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# Toxicity of Nanomaterials-Physicochemical Effects

**Rahi A[1], Sattarahmady N[1,2,3] and Heli H[1,2]***

[1]Department of Nanomedicine, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran

[2]Nanomedicine and Nanobiology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[3]Department of Medical Physics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

***Corresponding author:** Heli H, Department of Nanomedicine, Nanomedicine and Nanobiology Research Center, Shiraz University of Medical Science, Shiraz, Iran, Tel: +98 711 23 49 332; Fax: +98 711 23 49 332; Email: hheli7@yahoo.com, heli@sums.ac.ir

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**Abstract**

Nanomaterials are the structures with at least one dimension of <100 nm. Recently, development in nanotechnology has led to use of nanomaterials in many different fields. On other hand, increasing in the use of nanomaterials has led to release of these materials to the environment. Therefore, before employing of these materials in biological and environmental and living systems, they should evaluate in terms of biocompatibility and distribution. Although the toxic effects of nanomaterials on living organisms, human health and the environment have been studied by some researchers, however, there are too much uncertainty about the effects and mechanisms of toxicity of nanomaterials. Therefore, understanding the toxicity effects of nanomaterials is highly desirable. Cellular uptake mechanisms and dispersion of nanomaterials in biological environments depend on their physicochemical properties. Therefore, knowledge the unique characteristics of nanomaterials and the interactions of nanomaterials with biological systems, are important criteria for the safe use of nanomaterials. Properties of nanomaterials such as size, shape, aspect ratio, density, and surface and structural defects and dissolving rate are the main cause of cytotoxicity and side effects of these materials in the body. Exposure to nanomaterials may be cause a range of acute and chronic effects, including inflammation, exacerbation of asthma, metal fume fever, fibrosis, chronic inflammatory diseases and cancer.

**Keywords:** Nanotechnology; Nanomaterials; Safety; Toxicity

## Introduction

Nanomaterials have been greatly interested due to their novel properties arising from their high effective surface area and high reactivity. Moreover, with rapid developments in nanotechnology, nanomaterials have been synthesized in a wide variety of shapes and sizes, and are used in fabrication of various industrial and medical products. Typical applications of nanomaterials are in cancer treatment [1,2], drug design [3-5], drug and gene delivery [6,7], antibacterial and self-cleaning coatings [8-10], biological tags [11,12], identification of proteins [13-15], tissue engineering [16,17], hyperthermia [18], sensors [19-23], biosensors [24-28], and coatings [29,30]. However, recent studies have confirmed negative effects of these materials on the growth and survival of organisms; these lead to a range of acute and chronic effects [31-33]. Nanomaterials can transport in the body and the environment, while have a high surface-to-volume ratio, and can affect the organisms and the environment in a negative way. Therefore, the toxicity assessment of these materials is of a great importance. Beside, due to their small size, nanomaterials are absorbed by solid, liquid, or gas surfaces in heterogeneous environments. Therefore, in order to study their toxicity risks, we should pay special attentions to the nanomaterials floating in liquids, or those dispersed in gases. Since nanotechnology is a rather new technology, little information is available on the epidemiological effects of nanomaterials. In the past few years, hundreds of tons of nanomaterials have entered into the environment without having enough knowledge on their potential reactions with biological systems [34]. For instance, in England about 2000 die annually due to exposure to asbestos and the consequent asbestosis [35].

Recently, the number of articles published on nanomaterials has increased dramatically. But most of these studies focus on the synthesis and application of the nanomaterials and less than 1% of the studies deal with their biological effects. While the toxicity of many materials is well recognized, it is not yet know what concentration or quantities of them can causes new toxic properties at the nanoscale. Lack of adequate information about the nanomaterials properties and their toxic features, prevents the safe design of nanomaterials.

Based on the studies conducted on the biological and toxic effects of nanomaterials, there is a meaningful relationship between human exposure to nanomaterials and the occurrence of lung diseases, cardiovascular diseases, and mortality [36]. However, information on primary mechanisms which lead to toxicity of nanomaterials is lacking. For instance, nanomaterials penetration to different intracellular and extracellular parts, such as cytoplasm of mesothelial and epithelial cells of lung; it was verified by electron microscopy [37]. Therefore, identifying the potential risks of new improvements using nanomaterials is essential in order to avoid human injuries.

During the toxicology of nanomaterials, interactions between nanomaterials and biological systems are investigated to gain a logical relationship between the physicochemical properties of nanomaterials and biological responses [38]. Biological activity and toxicity of nanomaterials depends on their physicochemical properties to a great extent. In order to understand the biological activity and toxic effects of nanomaterials, studies on the certain physiochemical properties (such as size, shape, aspect ratio, density, structure and surface defects, and dissolution rate) are recommended. But the great variety of nanomaterials and their different properties make comparison between findings of the studies difficult. In spite of the vast number of studies in recent years, there is still a great gap in




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**Table 1:** Possible nanomaterials effects as the basis for pathophysiology and toxicity.

| Experimental nanomaterials effects | Possible pathophysiological outcomes |
|---|---|
| ROS generation | Protein, DNA and membrane injury, oxidative stress |
| DNA damage | Mutagenesis, metaplasia, carcinogenesis |
| Oxidative stress | Phase II enzyme induction, inflammation, mitochondrial perturbation |
| Mitochondrial perturbation | Inner membrane damage, permeability transition (PT), pore opening, energy failure, apoptosis, apo-necrosis, cytotoxicity |
| Inflammation | Tissue infiltration with inflammatory cells, fibrosis, granulomas, atherogenesis, acute phase protein expression (e.g., C-reactive protein) |
| Uptake by reticuloendothelial system | Asymptomatic sequestration and storage in liver, spleen, lymph nodes, possible organ enlargement and dysfunction |
| Protein denaturation, degradation | Loss of enzyme activity, auto-antigenicity |
| Nuclear uptake | DNA damage, nucleoprotein clumping, autoantigens |
| Perturbation of phagocytic function "particle overload," mediator release | Chronic inflammation, fibrosis, granulomas, interference in clearance of infectious agent |
| Endothelial dysfunction, effects on blood Clotting | Atherogenesis, thrombosis, stroke, myocardial infarction |
| Altered cell cycle regulation | Proliferation, cell cycle arrest, senescence |

toxicology of nanomaterials. Toxicology of nanomaterials has caused complications in nanotechnology so that researchers have realized that methods used for studying the toxic effects of nanomaterials are not always useful, because nanomaterials show different behavior and can have negative impact in toxicity assessments. Besides having unique physical and chemical properties, nanomaterials represent different responses in biological systems [34,35].

During recent years, there has been an increase in the number of studies on toxicology of nanomaterials. Among these studies, those on the mechanism of interaction of cells with nanomaterials show that the cells can easily bind to nanomaterials via active intracellular mechanisms. These mechanisms are hard to recognize because of these materials indicating different behaviors. For instance, differences in the surface coating, agglomeration rate, density, charge, and size of nanomaterials make their categorization in biological systems and identifying their potential risks difficult. Toxicological studies on animals indicate that respiratory system›s exposure to nanomaterials causes more harmful inflammatory responses compared to bigger particles having similar chemical composition and concentration [39]. Nowadays, people working in factories or nanomaterials research centers have the most exposure to these materials. Nanomaterials have commercial uses which in turn endanger the people. Therefore, knowledge about the mechanisms of toxicity inhibiting induced by nanomaterials as a health risk factor is of a great importance.

## Toxicity of Nanomaterials

### Biological toxicity

Nanomaterials can enter the body via intravenous, dermal, subcutaneous, respiratory, intraperitoneal and oral ways. After entrance to the body, they may distribute in different organs. The absorption of nanomaterials may happen via first interaction with biological components (cells and proteins). Nanomaterials which have entered the cells can stay there for a long time or leave the cells and move toward another cells and organs, or even leave the body without being absorbed [40]. Nanomaterials interactions with biological systems can cause toxic effects including allergies [38], fibrosis [41], metal fume fever [32], deposition in organs (causing defects and insufficiency in organs) [41], inflammation [4], cytotoxicity [41], tissue damage [42], producing reactive oxygen species [43] and DNA damage [42]. Potential damages caused by nanomaterials are summarized in Table 1.

Most intracellular and in vivo toxicities of nanomaterials are due to the production of large amounts of reactive oxygen species [41,44,45]. One of the common mechanisms is the induction of oxidative stress caused by dissolution of iron-based nanomaterials which catalyzes the production of reactive oxygen species and leads to the production of free radicals (OH and OOH) through fenton reaction. Some stable nanomaterials cannot increase reactive oxygen species spontaneously, but stimulate the production of them in biological conditions which is because of these materials ability in targeting the mitochondria. Specific amounts of the produced reactive oxygen species play an important role in combining multiple cellular events which include message transmission, gene expression, and regulation of proteins oxidation and reduction [46,47]. Due to the lipid peroxidation, proteins modifications, DNA fragmentation, and problem in gene cloning, reactive oxygen species may lead to cellular damage, cancer, renal diseases, nervous system destruction, and cardiovascular diseases [48]. Reactive oxygen species can take electrons from the lipids in the cell membranes and lead to the reduction of physiological function of cells, and finally to the cells death. For instance, the oxidative stress caused by titanium dioxide nanoparticles results in inflammatory responses like the increase of cells with pleomorphic nuclei and impairment of macrophage phagocytosis in rodents [49]. The toxicity caused by reactive oxygen species can negatively affect the central nervous system which is due to the increased peroxidation of unsaturated fatty acids [50]. Reactive oxygen species also cause cardiovascular disorders like artery stenosis, blood pressure and artery restenosis after angioplasty [51]. Induction of oxidative stress by nanomaterials has effects on cellular signaling. At lower stages and by using NRF2 (nuclear factor erythroid 2-related factor-2) transcription factor, oxidative stress increases transcription of defense genes. High levels of oxidative stress activate inflammatory signals via NFκB protein complex and at very high levels, activate apoptosis and necrosis pathways.

Oxidative stress may lead to DNA double-strand break which is common in the mortality caused by oxidative damages to DNA. The increase of reactive oxygen species may also damage mitochondrial DNA [52]. Damage to the mitochondrial DNA is a factor in causing several clinical syndromes such as Duchenne muscular dystrophy, ataxia, stroke, defects in the electrical conduction of the heart, and increased cerebrospinal fluid protein [53].

### Environmental toxicity

Research activities and working with nanomaterials cause transfer of some of these materials to the environment which finally leads to a kind of pollution known as nanomaterials related environmental pollution. So far, not many studies are conducted on the transfer mechanism and biodegradation of nanomaterials. But the presence of nanomaterials affects the ecosystem. In a study, C60 fullerene toxicity was measured in two aquatic species by measuring lipid peroxidation in the brain [54]. Lipid peroxidation had a significant increase in the gills and led to an increased gene expression associated with inflammatory reactions and metabolism. Not many studies have investigated the influence of nanomaterials on plants and microbes. Prior to careless release of large amounts of nanomaterials into the environment, their solubility and degradability in soil and water should be investigated and basic information on their safety, toxicity, and compatibility of nanomaterials with soil and aquatics be acquired.

### Reasons of toxicity

Toxicity of nanomaterials may occur in a cellular or system level. Uncontrolled toxicity can be fatal at any levels. Nanomaterials toxicity is relevant to the following features:

-Size and surface to volume ratio (factors increasing nanomaterials reactivity with other molecules).

-Chemical composition (reactivity factor) Surface charge (electrostatic interactions factor).

-Hydrophobicity and the existence of lipophilic groups.

-Nanomaterials connecting to biomolecules (the factor inhibiting enzyme activities in a competitive or non-competitive way).

-The large surface of nanomaterials.

-The presence of metallic species or toxic components in nanomaterials.

## Nanomaterial Exposure

Exposure to nanomaterials could be through an occupational exposure, consumer exposure, and/or environmental exposure. Occupational exposure includes people being directly in contact with nanomaterials in factories or during research projects. Consumer exposure includes people who use products made of nanomaterials (e.g. sunscreen creams or other cosmetics). Evaluating the amount and type of nanomaterials used in these products is impossible for users, because precise information is not usually presented to the public. Studies show that zinc oxide and titania particles in sunscreen creams are active photocatalysts which can produce free radicals under light and damage biomolecules [55]. With over time and entry of nanomaterials to the ecosystem, concentration of these materials increases in the ecosystem. If nanomaterials are used extensively, disregarding their side-effects, the major way of exposure to them might be via soil and underground waters.

## Behavior of Nanomaterials in the Body

After intravenous injection of nanomaterials, their surface is rapidly covered with the plasma proteins and a protein corona is formed. Finally after intravenous injection, nanomaterials can be found in the colon, lung, bone marrow, liver, spleen, and lymphatic nodes. Distribution of these materials depends on clearance rate from the circulation and being trapped in liver and spleen macrophages. Clearance and opsonization are processes which make macrophages eat foreign substances more effectively. The occurrence of such processes depends on the size and surface characteristics of nanomaterials. After intraperitoneal injection, nanomaterials can enter the uterus by passing through peritoneum cavity or placental membrane, which may lead to the fetal cerebral insufficiency or even its death.

After oral administration, nanomaterials are distributed in the kidneys, liver, spleen, lungs, brain and gastrointestinal tract. Nanomaterials may pass through the whole gastrointestinal tract and be excreted via feces or be absorbed by the gastrointestinal mucosa and then enter the bold and finally be excreted via urine through renal filtration [56].

If inhaled, nanomaterials may be distributed in the lungs, heart, liver, spleen and brain. Nanomaterials are trapped in alveoli during phagocytosis. The average half-life of nanomaterials is about 700 days in human respiratory system. After inhalation of nanomaterials, they deposit in different areas of the lung. Transport and deposition of nanomaterials in the respiratory tract are controlled by three main factors which are: anatomy of the respiratory tract, air flow pattern and aerodynamic characteristics of the particles. The way nanoparticles being deposited in the respiratory tract also depends on the particles، size. By inhaling aerosols, nanomaterials enter the respiratory tract and tend to move forward. Bifurcation or a sudden change in the airway may lead to the particles adhering to the surface of the respiratory tract. Particles deposit on different areas of the lung depending on their size. For example, larger particles (5-30 μ m) usually are deposited in the nasopharyngeal region by the inertial impaction mechanism. Smaller particles (1-5 μm), which are not absorbed in the nasopharyngeal region, are trapped in tracheobronchial region, mainly due to sedimentation; this may be further absorbed or removed by mucociliary clearance. Finally, the remaining submicron particles (<1 μm) and nanoparticles (<100 nm) with the smallest size distribution will penetrate deeply into the alveolar region where removal mechanisms maybe insufficient [57-59]. More time is needed for deposited particles in the deeper parts to get out of lungs. So the risk of their harmful effects increases which is due to the reactions taking place between the particles and cells/tissues [60]. Alveolar macrophage phagocytosis is more effective in eliminating smaller inhaled particles compared to larger ones [61-63]. Nanomaterials can enter alveolar regions of the lungs, enter the blood circulation in the exchange between the alveolar epithelium and blood flow and easily transfer to other organs. On the other hand, the insoluble particles may remain in the lungs for a long time causing damage and biological responses [64]. Penetration is one of the deposition mechanisms for particles smaller than 0.5 μ m in alveoli

which is due to the random motion of airborne particles and collision with air molecules. During the short pause between the inspiratory and expiratory phases, submicron and nanoscale particles with higher Brownian motions may be captured by diffusion. Diffusion is an important deposition mechanism for extremely small particles in the alveoli, where the air flow is very low. Diffusion plays a predominant role in deposition of nanoparticles deeper into the pulmonary region due to displacement, while they collide with air molecules.

When nanomaterials enter the body in other ways, they should pass physiological barriers such as the skin, gastrointestinal tract and lungs before entering the blood. In the meantime, some other molecules may join them [65]. Absorption of biomolecules to the surface of nanomaterials changes their biological behavior and results in different cellular responses [66].

## Metabolism

Polymer nanostructures and super paramagnetic nanostructures of iron oxide decompose in tissues, while quantum dots, fullerenes and silica nanoparticles are not like that [67-69]. Enzymes do not have much chance in affecting the metabolism of inert nanoparticles (e.g. silver and gold nanoparticles) [70]. The results of one study indicate that biological resistance of carbon nanotubes decreases by neutrophil myeloperoxidase [71]. Moreover, coatings and surface functional groups could be metabolized. For example, the quantum dots coated with a protein can be metabolized by proteases [72].

Nanomaterials can be metabolized via metabolism pathways phase I and II in liver. The activity of phase I includes alteration or formation of a new functional group by oxidation and reduction or hydrolysis reactions to increase the reactivity or polarity. Phase II includes reactions in which the binding of an endogenous compound (such as glucuronic acid or glycine) is performed to reassure solubility in water and decreased chemical reactivity. Metabolites of such processes have a high polarity and compared to the main molecules, they are rapidly excreted via kidneys through urine or through the bile excreted from the liver.

## Elimination

Eliminating nanomaterials from the body can occur through different pathways including vessels, mammary glands, saliva, respiration, urine, feces, and semen. Intraperitoneal injection of single-walled carbon nanotubes which are functionalized with hydroxyl groups leads to their accumulation in liver and kidneys and finally their excretion within 18 days via urine [73]. However, single-walled carbon nanotubes which are functionalized with ammonium, which intravenously injected, do not indicate hepatic uptake and are rapidly excreted by the kidneys [68]. Once quantum dots are injected to the body, they stimulate astrocytes› activity in the brain [74].

## Effect of Physicochemical Properties of Nanomaterials on Toxicity

### Size

Studies show that a materials› size affects its toxicity. There is an inverse relationship between size and toxicity, but there are contradictory results as well. Smaller particles have a higher surface to volume ratio which can explain this inverse relationship between size and toxicity [75]. For most nanomaterials, a critical size is defined as 30 nm and in sizes smaller than this, surface energy increases and the possibility of surface reactions increases which may lead to thermodynamic instability of the molecule and increase toxicity. The results of one study indicate that nanoparticles which have smaller sizes stimulate the production of reactive oxygen species, and compared to the bigger particles, cause more severe pulmonary inflammation [76]. Based on another study, copper oxide nanoparticles (28 nm) have a greater ability in fragmenting single-stranded DNA and apoptosis in A549 (adenocarcinomic human alveolar basal epithelial) cells, compared to the similar micron-particles (2.9 μ m) [77]. However, nanoparticles with a certain size may have more severe toxicity than smaller or larger particles. For instance, gold nanoparticles of 1.4 nm cause more severe toxicity in connective tissue, fibroblasts, epithelial cells, macrophages and melanoma cells compared to the smaller (0.8 nm and 1.2 nm) or larger (1.8 nm and 15 nm) particles. Also the mechanisms of the nanoparticles toxicity with different sizes are different. For example, 1.4-nm particles may cause cell necrosis and 1.2-nm particles may cause cell apoptosis. It is assumed that the high toxicity of 1.4-nm gold nanoparticles is due to their ability to enter the major groove of DNA, and cause fragmentation in DNA structure [78]. The ability of nanoparticles to move in different parts of the body depends on their size. After intravenous injection of 200-nm silica nanoparticles to the mice and 100-nm gold nanoparticles to the rats, these nanoparticles were distributed in large accumulations in the spleen and liver macrophages [79,80]. However, smaller nanoparticles were easily excreted through urine. In certain cases, toxicity increased with increasing size [81,82]. Erythrocyte membrane in human shows a strange response to nanoparticles, so that hemolytic activity against erythrocytes increases in exposed to larger silica nanoparticles. Although the accurate hemolytic mechanism is not well recognized, it is believed that silanol groups in the nanoparticles surface show an electrostatic reaction with ammonium groups on the red cell membrane. Therefore, larger particles adhere to a large surface of the cell membrane and deform or break the erythrocyte membrane [82].

Size plays a key role in physiological responses, distribution and clearance of nanomaterials [83,84]. The lung is an effective barrier against absorption and distribution of nanomaterials. Inside the human respiratory tract, inhaled particles of different sizes are placed on different areas. For instance, particles which are smaller than 100 nm may remain on any parts of the respiratory tract. However, particles which are smaller than 10 nm remain on the tracheobronchial region, and those between 10-20 nm remain the alveoli. Also, particles which are smaller than 20 nm may remain the nasopharyngeal region [85,86]. In general, the risk of exposure to nanomaterials could be due to the relationship between size and their ability to enter biological systems [87], or the change of the protein structure via protein-nanomaterial complex formation and increased protein exhaustion [88,89].

### Shape

Shape is one of the important parameters in which there are not much conclusive evidences with regard to its relevance with toxicity. In recent years, designing nanoparticles has attracted much attention and resulted in production of particles with varying shapes. Some of these shapes are sphere, rod, wire, sheet, etc. Also, special geometrical shapes such as squares and cubes can be produced. How shape and geometry affects absorption is not yet known. However,

recently a few models are presented which describe the activity of nanoparticles cellular uptake. In a study investigating the influence of shape and size of gold nanoparticles on the cellular uptake in mammals, spherical gold nanoparticles showed a 375-500% higher cellular uptake, compared to rod-shaped gold nanoparticles [90]. One of the mechanisms related to nanoparticles shape is their ability in causing direct physical damage. For instance, in theory it is easy to imagine that needle shaped nanocrystals can lead to cellular and tissue damage. For example, uric acid crystals cause severe damage and inflammation in tissues. Also, graphene oxide nanosheets cause toxicity in human cells which is due to the physical damages occurred by direct contact between these sheets and the cell membranes [91]. Another mechanism provided to explain the influence of shape on toxicity is based on the relationship between shape and toxicity via harmful effects on endocytosis or clearance by macrophages. For example, a particle's shape can affect the membrane warping during endocytosis or phagocytosis [92]. It seems that endocytosis of spherical nanomaterials is easier and faster than that of rod- or wire-shaped nanomaterials [93]. Sheet-like, cylindrical and non-spherical nanomaterials are less absorbed by macrophages, compared to spherical nanomaterials. Therefore, non-spherical particles are more prone to flow through the capillaries and stick to the walls of blood vessels which has other biological consequences [94]. Different toxic behavior is observed in titanium dioxide nanoparticles having varied crystal structures. For instance, rutile nanoparticles can cause oxidative damages in DNA, lipid peroxidation and form micronuclei. But compared to rutile, nanoparticles of anatase titanium dioxide can produce more reactive oxygen species [95,96].

### Aspect ratio

Aspect ratio is the ratio of length to width (or diameter) of a particle. Carbon nanotubes are an example of nanomaterials having a high aspect ratio. It has been shown that GHO (Chinese hamster ovary) cells uptake spherical nanoparticles much more than rod-shaped nanoparticles [97], or cellular uptake of rod-shaped gold nanoparticles is more than spherical nanoparticles [90]. Moreover, rod structure with a higher aspect ratio (1:5) compared to those with a lower aspect ratio (1:3) show a lower uptake [90]. In another study, silica nanoparticles having a 70-nm diameter and similar chemical composition and surface charges but different aspect ratios (5 and 1.5) were used [98]. After an intravenous injection to the mice, the effects of nanoparticles shape on the biological distribution, clearance and biocompatibility were investigated. The results indicated that particles having a lower aspect ratio were easily trapped in the liver, while particles with a higher aspect ratio were particularly found in the spleen. Nanoparticles with a higher aspect ratio remained longer in the blood flow and were excreted through urine or feces with a slower pace, compared to nanoparticles having a smaller aspect ratio [98]. Another research indicated that multi-walled carbon nanotubes having a small aspect ratio (length of over 220 nm and a diameter of 25 nm) were easily surrounded by macrophages, compared to those having a high aspect ratio (length of 825 nm and a diameter of 25 nm) [98]. Multi-walled carbon nanotubes with a small aspect ratio which were injected subcutaneously were observable in macrophages after 4 weeks. However, carbon nanotubes with a high aspect ratio were not found in macrophages and mainly had caused cellular inflammation [99]. Therefore, multi-walled carbon nanotubes which have a higher aspect ratio leave more toxic effects. Besides, multi-walled carbon nanotubes cause different diseases such as asbestosis, depending on their length [100].

### Composition

The composition and inherent chemical properties of materials may lead to toxicity. As an example, carbon nanoparticles cause more severe lung inflammation and epithelial injuries in rats, compared to titanium dioxide nanoparticles. Furthermore, smaller sizes of these nanoparticles lead to more severe effects than bigger ones [101]. Metallic iron can fortify toxicity of carbon nanoparticles which is due to increased reactivity and oxidative stress [102].

### Physical properties of surfaces (Porosity, surface defects, impurities)

Nanomaterials have a rather high ratio of surface atoms and depending to their geometry, this ratio also depends on their size, porosity, smoothness and roughness of surface. For instance, nanoparticles of porous silica have a higher biocompatibility compared to nanoparticles of non-porous silica. Also, hemolytic activity of the porous silica is significantly lower than non-porous silica [103].

The influence of defects found in nanoparticles structure on pulmonary toxicity was investigated [104,105]. According to the results, reactive oxygen species are produced on the surface defects of nanoparticles and increase the toxicity of nanoparticles at in vivo conditions [104,105]. Based on another study, silver nanosheets indicate a higher toxicity level, compared to nanospheres and nanowires; this is due to large defects on their surface causing surface reactions [106].

By changing the electrical properties, impurities may change the toxic effects of nanomaterials. The results of a research demonstrate that cytotoxic reactions caused by nanoparticles of zinc and copper oxide depend on their purity [107]. Zinc oxide nanoparticles with aluminum impurities have more toxic effects; this is due to increased electric charge resulting from increased impurities.

Surface roughness plays a role in non-specific bindings leads to increased cellular uptake of nanoparticles [105,108] and is ineffective in reaction rate of nanomaterials with cells. Nanomaterials may cause cytotoxicity by disorder in the plasma membrane and creating a transient hole in it [109].

### Solubility

Most common nanomaterials are insoluble which leads to their increased accumulation in biological systems and cells. It is proved that toxicity of nanomaterials has a significant relationship with their solubility [110].

While some acute toxicity responses are due to the high solubility of nanomaterials, low solubility may also cause a range of long-term effects such as carcinogenesis. During dissolution, crystal structures break down into smaller parts and create discrete crystal sheets.

This in turn leads to defects in nanomaterials surface; the consequence of which is reactions producing reactive oxygen species. Insoluble nanomaterials can remain in the respiratory system for years. Long residence of the particles in the lung may result in damage

and biological responses [94]. Frequent exposure to nanomaterials in low concentrations may impair the immune system and cause adverse health effects.

### Stabilizers

Since most nanomaterials are hydrophobic, they do not have a stable suspension in aquatic environments. Therefore, they are usually made stabilized by surfactants, polymer coatings and functional groups. For instance, gold nanoparticles are usually functionalized with citrate. Some studies indicate that chemical properties of stabilizers and functional groups may cause toxicity and immune responses in the body [111].

### Protein corona

Proteins can adhere to the nanoparticles surface. Proteins which tend to have a physical or chemical absorption to the nanoparticles surface, form a hard corona. Some other proteins have a weak interaction with nanoparticles surface and form a soft corona. Association or dissociation of proteins depends on physiochemical properties of nanoparticles. Nanomaterials binding to proteins can act as a mediate for nanomaterials uptake via cellular receptors [112]. Therefore, if identical nanoparticles have different protein bindings, they can show varied toxic effects. Multi-walled carbon nanotubes which are bound to pulmonary surfactant proteins A and D cause lung infection and emphysema in mice [113]. Similarly, single-walled carbon nanotubes and α-chymotrypsin complex inhibits enzyme activity [114]. However, reactions between the nanomaterials and proteins can increase the biocompatibility of nanoparticles and make them non-toxic or less toxic. The results of a study showed that cytotoxicity of single-walled carbon nanotubes and graphene oxide nanosheets were reduced when coated with fetal bovine serum [115].

### Surface charge

Upon increasing in the applications of nanomaterials in medicine, special attention has been given to the effects of surface charge of nanomaterials on their cellular uptake [116] and several studies are done to identify the relationship between the surface charge and toxicity of nanomaterials. The findings of a research showed that positively charged polystyrene nanoparticles cause a more severe cytotoxicity compared to negatively charged nanoparticles in HeLa cells [117]. Positively charged particles cause DNA damage and activate checkpoints in the cell cycle. However, negatively charged particles do not have a significant effect on the cell cycle [117]. In bacteria, positively charged nanoparticles of silver, gold and silica cause a more severe cytotoxicity compared to the negatively charged nanoparticles [118]. It seems that positively charged nanoparticles are digested by lysosome with more ease and resulting in cytotoxicity. Surfaces having a positive charge are more inclined to stimulate hemolysis and platelet agglomeration. But neutral surfaces are more biocompatible [119]. This can be due to the tendency of positively charged particles to the negative parts of phospholipid groups or proteins on the cell membrane. Contrary to the aforementioned studies, another research indicated no relationship between the surface charge of gold nanoparticles and their cytotoxicity in HaCaT cells [120]. Another study investigated the effects of polystyrene nanoparticles on the formation of blood clots in arteries after intravenous injection and mouth breathing [121]. After intravenous injection and mouth breathing, polystyrene nanoparticles which were bound to the amine groups (positively charged) led to the formation of blood clots. On the other hand, after mouth breathing, nanoparticles which were bound to the carboxyl groups (negatively charged) significantly inhibited blood clots in vessels. Polystyrene nanoparticles which were not bound to amine and carboxyl groups did not have any influence on the formation of blood clots in the vessels [121].

Surface charge of nanomaterials is of importance from another perspective. Surface charge is a key factor determining colloidal behavior of nanomaterials which can affect the cellular responses by altering their shapes and sizes because of agglomeration [122]. High concentrations of anionic or cationic materials may impair blood-brain barrier function. Also, surface charge of nanoparticles hurts the skin permeability [123].

## Conclusion

There is no doubt that development of nanotechnology has beneficial and harmful effects on the environment and living beings' health. Potential adverse effects are due to the nanomaterials harmful reactions with biological systems. In recent years, investigating the toxicity of nanomaterials has turned into a major challenge. Delineating a clear conclusion on the way nanomaterials cause toxicity is difficult. Mechanisms in studying toxicity of nanomaterials include production of reactive oxygen species, protein folding, disrupting the membrane activity and direct physical damages. Toxicological studies indicate that the potential relationship between toxicity of nanomaterials and their unique physiochemical properties such as their size, shape, aspect ratio, agglomeration, solubility and surface defects. These properties and their biological effects make a significant difference in similar particles having larger sizes. Therefore, it is essential to get accurate information on the physiochemical properties of nanomaterials. Similar nanomaterials can cause different cellular responses in different cells and the severity of toxicity differs depending on the kind of the exposed cell. Having Conflicting information in this regard, more studies should be conducted on the toxicity mechanism of nanomaterials. But it seems that exposure to nanomaterials can cause a range of acute and chronic effects such as inflammation, fibrosis, cancer, and metal fume fever. As a prerequisite for the development of nanotechnology, and regulating safety standards, more studies should be done on the toxic effects of nanomaterials. Therefore, in order to prevent the harmful effects of nanomaterials on our health when working with them or having an exposure of any kind, we should deal with them with caution and carefulness.

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