases with greater efficacy and less side effects than traditional chemotherapies. Disulfide and hydrzone have been used to synthesize pH-sensitive nanocarriers, which can cut off drug molecules and kill cancer cells without affecting normal cells. Nanocarriers can be formulated with lipids (liposomes), polymers (macromolecules, micelles or dendrimers) and viruses [21, 22].

Chen XS, et al. reported a design method of thick shell stabilized core-shell nanoparticles for deep drug delivery [23]. Large reduction in size and charge reversal is beneficial to tissue infiltration and cell absorption. Dimethylmaleic anhydride modified polypeptide stacks the shells by electrostatic action. In the acidic microenvironment of tumor tissues, the size of shell-stacked nanoparticles decreased significantly from 145 nanometers to 40 nanometers, while the surface charge changed from -7.4 millivolts to 8.2 millivolts. The disulfide-linked nuclei disintegrate in the cells, which accelerates the release of intracellular drugs and enhances the antitumor activity. This nanocarrier can transfer antineoplastic drugs to deeper tumor sites.

Nano-electronic technology

Traditional silicon chips have already accommodated millions of components, but their capacity has become more difficult to increase. Especially when entering the nanometer scale, the circuit becomes very small. If you are not careful, there may be big errors in circuits. Nanotechnology offers a new approach to precisely controlling circuits at the atomic scale. At present, the chips on mobile phones can achieve 7nm level. Nanotechnology will work with quantum technology to push electronic products to a new height in the future. Nano-quantum devices can be designed to make integrated circuits smaller and more accurate. For example, nano-electronic technology can be used to make ultra-micro magnetic field detector, making the information detection, collection and processing ability stronger. In the future, nano-electronic technology will mainly focus on the research and development and application of intelligent micro-electromechanical navigation system, which can realize the miniaturization of micro-missile, and the longer range and more accurate.

Graphene-nanocellulose composites have become a promising nanomaterial for flexible supercapacitors. Supercapacitor requires good electrochemical performance and flexibility. Graphene and nanocellulose are excellent materials for preparing supercapacitors. Nanocellulose has good biodegradability, flexibility and chemical reactivity, which is often used as the base material for electronic devices [24].

Reinforcement

Carbon and inorganic nanomaterials were used to reinforce and modify polypropylene fumarate. Nanomaterials had good dispersion in polymer matrix. The reinforcement effect was closely related to the morphology of nanomaterials: nanoplates > nanobelts > nanotubes. Differences in nanostructure, chemical compositions and structural defects may be the key factor affecting mechanical properties of nanomaterial-reinforced polymer polypropylene fumarate [25].

Poly(p-aminophenylacetylene)/multi-walled carbon nanotubes were compounded with superparamagnetic ferric oxide nanoparticles. Orientation alignment of carbon nanotubes was achieved by magnetic field induction method, thus enhancing the mechanical properties of the modified chitosan rods. Modified magnetic carbon nanotubes were uniformly dispersed in chitosan solution, aligned under external magnetic field and embedded in chitosan matrix by in-situ precipitation reaction. The bending strength and modulus of chitosan rods were 124.6 MPa and 5.3 GPa, respectively, which were 34.8% and 29.3% higher than pure chitosan rods. The modified magnetic carbon nanotubes have good application prospects in the field of bone fracture internal fixation. [26].

Water treatment

The traditional wastewater treatment materials are limited by size and specific surface area, resulting in low adsorption. Nanomaterials have large surface area than traditional water treatment materials, and have high adsorption capacity and efficiency. Carbon nanotubes with porous structure and high adsorption surface area have good adsorption performance for methylene blue and Congo red [27]. Fe3O4 magnetic nanoparticles about 15 nm were fabricated by chemical precipitation method. The magnetic nanoparticles were silylated to make the ends rich in amino groups. Amidation is carried out to obtain magnetic nanoparticles with carboxyl groups. The wastewater was simulated by methylene blue and ethyl violet. The results showed that the amino functionalized magnetic nanoparticles had the best adsorption effect on methylene blue at pH=9, and the carboxyl functionalized magnetic nanoparticles had the highest adsorption capacity to ethyl violet at pH=4.5 [28].

Potential threats and hazards of nanomaterials and nanotechnology

Nanotoxicity and biosafety of nanomaterials

Nanomaterials are widely used in the electronics industry, biomedicine, cosmetics, etc. However, up to now, the safety of nanomaterials is still controversial [29]. Nanotoxicity is potential threat to human health. The research on the biosafety of nanomaterials is a challenge for the frontier science and technology in the 21st century, and it is also a major scientific problem faced by the scientific community in various countries.

Numerous studies have investigated the hazards of nanomaterials to human health. Nanoparticles could get into the body of living beings through ingestion, inhalation and skin permeation, and interact with cells and tissues depending upon their physicochemical properties and extent of penetration. Nanomaterials, like carbon-based, metallic-based and polymer-based nanoparticles, can cause damage at the cellular or protein level because of its small size and large specific surface area [30, 31]. When nanoparticles enter the biological system, they interact with the immune system, and interact dynamically with biological macromolecules to form "biological crown", so nanoparticles belong to the category of biological aggressors. [32, 33].

Ingestion is the most effective way of nanoparticles to get into the body. Along with food, water or drugs, nanoparticles get orally ingested and are absorbed in gastrointestinal ways, which may cause certain bad effect on the organic health [34].

Nanoparticles could even get to the blood through vascular wall, and spread into other body organs after ingested in the gastrointestinal position. Nanoparticles may have hepatotoxicity when they enter hepatic circulation. It has been demonstrated that copper nanoparticles can severely damage the liver, spleen and kidney of rat after oral ingestion [35].

Dermal exposure is the second way of nanoparticles to get into the body. Nanoparticles can penetrate the skin through diffusion or intercellular transepidermal pathway. Skin acts as an effective barrier for the penetration of toxic substances or nanoparticles inside the body. Nanoparticles could only reach the upper layers of the epidermis through skin, and eventually permeate into the zone close to hair follicles [36]. Hair follicles and sweat glands promote the entry of nanoparticles. When the upper layer of skin is wounded or removed, nanoparticles enter inside the skin through hair follicles and may lead to toxic side-effects. For example, carbon nanotubes incubated with keratinocytes led to mitochondrial dysfunction, and oxidative stress due to formation of active oxygen [37].

Another important way of nanoparticles penetration is inhalation by which nanoparticles enter deeply into lungs. Further, these particles cause inflammation and chronic side-effects after interacted with interstium and then get translocated to lymph nodes [38]. Deposition of nanoparticles and their clearance from lungs and respiratory tract depends upon many factors like characteristics of nanoparticles, respiratory tract structure and airflow patterns [39]. Extremely small sized nanoparticles may enter the lung alveoli through diffusion mechanism. As nanoparticles enter deep into the lung tissues, their interactions with cells and tissues also increases and further causes negative side-effects to the exposed organs [40]. Nanoparticles deposited in the lungs may also cross the blood-air tissue barrier and enter the blood stream, penetrate and affect the neighboring organs. Large number of intra-tracheal instilled Au nanoparticles (30 nm) and TiO2 nanoparticles (20 nm) were accumulated in platelets inside lung capillaries of rats within only 30 min of incubation [41].

Size, charge and shape are the main factors which influence the interactions of nanoparticles with cells [42]. 5 nm Au nanoparticles exposed to mouse fibroblasts had shown more remarkable toxicity and disruption of actin cytoskeleton as compared to 15 nm Au nanoparticles [43]. Negatively charged sodium citrate coated silver nanoparticles have the minimum toxicity to bacteria, but positively charged silver nanoparticles have more toxic to bacillus species [44]. Dendritic cluster of Ni nanoparticles showed more toxicity in zebrafish as compared with spherical shaped nanoparticles [45].

Nanomaterials play a vital role in nanomedicine. However, recent research indicated that the commonly used inorganic nanoparticles, including Au, SiO2 and TiO2 nanoparticles, can accelerate vascular infiltration of breast cancer cells after intravenous injection into animal models, increasing tumor metastasis, and promoting the emergence of new transfer sites [46].

Environment pollution

The release of nanoparticles into the ecological environment endangers the health of the ecosystem, which is an urgent problem to be solved. Nanoparticles releases may come from factories, landfills, wet deposition, and wear of product containing nanomaterials [47]. Nanomaterial circulation involves transformation, accumulation, and degradation in organisms. Metal and metal oxide nanoparticles have been used to remedy contaminants in water and air. The widespread usage of nanomaterials enhanced the releases to environment. Inorganic nanomaterials, such as SiO2, TiO2, ZnO, have oxidative stress effects by producing reactive oxygen species, and caused high toxicity to microorganisms. Fullerene (C60) colloid has oxidative stress effect, which can cause severe lipid peroxidation in fish brain, also exhibited antibacterial activity [48]. However, microorganisms are the basis of ecosystem and food chain, and the main driving force of the geochemical cycle. Therefore, it is very important to understand the interactions between nanomaterials and microorganisms for ecological health. The synthesis and release of nanomaterials will affect the ecological environment. Metal ions released from power generation in the production process of nanomaterials cause serious ecological toxicity. [49].

Misuse and moral disputes of nanotechnology

Scientific and technological researches are mostly employed by the government, enterprises, schools and other institutions. Science is no longer simply to explore the mysteries of nature, but to meet the needs of social and economic development, to serve its "employer", financial provider or sponsor. Researchers should subject to common social ethical and moral standards. Ethical responsibility is not only the individual moral behavior, but also related to the development of the whole society. The basic moral responsibility of scientists and engineers prevents them from harming their colleagues, bosses, customers and products [50].

Due to the tremendous development of nanotechnology, there are some problems in using nanomaterials, and have been caused widespread controversy in society. Advanced nanotechnology will replace part of the labor force in agriculture, manufacturing and industry, affecting their employment. Devices using nanotechnology can work faster and more accurately, reducing dependence on people; nanotechnology can be used to produce micro-recording devices, which will not be detectable and will endanger privacy and security. Nanotechnology will also be used to manufacture nano-weapons, which will be more destructive. If it falls into the wrong hands, it will seriously endanger social security.

Humans could find out their genetic codes that resulted in genetic diseases and defects through nano-gene chips, and use nanotechnology to rearrange the genetic code on a nanoscale, and even can add good genes to strengthen themselves. But misuse of the technology, such as using nanotechnology to identify the sex of a fetus, would lead to gender imbalance and a range of social problems. In addition, conditional parents create better children, which will further trigger social inequality. Children should not be regarded as the objects of parents' design and reform, but should be welcomed unconditionally. Parents' attitude is particularly important for the intergenerational relationship. Nano-gene technology expands the scope of disability and discrimination, and also gives parents some pressure that whether to use new technology to change their offspring [51].

Development and prospects

Nanotoxicology mechanism and safety assessment techniques

The rapid development of nanotechnology requires complementary safety assessment techniques and strategies. The safety and effect of nanomaterials in clinical application majorly depend on nanomaterial biodegradability, biocompatibility and biodistribution. Nanomaterials with poor biocompatibility, biodistribution and biodegradability might induce the oxidative stress, DNA damage and inflammation in the organism. However, with the further development of technology, it is very hopeful that this problem will eventually be solved.

Mechanism of nanotoxicology needs to be further studied. Under the theoretical framework of original toxicology, it is necessary to introduce new concepts and parameters to establish a new nanotoxicology system. Biological and chemical properties of nanomaterials will be changed after entering the body, and new metabolites will further affect its biological effects, such as the distribution and metabolism in life, the interaction mechanism with biological macromolecules, etc. Nanotoxicology detection methodology is urgently needed [52]. The detection technology of laboratory for single nanomaterial is difficult to directly test the complicated systems of nanoproducts. This emerging discipline brings many important challenges, especially the development of nanomaterial characterization technology, biological and chemical analysis technology, which brings many opportunities for technology development. Developing high-throughput and high-volume screening protocols to study the nanomaterial toxicity, hazard grading, animal differentiation, nanostructure-activity relationship models, and used as a universal tool for better designing and using nanomaterials to ensure human safety [53].

Accelerating the research and development of nanomedicine

In the past 30 years, a large number of researchers have studied nanomedicine for cancer treatment, published hundreds of thousands of scientific papers and invested trillions of dollars, but no substantial progress has been made. The nanomedicine on the market is still basically liposome and protein-based nanodrug [54-57]. How to realize the clinical transformation of nano-drugs is still a big problem. There are two important criteria for each new drug: safety and efficacy. In order to develop nanomedicine better, we need to understand three basic scientific issues in nanomedicine: the correlation between EPR effect and cancer metastasis, and its role in nanomedicine; the interactions between nanoparticles and immune system; and the amount of active nanodrugs released in tumors to make them truly remain inside tumor cells. [58].

Nanoproduct standards and ethical responsibility

The possible environmental safety risks caused by the application of nanomaterials could be reduced to the allowable range by constituting the nanoproduct standards, including discarded electronic devices, household appliances, plastic products, rubber products, daily cosmetics and antibacterial materials. Particularly, chemical products, such as pesticides, fertilizers and insecticides, are closely related to agriculture. Inorganic nanoparticles, organic modified nanoparticles and complexes of nanoscale organic metal ions are directly exposed to air, water and soil, which will bring risks to environmental safety. If not dealt with in time, the long-term cumulative effect will not only bring serious impact on the ecological environment, but also directly affect human health through the biosphere and food chain. Therefore, it is very important to establish nanoproduct standards to evaluate the environmental safety influenced by nano-modified products.

In addition, educating and publicizing the concept of ethical responsibility of science and technology, so as to improve the sense of responsibility of researchers. Stop scientific and technological activities that may cause harm or risk to the public. We should fully assess the social consequences of an upcoming scientific research result, and consider the negative impact of the results that will affect human health and ecological environments.

Conclusions

In a word, nanomaterials have a leap-forward development in recent decades, showing a wide range of applications in many fields. They are able to offer new properties to materials. However, there are also many challenges due to the toxicity and pollution. Increasing the production of nanomaterials, the potential for their release in the environment and subsequent effects on ecosystem health is becoming an increasing concern that needs to be addressed. We should strengthen the research on the nanotoxicology mechanism and safety assessment techniques. In the future, understanding the relationship between biosafety and nanomaterial is essential for the sustainable development.

Acknowledgements

This work was financially supported by the Soft Science and Technology Research Project of Zhejiang Province (No. 2019C35009).

References

1. B. Fonseca-Santos, M.P.D. Gremiao and M. Chorilli, Nanotechnology-based drug delivery systems for the treatment of Alzheimer’s disease, *Int. J. Nanomed.*, **10**, 4981(2015).
2. U. Atzmony, Z. Livne, R.D. Mcmichael and L.H. Bennett, Magnetic viscosity investigations of nanograin iron powder, *J. Appl. Phys.*, **79**,5456 (1996).
3. C.A. Charitidis, P. Georgiou, M.A. Koklioti, A.F. Trompeta and V. Markakis, Manufacturing nanomaterials: from research to industry, *Manufacturing Rev.*, 2014, **11**, 1(2014).
4. A.G. Chmielewski, D.K. Chmielewska, J. Michalik and M.H. Sampa, Prospects and challenges in application of gamma, electron and ion beams in processing of nanomaterials, *Nucl. Instrum. Methods Phys. Res. Sect. B-Beam Interact. Mater. Atoms*, **265**, 339(2007).
5. S. Dimov, E. Brousseau, R. Minev and S. Bigot, Micro- and nano-manufacturing: Challenges and opportunities, *Proc. Inst. Mech. Eng. Part C-J. Eng. Mech. Eng. Sci.*, **226**, 3 (2012).
6. M. Srikanth and J.A. Kessler, Nanotechnology—novel therapeutics for CNS disorders, *Nat. Rev. Neurol.*, **8**, 307 (2012).
7. M. Vijayan and P.H. Reddy, Stroke, vascular dementia, and Alzheimer’s disease: molecular links, *J. Alzheimer Dis.*, **54**, 427 (2016).
8. W.X. Zhang, Nanoscale iron particles for environmental remediation: an overview, *J. Nanopart. Res.*, **5**: 323 (2003).
9. H.A.E. Benson, V. Sarveiya, S. Risk and M.S. Roberts, Influence of anatomical site and topical formulation on skin penetration of sunscreens, *Ther. Clin. Risk. Manag.*, **1**, 209 (2005).
10. D. Astruc, E. Boisselier and C. Ornelas, Dendrimers designed for functions: from physical, photophysical, and supramolecular properties to applications in sensing, catalysis, molecular electronics, photonics, and nanomedicine, *Chemical Reviews*, **110**, 1857 (2010).
11 J.W. Rasmussen, E. Martinez, P. Louka and D.G. Wingettt, Zinc oxide nanoparticles for selective destruction of tumor cells and potential for drug delivery applications, *Expert Opin. Drug Deliv.*, **7**, 1063 (2010).
12 X.F. Huang, Y.C. Pang, Y.L. Liu, Y. Zhou, Z.K. Wang and Q.L. Hu, Green synthesis of silver nanoparticles with high antimicrobial activity and low cytotoxicity using catechol-conjugated chitosan, *RSC Advances*, **6**, 64357 (2016).
13 X.F. Huang, X.J. Bao, Y.L. Liu, Z.K. Wang and Q.L. Hu, Catechol-functional chitosan/silver nanoparticle composite as a highly effective antibacterial agent with species-specific mechanisms, *Scientific Reports*, **7**, 1860 (2017).

14 X.F. Huang, X.J. Bao, Z.K. Wang and Q.L. Hu, Novel silver-loaded chitosan composite sponge with sustained silver release as a long-lasting antimicrobial dressin, *RSC Advances*, **7**: 34655 (2017).

15 M.R. Azarpazhooh, M.M. Etemadi, G.A. Donnan, N. Mokhber, M.R. Majdi, M. Ghayour-Mobarhan, K. Ghandehary, M.T. Farzadfard, R. Kiani, M. Panahandeh and A.G. Thrift, Excessive incidence of stroke in iran evidence from the mashhad stroke incidence study (MSIS), a population-based study of stroke in the middle east, *Stroke*, **41**, e3 (2010).

16 N. Yang, X.P. Chen, T.L. Ren, P. Zhang and D.G. Yang, Carbon nanotube based biosensors, *Sensors and Actuators B: Chemical*, **207**, 690 (2015).

17 R. Siegel, J.M. Ma, Z.H. Zou and A. Jemal, Cancer statistics, 2014, *CA-Cancer J. Clin.*, **64**, 9 (2014).

11. S.E. Jin, H.E. Jin and S.S. Hong, Targeted delivery system of nanobiomaterials in anticancer therapy: from cells to clinics, *Biomed. Res. Int.*, 814208 (2014).

12. T. Singh, V. Kaur, M. Kumar, P. Kaur, R.S.R. Murthy and R.K. Rawal, The critical role of bisphosphonates to target bone cancer metastasis: an overview, *J. Drug Target.*, **23**, 1 (2014).

13. C.L., Ventola, Progress in nanomedicine: approved and investigational nanodrugs, *P&T*, **42**, 742 (2017).

14. R. Shankar, A. Samykutty, C. Riggin, S. Kannan, U. Wenzel, and R. Kolhatkar, Cathepsin B degradablestar-shaped peptidic macromolecules for delivery of 2-methoxyestradiol, *Mol. Pharma.*, **10**, 3776 (2013).

15. D. Peer, J.M. Karp, S. Hong, O.C. FaroKHzad, R. Margalit and R. Langer, Nanocarriers as an emerging platform for cancer therapy, *Nat. Nanotechnol.*, **2**, 751 (2007).

16. J.J. Chen, J.X. Ding, Y.C. Wang, J.J. Cheng, S.X. Ji, X.L. Zhuang and X.S. Chen, Sequentially Responsive Shell-Stacked Nanoparticles for Deep Penetration into Solid Tumors, *Advanced Materials*, **29**, 1701170 (2017).

17. J.H. Xing, P. Tao, Z.M. Wu, C.Y. Xing, X.P. Liao and S.X. Nie, Nanocellulose-graphene composites: A promising nanomaterial for flexible supercapacitors, *Carbohydrate Polymers*, **207**, 447 (2019).

18. G. Lalwani, A.M. Henslee, B. Farshid, L.J. Lin, F.K. Kasper, Y.X. Qin, A.G. Mikos and B. Sitharaman, Two-Dimensional Nanostructure-Reinforced Biodegradable Polymeric Nanocomposites for Bone Tissue Engineering, *Biomacromolecules*, **14**, 900 (2013).

19. Z.K. Wang, H. Zhao, L. Fan, J. Lin, P.Y. Zhuang, W.Z. Yuan, Q.L. Hu, J.Z. Sun and B.Z. Tang, Chitosan rods reinforced by aligned multiwalled carbon nanotubes via magnetic-field-assistant in-situ precipitation, *Carbohydrate Polymers*, **84**, 1126 (2011).

20. M. Szlachta and P. Wojtowicz, Adsorption of methylene blue and Congo red from aqueous solution by activated carbon and carbon nanotubes, *Water Science & Technology*, **68**, 2240 (2013).

21. M.J. Gao, PhD thesis, Construction of functional magnetic nanospheres and removal of simulated dyeing wastewater, *Yanan University*, (2011).

22. G. C. Delgado-Ramos, Nanotechnology in Mexico: global trends and national implications for policy and regulatory issues, *Technology in Society*, **37**, 4 (2014).

23. R. Singla, C. Sharma, A.K. Shukla and A. Acharya, Toxicity Concerns of Therapeutic Nanomaterials, *J. Nanosci. Nanotechnol.*, **19**, 1889 (2019).

24. A. Kumari, R. Singla, A. Guliani, S.K. Yadav, Nanoencapsulation for drug delivery, *Excli Journal*, **13**, 265 (2014).

25. M. Neagu, Z. Piperigkou, K. Karamanou, A.B. Engin, A.O. Docea, C. Constantin, C. Negrei, D. Nikitovic and A. Tsatsakis, Protein bio‐corona: critical issue in immune nanotoxicology, *Arch. Toxicol.*, **91**, 1031 (2017).

26. A.A. Shvedova, V.E. Kagan and B. Fadeel, Close encounters of the small kind: adverse effects of man-made materials interfacing with the nano-cosmos of biological systems, *Annu. Rev. Pharmacol. Toxicol.*, 2010, **50**, 63 (2010).

27. B. Wang, W.Y. Feng, M. Wang, T.C. Wang, Y.Q. Gu, M.T. Zhu, H. Ouyang, J.W. Shi, F. Zhang, Y.L. Zhao, Z.F. Chai, H.F. Wang and J. Wang, Acute toxicological impact of nano- and submicro-scaled zinc oxide powder on healthy adult mice, *J. Nanopart. Res.*, **10**, 263 (2008).

28. Z. Chen, H.A. Meng, G.M. Xing, C.Y. Chen, Y.L. Zhao, G.A. Jia, T.C. Wang, H. Yuan, C. Ye, F. Zhao, Z.F. Chai, C.F. Zhu, X.H. Fang, B.C. Ma and L.J. Wan, Acute toxicological effects of copper nanoparticles in vivo, *Toxicol. Lett.*, **163**, 109 (2006).

29. M.A. Zoroddu, S. Medici, A. Ledda, V.M. Nurchi, J.I. Lachowicz and M. Peana, Toxicity of nanoparticles, *Curr. Med. Chem.*, **21**, 3837 (2014).

30. A. Shvedova, Exposure to carbon nanotube material: assessment of nanotube cytotoxicity

using human keratinocyte cells, *J. Toxicol. Environ. Health A*, **66**, 1909 (2003).

31. M. Sajid, M. Ilyas, C. Basheer, M. Tariq, M. Daud, N. Baig and F. Shehzad, Impact of nanoparticles on human and environment: review of toxicity factors, exposures, control strategies, and future prospects, *Environ. Sci. Pollut. Res.*, **22**, 4122 (2015).
32. S. Bakand, A. Hayes and F. Dechsakulthorn, Nanoparticles: a review of particle toxicology following inhalation exposure, *Inhal. Toxicol.*, **24**, 125 (2012).
33. P.J.A. Borm and W. Kreyling, Toxicological Hazards of Inhaled Nanoparticles - Potential Implications for Drug Delivery, *J. Nanosci. Nanotechnol*., **4**, 521 (2004).
34. F. Zhao, Y. Zhao, Y. Liu, X.L. Chang and Y.L. Zhao, Cellular uptake, intracellular trafficking, and cytotoxicity of nanomaterials, *Small*, **7**, 1322 (2011).
35. A. Nel, T. Xia, L. Madler and N. Li, Toxic Potential of Materials at the Nanolevel, *Science*, **311**, 622 (2006).
36. R. Coradeghini, S. Gioria, C.P. Garcia, P. Nativo, F. Franchini, D. Gilliland, J. Ponti and F. Rossi, Size-dependent toxicity and cell interaction mechanisms of gold nanoparticles on mouse fibroblasts, *Toxicol. Lett.*, **217**, 205 (2013).
37. A.M. El Badawy, R.G. Silva, B. Morris, K.G. Scheckel, M.T. Suidan and T.M. Tolaymat, Surface Charge-Dependent Toxicity of Silver Nanoparticles, *Environ. Sci. Technol.*, **45**, 283 (2010).
38. C. Ispas, D. Andreescu, A. Patel, D.V. Goia, S. Andreescu and K.N. Wallace, Toxicity and Developmental Defects of Different Sizes and Shape Nickel Nanoparticles in Zebrafish, *Environ. Sci. Technol*., 2009, **43**, 6349 (2009).
39. F. Peng, M.I. Setyawati, J.K. Tee, X.G. Ding, J.P. Wang, M.E. Nga, H.K. Ho and D.T. Leong, Nanoparticles promote in vivo breast cancer cell intravasation and extravasation by inducing endothelial leakiness, *Nat. Nanotech*., **14**, 279 (2019).
40. M.R. Wiesner, G.V. Lowry, P. Alvarez, D. Dionysiou and P. Biswas, Assessing the risks of manufactured nanomaterials, *Environ. Sci. Technol.*, **40**, 4336 (2006).
41. E. Oberdörster, Manufactured Nanomaterials (Fullerenes, C60) Induce Oxidative Stress in the Brain of Juvenile Largemouth Bass, *Environmental Health Perspectives*, **112**, 1058 (2004).
42. E. Fernandez-Rosas, G. Vilar, G. Janer, D. Gonzalez-Galvez, V. Puntes, V. Jamier, L. Aubouy and S. Vazquez-Campos, Influence of Nanomaterial Compatibilization Strategies on Polyamide Nanocomposites Properties and Nanomaterial Release during the Use Phase, *Environ. Sci. Technol.*, **50**, 2584 (2016).
43. R. McGinn, Ethical responsibilities of nanotechnology researchers:a short guide, *Nanoethics*, **4**, 1 (2010).
44. S. Camporesi, The ethics of the new eugenics, *J. Bioethical Inq.*, **12**, 353 (2015).
45. H.E. Gendelman, V. Anantharam, T. Bronich, S. Ghaisas, H.J. Jin, A.G. Kanthasamy, X.M. Liu, J. McMillan, R.L. Mosley, B. Narasimhan and S.K. Mallapragada, Nanoneuromedicines for degenerative, inflammatory, and infectious nervous system diseases, *Nanomed. Nanotechnol. Biol. Med*., **11**, 751 (2015).
46. N.O. Fischer, D.R. Weilhammer, A. Dunkle, C. Thomas, M. Hwang, M. Corzett, C. Lychak, W. Mayer, S. Urbin, N. Collette, J.C. Chang, G.G. Loots, A. Rasley and C.D. Blanchette, Evaluation of nanolipoprotein particles (NLPs) as an in vivo delivery platform, *PLoS One*, **9**, e93342 (2014).
47. A.C. Anselmo and S. Mitragotri, Nanoparticles in the clinic, *Bioengineering & Translational Medicine*, **1**, 10 (2016).
48. U. Bulbake, S. Doppalapudi, N. Kommineni and W. Khan, Liposomal Formulations in Clinical Use: An Updated Review, *Pharmaceutics*, **9**, UNSP12 (2017).
49. D. Bobo, K.J. Robinson, J. Islam, K.J. Thurecht and S.R. Corrie, Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date, *Pharmaceutical Research*, **33**, 2373 (2016).
50. S. Tran, P.J. DeGiovanni, B. Piel and P. Rai, Cancer nanomedicine: a review of recent success in drug delivery, *Clinical & Translational Medicine*, **6**, 44 (2017).
51. T.J. Anchordoquy, Y. Barenholz, D. Boraschi, M. Chorny, P. Decuzzi, M.A. Dobrovolskaia, Z.S. Farhangrazi, D. Farrell, A. Gabizon, H. Ghandehari, B. Godin, N.M. La-Beck, J. Ljubimova, S.M. Moghimi, L. Pagliaro, J.H. Park, D. Peer, E. Ruoslahti, N.J. Serkova and D. Simberg, Mechanisms and Barriers in Cancer Nanomedicine: Adressing Challenges, Looking for Solutions, *ACS Nano*, **11**, 12 (2017).