Toxicity of nanostructured biomaterials

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9.1 Nanotoxicology: Concepts and claims

In recent years, tremendous growth has been observed in the understanding and biomedical applications of nanostructured biomaterials [1–3]. An array of biomaterials has been developed for their prospective applications in drug delivery, diagnosis, theragnosis, photothermal therapy, photodynamic therapy, bioengineering, etc., to name a few [4,5]. Toxicology refers to nanobiomaterials' unwanted side effects as they manifest within living organisms including humans, plants, and animals [6]. Traditionally, the toxicity of a materials depends on its exposure dose and exposure time [7]. The toxicity attributes of any nanobiomaterial largely depend upon its working concentration (administered dose) and dosing time (exposure period). It is thus rightly stated that "the dose makes the poison" [8], implying a linear relationship between dose and toxic effect.

The concept of nanotechnology has long been well established, but only recently have toxicity elicitations have started to emerge [9]. Looking towards the immense range and number of potential applications for, and adoptability of nanomaterials, there is an increasing need to understand, analyze, and establish their toxicity profile. It is imperative to know whether the administration of these nanobiomaterials is safe, or if they impart toxicity to healthy cells and produce long term health issues. The determination of these attributes for individual materials is easy, and once its properties are established, it becomes easy to determine the different concentration levels under which a material may be recognized as "safe" or "harmful" [9].

There is a difference between the properties of materials in bulk quantities and at reduced quantities (nanodimensions) [10]. At nanoscale, nanoparticles (NPs) may have important, enhanced optical, mechanical, electrical, physical, chemical, and biological properties as shown in Fig. 9.1. This results from variations in the material's surface properties (↓particle size leads to ↑surface area), which in turn amends the material's chemical reaction (↑surface area leads to ↑chemical reactivity). For the readers' better understanding, Table 9.1 presents properties corresponding to effective surface modifiers/stabilizers used in the development of nanostructured biomaterials. Nanobiomaterials' surfaces at the nanoscale level are highly reactive because of the enhanced surface-to-volume ratio [21]. The net surface-to-volume ratio of nanomaterials is critical in nanotoxicology.

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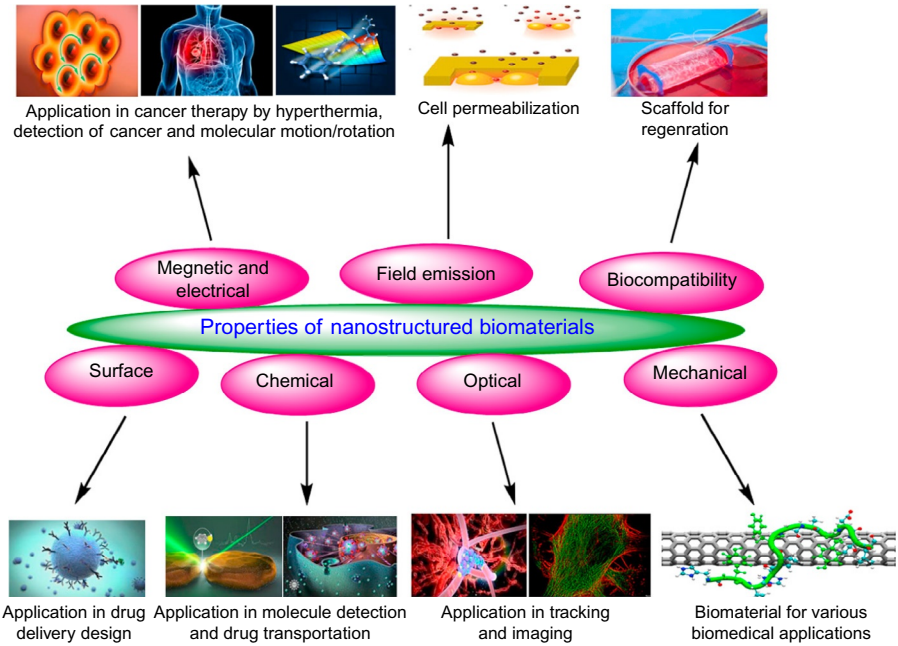

Fig. 9.1 Illustration of properties of nanostructured biomaterials.

Table 9.1 Properties of nanostructured biomaterials and associated surface modifying agents/stabilizers

Type of nanostructured biomaterials	Properties	Surface modifying agents/stabilizers	Ref.
Gold (Au)	✓ Semiconductor ✓ Chemically inert ✓ Available in different sizes ✓ High biological compatibility	✓ PEG ✓ Folic acid ✓ Chitosan ✓ Hyaluronic acid	[11]
Silver (Ag)	✓ High electrical conductivity ✓ High thermal conductivity ✓ Surface-enhanced raman scattering ✓ Nonlinear optical behavior	✓ Acrylic acid ✓ Arachidic acid ✓ Tannic acid ✓ C-terminal antibody of Aβ(1–40/1–42) (Ab-AgNPs)	[12]
Silica (SiO_2)	✓ High stability ✓ Low toxicity ✓ Reactive surface ✓ Excellent flowability and compressibility	✓ Cyclodextrin ✓ Poly [2-(dimethylamino) ethyl methacrylate] ✓ EpCAM antibody ✓ Transferrin	[13]

Table 9.1 Continued

Type of nanostructured biomaterials	Properties	Surface modifying agents/stabilizers	Ref.
Selenium (Se)	✓ High thermal expansion ✓ High thermal conductivity ✓ Reactive surface ✓ High tensile strength	✓ Quercetin ✓ Sialic ✓ Poly(lactide-*co*-glycolide) ✓ RGD-peptide	[14]
Titanium (TiO_2)	✓ Good rheological properties ✓ High stability ✓ UV light absorber ✓ Good photocatalyst	✓ Poly(vinyl alcohol) ✓ Poly(lactide-glycolide acid) ✓ Di(2-pyridyl) ketone ✓ Glycyrrhizic acid	[15]
Zinck oxide (ZnO)	✓ Good rheological properties ✓ High stability ✓ UV light absorber ✓ Good photocatalyst	✓ Sodium alginate ✓ Gum acacia ✓ Meso-tetra(4-carboxyphenyl) porphyrin ✓ *N*-Halamine	[16]
Carbon nanotubes (CNTs)	✓ High electrical conductivity ✓ High thermal conductivity ✓ High mechanical strength ✓ High surface to volume ratio	✓ Platinum NPs ✓ Gold NPs ✓ Silver NPs ✓ Polydopamine	[17]
Graphene (GO) and reduced graphene oxide (rGO)	✓ High chemical reactivity ✓ Easily modifiable surface ✓ High mechanical strength ✓ Prefect thermal conductivity	✓ B-Cyclodextrin ✓ Glycine derivatives ✓ Polyoxometalates ✓ 2,3-Diaminopyridine	[18]
Cerium oxide (CeO_2)	✓ Highly catalytic ✓ Neuroprotective ✓ High ionic conductivity ✓ Antibacterial in nature	✓ Albumin ✓ Europium ✓ Levan ✓ Polyvinylpyrrolidone	[19]
Polymeric NPs	✓ More highly biocompatible than metallic nanoparticles ✓ More stable ✓ Able to modify the drug release pattern ✓ Targeting abilities	✓ Poly-L-*co*-glycolic acid ✓ Poly-ethylene glycol ✓ Chitosan ✓ Hyaluronic acid	[20]

This makes knowledge of the nanotoxicology of nanostructured biomaterials imperative. The use of unregulated nanomaterials may lead to undesired effects on the environment and human health, as well as on biosystems. These concerns have gained huge attention from investigators throughout the world, who seek to develop a versatile nanomaterial with a balance between its applications and associated toxicities [22].

However, it may be noted that exposure of nanomaterials (like asbestos) to the environment is not new, and there is a lot to learn from these matters for future development

of nano-based medicines [23]. Grime-powdered particles (like carbon, etc.) derived from combustion processes, and their toxicology in the lungs, are another example indicating that nanoparticles (NPs) could potentially be dangerous [24]. The conclusion derived from these examples is that it would be safer to explore nanomaterials' hazardous effects before they become a barrier to technological development.

There is limited information regarding the long-term toxicity of a vast family of nanomaterials including gold [25,26], silver [27], silica [28], polymer-based [29–32], and carbon-based materials [33,34]. And with the exception of data on dust and airborne particles smaller than 100 nm, human epidemiological data on this toxicity still awaits publication.

9.2 Dose and dosimetry of nanobiomaterials

It is the dose which is responsible for either the therapeutic or toxic effects. In nanotoxicology, it is imperative to determine appropriate dose regimes to establish valid conclusions from pharmacokinetic and pharmacodynamic evaluations for human risk assessment. There is an obvious need to evaluate NPs' toxicity while determining practically feasible doses (rather than unrealistically high doses) to attain a pharmacological response [35]. It is necessary to calculate the effect of exposure to high doses of nanomaterials, and corrective/protective protocols must be established, too. Chronic low-dose exposures for extended periods (>30 years/lifetime) may increase the likelihood of developing severe disorders including neurodegenerative diseases, diabetes, asthma, etc. Thus, determining nanobiomaterials' dosage, dosing frequency, exposure time, the effects of the chosen administration route, and drug retention in the body are matters of prime importance [36].

Considering the particulate nature of NPs, dose calculation should mandatorily consider the number of particles accumulating in target cells or organs, which is not an easy task. This task is further complicated by NPs' ability to allow other molecules to attach to their surfaces [37].

Another problem in dose determination is the difficulty in predicting the correct number of particles arising, given the nature of some NPs to agglomerate. Hence, the interaction of nanoparticles with biological interfaces must be clearly established through a critical account of volume and size of aggregates under both in vitro and in vivo settings [38].

9.3 Surface topography of nanobiomaterials and associated surface reactivity

As mentioned above, when bulk material is resized to nanoscale dimensions, the physicochemical and biological interactions of particles are increased significantly; this is important with regard to its potential interaction with cellular compartments [39,40]. This has reasonably attracted significant attention to nanoparticles' surface

topography, rather than their core bulk material. Innovative and meaningful design of NPs depends upon suitable modification of their surface in order to integrate biocompatible synergistic properties [41,42].

NPs' interaction with smaller architects such as atoms, molecules, certain liquids, gases, and some biomolecules (proteins, amino acids, lipids, etc.) determines the nature of attachment, which may be either strong or weak. When the nanomaterial's surface is modified with protein or polymers, the region of this interaction is called the "corona" [43]. Investigations have demonstrated that this corona, not the NP itself, is directly responsible for defining the NPs' properties. Therefore, it is imperative to test the NPs' environment for nanotoxicity, as well as the NPs themselves.

9.4 NPs and the environment

The interaction of a nanomaterial with its bioenvironment often results in agglomeration, alteration in surface charge, or amendments to desirable surface characteristics. These alterations have also been investigated in aquatic and terrestrial ecosystems, revealing the significance of understanding nanoparticulate matter and its relationship with the environment. It is particularly important to understand a nanomaterial's setting within the context of its environment. In this chapter, we discuss the toxicology of various NPs and their effects on cellular systems and the environment [44].

9.5 Interfaces between nanobiomaterials and target cells

Within the boundary between nanobiomaterials and target cells, phagocytosis and endocytosis are well-known mechanisms for the cellular uptake of particulate matter [45]. Endocytosis is the primary mode of uptake for NPs (and requires a recognition step), and phagocytosis involves the transport of materials such as water and biomolecules through the cellular structure. One well-known example of endocytosis is viruses (natural NPs) spreading from one cell to another [46]. It may be concluded that surface-modified engineered NPs follow the same routes for cellular entry and subsequent translocation into deeper sections of body tissues.

Today, with advancements in molecular and cellular biology, several methods have been made available for the measuring nanomaterial uptake and cellular internalization [47]. There are two different mechanisms for nano/biointerface: chemical and physical. Reactive oxygen species (ROS) is the most important, most reported chemical process in nanotoxicology; it functions by causing cellular disruption and sometimes cell death. In addition, ROS also seems to be involved in inflammatory processes. ROS manipulates gene expression to mediate cellular function. For instance, during inflammation, ROS upregulates certain genes which participate in the release of inflammatory cytokines (i.e., nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB; AP-1). Moreover, generation of free radicals can directly or indirectly

interfere with cell integrity. Like chemical mechanisms, particle dimensions and surface characteristics also govern the physical interaction of particles at the point of interface. This primarily involves disruption of cellular membranes, cellular activity, transportation blockade, and protein denaturation/aggregation/fibrillation [48].

However, both mechanisms cause sequential progressions in the cell membrane, forming the basis for clinical responses. These cell-mediated responses may occur before or after cell entry, and/or as a stimulus to cell uptake itself, and they relate to the condition known as frustrated phagocytosis (a process in which cells attempt to engulf particles but often fail due to the size or shape of nanomaterial) [49].

9.6 Routes of entry of nanobiomaterials

Nanomaterials can enter the body via inhalation, permeation of the skin, and ingestion [50]. However, transfer to secondary organs or tissues via these routes is not fully demonstrated, and only a few reports are available that shed light on this attribute. Respiration is an important entry mechanism for airborne particles. Many published reports suggest the effects of ultrafine particles (such as dust, airborne particles, carbon-black, and other contaminants) on the airways and lungs. Research on nanomaterials entry via respiration is increasing. However, nanomaterials' entry into the lungs can lead to their distribution to other body parts as well, which is the real concern. It is well known that the body has well-defined mechanisms to protect against entry by particles.

Nanomaterials administered through the inhalation route are translocated from the lungs to other organs such as the liver, heart, spleen, and possibly more. The endocytosis mechanism underlying transport of nanomaterials from one organ to another involves alveolar epithelial cells. Besides the lungs, the olfactory bulb provides a direct entry route for nanomaterials to the central nervous system, and this is very important from a neurotoxicological perspective [51].

Another major entry route for nanomaterial involves the skin, through dermal absorption [52]. Recently, titanium dioxide-based biomaterials have been used in the formulation of sunscreen products, providing them an opportunity to gain access via hair follicles/shafts or skin cuts (wounds) [53]. Although it is too early to form an assumption, because complete data on the dermal absorption of titanium dioxide is lacking, some carbon-based nanomaterials and quantum dots are also reported to cross the dermis, depending on size and surface engineering [54].

Ingestion is a route by which nanomaterials gain entry into the human body through the digestive system; these materials are widely used in food products/food processing/food packaging [55]. It has been reported that nanomaterials can enter through the gut, depending upon the size of the particles, but more efforts are required to know the exact mechanism. However, the human body possesses a variety of natural barriers to restrict the entry of other particles to cellular compartments (i.e., barriers in the lung/brain, and the placental barrier and mucus in pregnant women) [56]. Some reports on the distribution profiles of these nanomaterials revealed very low accumulation

amounts in the brain, heart, spleen, and liver. The localization/distribution of nanomaterials inside different organs requires more attention and exploration of the various routes by which they are eliminated [57].

9.7 Effect of nanobiomaterials on biomolecules

Proteins and other biomolecules have a strong influence on cell membranes and cellular apparatus. These involve gastrin (enzyme), hormones (cell signaling molecules), or tubulin (structural proteins) [58]. All body functions depend on the normal functioning of these biomolecules. Any change in the performance of these molecules will directly or indirectly affect the body's homeostasis. Exposure to nanomaterials may alter the correct molecular conformation for a protein, which may lead to destruction of the protein's function. The size of these protein molecules is similar to nanomaterials, which promotes interference with cellular response or results in protein dysfunction [59]. Research focusing upon the possibility for altered generation and overproduction of biomolecules (like proteins) at the cellular level is essential as far as nanotoxicity is concerned.

9.8 Nanobiomaterials and their effect on DNA

As DNA is an important component of cellular structure and organelles, genotoxicological risks are of prime importance. Attention should be paid to NPs' possible genotoxicity, as it is evident that NPs can gain access to the nuclear compartment. Reports are available evaluating various NPs for genotoxicity [60]. However, these investigations offered no clear differentiation between positive and negative results with regard to the evaluated parameters. In addition, the mechanism by which DNA is damaged is still unclear to some degree. Other than direct interference, or physical/chemical interference with nanomaterials, ROS is considered a potential cause for DNA damage. ROS enables nanomaterials to damage DNA without reaching the nuclear compartment via oxidative stress, promoting genotoxicity [61].

9.9 In vivo toxicology of nanobiomaterials in humans: Prospective mechanisms

In vitro characterization to calculate the nanotoxicity of nanomaterials would not ensure human safety [62]. In vivo studies are required to illustrate entry route, cellular uptake approaches, and pathways of NPs in a complex multicellular organism. Nanomaterials' toxicity is not only important as related to the therapeutic exposure of humans, but it is also occupationally relevant, for example, in the formulation of nanoscale therapeutics. To what extent may persons handling nanomaterials while working in pharmaceutical

industries be exposed before they suffer harm? Hereinafter, we explore various nanomaterials which currently fall into this category, such as those utilizing gold, silver, silica, selenium, titanium dioxide, zinc oxide, cerium dioxide, as well as polymeric and carbon-based nanomaterials [63,64]. In the following section, we summarize literature regarding the toxicity of these nanostructured biomaterials (Table 9.2).

9.10 Toxicity of different nanostructured biomaterials

9.10.1 Gold NPs

The design and production of novel nanoscale materials has gained much attention in the last decades because of their versatile applications. Among them, AuNPs has been significantly studied and explored for use in biomedical fields. AuNPs are emerging as potential biomaterials for the design of novel nanoscale medicaments and biomolecule delivery systems [93]. Despite the use of AuNPs in various fields including development of nanomedicines, attention must be paid to their toxicity. It is worth note that the liver is the primary site for the deposition of AuNPs in humans. Recently, vast numbers of reports have been published on the toxicity of AuNPs as nanostructured biomaterials. For this reason, Coradeghini et al. investigated the role of two different sized AuNPs (5 and 15 nm) in vitro on Balb/3T3 mouse fibroblasts by exposing them for 72 h. Outcomes demonstrated significant cellular toxicity of 5 nm AuNPs at a concentration of ≥50 μM (Fig. 9.2). Toxicity resulted in altered cellular function, including degradation of the actin within the cytoskeleton (with cell footprints narrowed and/or contracted) and decreased expression and decomposition of the clathrin heavy chain [94].

Paino et al. studied the geno- and cytotoxicity of two different AuNPs (AuNPs coated with sodium citrate/polyamidoamine dendrimers) against human hepatocellular carcinoma-cells (HepG2) and peripheral blood mononuclear-cells (PBMC) from healthy human volunteers. The outcomes suggested that (both) sodium citrate/polyamidoamine dendrimer-coated AuNps significantly react with HepG2 cells and PBMC and revealed in vitro geno-/cytotoxicity even at smaller doses. Exposure to different AuNPs formulations was found to be disturbing to normal cellular activities and imparted potential cytotoxic/genotoxic effects and damaged DNA. Authors also claimed to have significant relation between the toxicity of AuNPs with their physical and chemical surface characteristics [95].

In addition, Ortega et al. performed a study based on the fact that AuNPs adsorbs the macromolecules on its periphery to construct a protein corona (PC) upon intravenous administration, for which the kidney is the primary excretory organ. The authors evaluated the role of the PC on AuNPs cellular uptake and cytotoxicity in vitro in human proximal tubule cells (HPTC) using 40.0 and 80.0 nm branched polyethylenimine (BPEI), lipoic acid (LA), and polyethylene glycol (PEG) grafted AuNPs. At the nontoxic dose, 40.0 nm bare BPEI-AuNP significantly altered gene expression associated with immune-toxicity, steatosis, and mitochondrial metabolism, whereas larger doses affected DNA damage/repair mechanisms, and the pattern of cell death, fatty acid metabolism, and heat-shock response were changed [65]. However, some reports

Table 9.2 Various nanostructured biomaterials and their associated toxicity perspectives

Type of nanostructured biomaterials tested	Animal/plant/cell type/cell line used	Toxicity perspectives	Ref.
AuNPs	Human proximal tubule cells	Size-dependent toxicity was observed. AuNPs of size 80 nm were found to be more cyto-/genotoxic as compared to 40 nm AuNPs	[65]
Gold nanorods (GNRs)	Rats lung using bronchoalveolar lavage	Dose and size-dependent pulmonary toxicity was observed following intratracheal instillation of 10 and 25 nm GNRs	[66]
GNRs	Dogs and cats	No toxicity was observed in regards to blood profile, liver, or kidney functions following administration at a dose of 75 μg gold nanorods/kg of body weight	[67]
AuNPs and AgNPs	Zebrafish embryo	In zebrafish embryo, AgNPs showed 100% mortality at 3 μg/mL dose, while AuNPs revealed the same at dose of 300 mg/mL	[68]
AuNPs, AgNPS, SiO_2 and CNTs	BALB/c 3T3 fibroblasts, NR8383 macrophages, and U937 monocytes	Toxicity followed the pattern: AuNPs > CNTs > AgNPs > SiO_2 and observed greater with AuNPs	[69]
Gold nanostar	Metastatic breast cancer cells and fibrosarcoma cells	Distribution of gold nanostar was five times greater in metastatic breast cancer cells in comparison to fibrosarcoma tumors	[70]
AuNPs	Rats	Liver was found to be the site of higher accumulation upon single dose of 20 nm gold nanoparticles. Also, spleen atrophy and mild anemia was observed following 28 days' study	[71]
AuNPs	Hypoxic MDA-MB-231 breast cancer	Uptake of AuNPs occurred in hypoxic conditions, causing radiosensitization in moderate, but not extreme hypoxia in a breast cancer cell line	[72]
AuNPs	Nonpregnant and pregnant mice	It was reported that 30 nm AuNPs induced mild emphysema-like alterations in lungs of pregnant mice	[73]

Continued

Table 7.1 Continued

Type of nanostructured biomaterials tested	Animal/plant/cell type/cell line used	Toxicity perspectives	Ref.
Silica poly (ε-caprolactone) (Si-PCL-) and silica poly-L-lactide (Si-PLLA) and AuNPs	Microglial cells and undifferentiated/ differentiated SH-SY5Y cells	Si-PCL-NPs induced the strongest effect of reduced glutathione depletion followed by Si-PLLA-NPs and Au-NPs	[74]
Ficus religiosa AgNPs	A549 and Hep2 cells	Results exhibited deposition of AgNPs in liver, brain, and lungs on day 29 with respective concentration of 4.77, 3.94, and 3.043 µg/g tissue, although complete elimination of silver was observed during wash out period	[75]
AgNPs	Human sperm	ROS production and DNA fragmentation were markedly increased after 60 min of exposure to AgNPs at 200 and 400 µg/mL	[76]
AgNPs	*Allium cepa*	Biogenic AgNPs can induce significant clastogenic effects on both meristematic and reproductive plant cells at dose of 5, 10 and 20 µg/mL	[77]
PVP/PEI modified AgNPs	Zebrafish	After 3 weeks, biochemical pathways related to lipid transport/localization, cellular response to chemical stimulus/ xenobiotic stimulus were found down-regulated in the liver	[78]
Ficus carica L *modified* AgNPs	MCF7cell lines	Potential toxicity on MCF7cell lines at size range 55–90 nm as revealed by *Ficus carica* L *modified* AgNPs and chemical synthesized AgNPs both	[79]
PVP/PEI modified AgNPs	Zebrafish	Malformations in embryos in second week following administration of *PVP/ PEI modified* AgNPs	[80]
Ammonia and PVP modified AgNPs	Mouse fibroblast cell line L929	It was reported that PVP and ammonia modified AgNPs were cytotoxic to L929 in concentrations above 50 µg/mL	[81]
PVP modified AgNPs	*Pseudokirchneriella subcapitata*, *Artemia salina* and *Daphnia similis*	Among the plants tested, *Daphnia similis* revealed the EC_{50} values in a toxicity range in following administration of PVP modified AgNPs after 2 days	[82]

Table 7.1 Continued

Type of nanostructured biomaterials tested	Animal/plant/cell type/cell line used	Toxicity perspectives	Ref.
Tannic acid modified AgNPs	VK2-E6/E7 cells	Tannic acid-modified AgNPs with sizes of more than 30 nm were toxic to VK2-E6/E7	[83]
AgNPs	Zebrafish	AgNPs induced apoptotic hair cell disruption and thus found as embryotoxic in the neuromasts	[84]
Iron-doped silica nanoshells	Mice	No acute or chronic toxicity in mice at dosages of 10–20 mg/kg body weight in mice	[85]
SiO_2NPs	Zebrafish	Generation of ROS and inflammatory response in transgenic zebrafish line	[86]
SiO_2NPs	Wistar rats	No significant malformations/ variations were noted in the fetuses following administration of SiO_2NPs	[87]
SiO_2NPs	Wistar rats	Oral administration of silica nanoparticles up to 1000 mg/kg body weight per day reveals no toxic effects on the reproductive performance/ growth of animals	[88]
SiO_2NPs combined with lead acetate	A549 cells	Noncytotoxic concentration of SiO_2NPs exposure alone not induced apoptosis in A549 cells, but changes noticed when combined with lead acetate	[89]
Various Se based particles	HaCaT cell culture	In vivo/ex vivo/in vitro analysis showed the following pattern of Se toxicity: selenate > selenite > SelPlex = nanoSe > lactomicroSe	[90]
CeO_2NPs	Macrophages from the RAW264.7	Outcomes demonstrated no significant ROS generation, whatever the shape of CeO2NPs were used	[91]
GO and rGO	Mouse dams	Abortion was reported at a dose of 6.25 or/and 12.5 mg/kg at a late gestational stage (approximately 20 days). The 80% of pregnant mice died at high dose of rGO at this stage of pregnancy	[92]

suggested that glutathione might be a safe alternative to PEG. Simpson et al. demonstrated glutathione-grafted AuNPs ~1.2 nm, and their results showed zero morbidity at each administered dose up to 60 μM. The findings of Simpson et al. explored to find a safer and more biocompatible alternative way to decorate the surface of AuNPs in order to completely eliminate cytotoxicity [96].

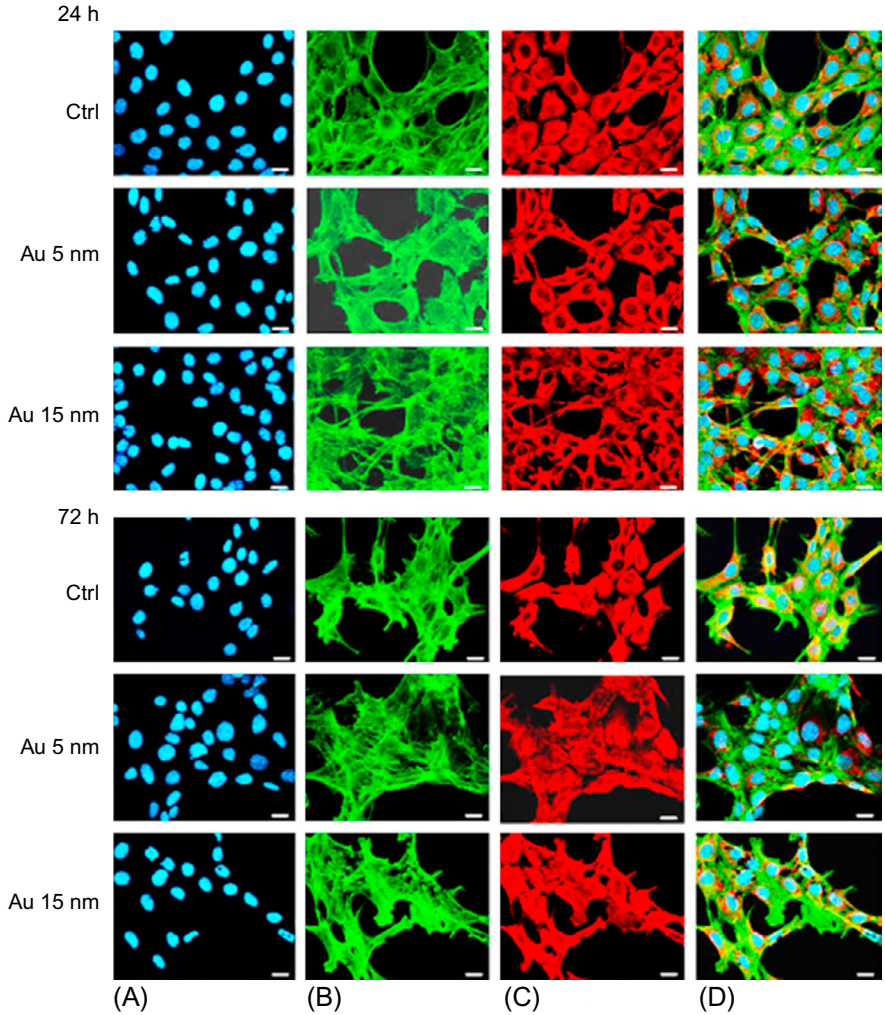

Fig. 9.2 Images of Balb/3T3 cells incubated with or without AuNPs (5 and 15 nm) for 24 and 72 h and stained with (A) caveolin antibody (DsRed, *red channel*), (B) phalloidin (Alexa 488, *green channel*). Nuclei are counterstained with (C) Hoechst 33258 (DAPI, *blue channel*), (D) merge images (A + B + C).
Courtesy R. Coradeghini, S. Gioria, C.P. García, P. Nativo, F. Franchini, D. Gilliland, J. Ponti, F. Rossi, Size-dependent toxicity and cell interaction mechanisms of gold nanoparticles on mouse fibroblasts, Toxicol. Lett. 217 (2013) 205–216.

9.10.2 Silver NPs

Besides AuNPs, AgNPs are also widely employed nanostructured biomaterial in consumer products because of their well-recognized antibacterial and antifungal activities [97]. In addition, their surface is important to modulation and/or enhancement of their application, especially in the development of nano-based products. However, because

of their increasing applicability in various fields, categorical attention should be paid to safer delivery in terms of their toxicity to targeted species (humans/plants/animals).

In this context, Gliga et al. characterized AgNPs of different sizes, exposed them to human lung cells, and elucidated the pathways of toxicity. Authors claimed significant cytotoxicity with 10 nm AgNPs, while surface coating did not impart any significant cellular changes. However, all investigated AgNPs exhibited an incremental increase in overall DNA impairment following 24 h' administration, as confirmed using comet assay. This greater cytotoxicity with 10 nm AgNPs was attributed to particle agglomeration in cellular medium/uptake/internalization and Ag release [98].

Cvjetco et al. demonstrated the toxicity of silver nitrate and three types of laboratory-produced AgNPs, applying different surface capping such as citrate, polyvinylpyrrolidone (PVP), and cetyltrimethylammonium bromide (CTAB) on *Allium cepa* roots (plant organism widely used in abiotic stress research). Outcomes of the investigation revealed that ionic silver was more cytotoxic than any other AgNPs investigated. However, all the investigated AgNPs were found to have oxidative stress and cellular toxicity in large doses (75 to 100 μM). In particular, AgNPs capped with CTAB exhibited increased Ag uptake in the roots, consequently leading to strong reduction of the root growth and oxidative damage [99]. This reveals how exposure to nanostructured biomaterials affects plants as well as humans.

Apart from humans and plants, Ag and AgNPs may harm microbial genera (bacteria, yeast, and algae). Dorobantu et al. studied citrate and 11-mercaptoundecanoic-coated AgNPs' effects on microorganisms belonging to different genera (bacteria, yeast, and algae). It was concluded that when using equimolar Ag solutions, silver nitrate has greater toxicity potential on all the microbes than both NPs tested. Moreover, authors concluded that some microbes are more highly sensitive to Ag than others, and the selection of coating material is relevant to toxicity [100].

9.10.3 Silica NPs

Silica (SiO_2) exists in nature as either crystalline or amorphous forms, and exposure to it (mainly crystalline form) may lead to respiratory diseases such as silicosis [101]. SiO_2 NPs have gained attention because of their increasing importance in making tailored drug delivery systems/imaging devices/chemical sensors and catalysts, as their surface can be modified using suitable stabilizers [102]. In relation, McCarthy et al. formulated different size SiO_2 NPs (10, 150, and 500 nm) and studied their effects on human lung submucosal cells for 2–24 h in vitro. The outcome of this investigation matches with those mentioned in gold and silver nanoparticles, that is, toxicity is size-dependent. In particular, SiO_2 NPs 150 and 500 nm in size were found to be nontoxic on Calu-3 cells. Authors further concluded that the cytotoxicity of amorphous SiO_2NPs averaging 10 nm in size on submucosal cells can be correlated with inflammation and the release of ROS, leading to apoptosis and reduced cell survival [103].

Similarly, Kim et al. revealed that the toxicity of SiO_2NPs is associated with size, dose, and cell type when studied using A549 and HepG2 epithelial cells and NIH/3T3 fibroblasts. Therefore, research on the mechanism of SiO_2 uptake/retention/cytotoxic effects, and cellular interfaces reactions in varied cells/tissues/organs are of immense

potential, as these technologies are fast developing. Extensive in vitro and in vivo research pointing to the cellular toxicity of SiO_2 revealed nanoparticles' surface area as a key parameter and particle radius as one of the most important aspects responsible for nanotoxicity [104].

9.10.4 Selenium NPs

Currently, many nanostructured biomaterials are employed in biomedical, engineering, soil, and food industries. Se NPs are emerging as possible nanoarchitecture that can be applied to variety of applications such as biomedical and food additives. Se is a well-known trace element essential for animal and human health and having many health benefits. A Normal Se value in an adult is ~80 µg, and the dietary requirement is ~56 µg/day. In general, Se is available as Se^{+6} (selenate), Se^{+4} (selenite), Se^{-2} (selenide), and as Se^{0} (elemental selenium). Se^{0} is not soluble in water or aqueous medium and is regarded to be biologically inactive. However, Se NPs pose greater risks to human health and the environment due to their specific properties and ease of access [105].

In an exhaustive study, He et al. injected Se NPs at doses of 0/0.2/0.4/0.8/2.0/4.0/8.0 mg/kg body weight (bw) in 2.0 mL of 0.9% saline for 2 weeks consecutively in male Sprague-Dawley rats and evaluated the toxic effects. They observed a variety of results, such as reduction in bw with the animals which received 2.0/4.0/8.0 mg Se/kg bw, but enhanced in the groups administered lower doses of 0.2/0.4 mg Se/kg bw. Similarly, the viscera index and few biochemical factors in the 8.0 mg Se/kg bw (High dose) group were found to be on the negative side and significantly affected by Se toxicity, as evidenced by inflammation in the liver, kidneys, lungs, and thymus, and apoptotic liver cells [106]. However, fewer investigations are available on toxicity for Se nanoparticles administered via either injectable or dermal routes, and very little information is available on their chemopreventative activity and underlying mechanisms.

9.10.5 Titanium dioxide NPs

TiO_2NPs are gaining tremendous attention due to their numerous applications in different areas of life, cosmetic, and packaging science. Due to their exceptional surface properties, in comparison to particles in bulk (greater size), they are gaining attention for the formulation of nanomedicines, too [107]. However, their increasing use raises questions regarding their safety in the context of environmental and human exposure.

TiO_2NPs can enter the body via inhalation, can cross blood-brain barrier, and can gain access to the cortex and hippocampus. Also, dermal route TiO_2 exposure imparts toxicity upon long-term use of some cosmetic products. In context, Tan et al. studied a sunscreen formulation comprising ~8.0% TiO_2 NPs ranging from 10.0 to 50.0 nm, applied two times a day for 14–42 days on the skin of human volunteers (aged 58–83 years) and determined the skin permeation of TiO_2NPs. Their outcomes revealed that the concentrations of TiO_2NPs in the skin layers (epidermis/dermis) of volunteers treated with TiO_2NPs were greater than the concentrations of TiO_2NPs recorded in controls. It was suggested that a larger sample size would be required to determine exact significance [108].

However, the data on molecular pathways by which TiO_2NPs may induce cancer (either upon intravenous or dermal administration) is not clear, and extensive study is required to conclusively establish toxicological protocols.

9.10.6 Zinc oxide NPs

ZnO NPs are extensively employed in cosmeceuticals, coatings technologies, engineered devices, and catalysts. As is evident from their wide applications, skin and airways are the main entry routes for ZnO NPs. Therefore, utilization and safety of ZnO NPs are a main concern for humans and environmental health. Dermal absorption of ZnO NPs supports the view that these particles, when present in sunscreens, do not cross beyond the stratum corneum [109]. Heng et al. studied inhalational exposure to ZnO NPs 10 nm in size by exposing BEAS-2B human bronchial epithelial cells to them. The authors suggested that few pathological conditions were compromised due to generation of ROS and associated oxidative stress to the airway epithelium, that is, COPD or asthma [110].

Conclusively, airway and dermal exposure of ZnO NPs pose severe risks to human health, and there is an urgent need for extensive risk-assessment investigation and establishment of exposure levels at which there are no undesired effects observed.

9.10.7 Cerium oxide NPs

CeO_2 is a rare element of the lanthanide class. Ce behaves in dispersion as Ce^{3+} and Ce^{4+}, dependent upon the surrounding medium. CeO_2NPs have potential applications in manufacturing and biomedical sciences [111]. Despite their medically effective role, their toxic effects on humans and the environment must be considered.

Numerous investigations addressing the toxic/adverse effects of CeO_2NPs on environmental/human health were reported, but they ended with unclear conclusions. CeO_2NPs can work as cellular antioxidants following localization into cellular structures. Current literature lacks reports on the genotoxicity of CeO_2NPs. However, some past investigations revealed that CeO_2NPs are able to generate oxidative stress, and therefore, produce apoptosis in human lung epithelial cells [112,113]. Therefore, it was concluded that CeO_2 nanoparticles may cause cell toxicity and genotoxicity upon cellular uptake. Moreover, it was documented that CeO_2NPs of different sizes displayed potential toxicity on *Escherichia coli* and a few human cells, because of adsorption of NPs and oxidative stress [114]. Taken together, the available literature hypothesized that CeO_2NPs of smaller radius do not exhibit any serious effects, and instead can protect cells from unwanted effects of radiation and oxidative stress, but this protection is purely cell type-specific [113].

9.10.8 Polymeric NPs

Polymer-based NPs (either natural or synthetic polymers) can modulate drug release and therefore can be employed as smart therapeutics, especially in targeting cancer. Their application starts from encapsulation of several biomolecules inside engineered

NPs to develop consumer-acceptable nanomedicines. They also benefit the delivery system by providing sustained characteristics and enhanced biocompatibility with cells and tissues [115]. In addition, they have the potential to be successfully used in encapsulation of peptides, nucleic acids, and proteins. However, some recent studies indicate their toxicity to cellular structures.

Grabowsk et al. reported that surface functionalization of poly(lactide-*co*-glycolic) NPs with chitosan, Poloxamer 188 (PF68), and poly(vinyl alcohol) (PVA) induce toxicity towards human-like macrophages when concentration increased from 0.1 to above 1 mg/mL [115]. In another study, Voigt et al. reported that polybutylcyanoacrylate (PBCA) NPs can enter the brain by crossing the blood-brain barrier, but surprisingly no significant toxic effects were reported even after the study of 4 weeks. With regard to polymeric NPs, further exploration is required to establish a nanotoxicity profile for various polymers if they are to be safely used as stabilizers and/or coating agents [116].

9.10.9 Carbonaceous NPs

9.10.9.1 Carbon nanotubes

CNTs are extremely demanding due to their excellent surface properties, which make them suitable for the transport of therapeutic and/or imaging agents into target sites. However, their interaction with biological surfaces most often results in cytotoxicity; therefore, these issues regarding the safety and biocompatibility of CNTs are of utmost significance [117]. Here it is proposed to highlight a portion of the reviews reported in this field without any endeavor to make definitive inferences. The biocompatibility of some settled types of carbon structures merits consideration [118]. Carbon materials such as pyrolytic carbon and diamond-like carbon are generally utilized as a part of medication. But high-virtue carbon black can enhance oxidative stress in human lung cells in vitro and pulmonary tumors in rats [119,120]. Significantly, the poisonous quality of little carbon black particles was observed to be more noteworthy than that of bigger particles, which recommends that uncommon care should be taken with very scattered carbon materials [121].

There are many CNTs toxicity studies that confirm that CNTs interfere with the functioning of normal cells, harm human keratinocytes, and exhibit varying levels of lethality to human lung cells [122,123]. The toxicity of sidewall functionalized (SWNTs) was considerably less than that of nonfunctionalized tubes [124]. Irritation is a toxic side effect incited by CNTs, and chemical degradation of CNTs happens under harsh conditions involving strong acids and oxidants [125].

Huczkoet al. investigated the impact of nanotube-containing ash on the pneumonic capacity of guinea pigs, and found no confirmation of any irregularities. A similar group revealed that exposure to nanotubes might instigate quantifiable pneumonic pathology in guinea pigs, and confirmed that nanotubes could cause lung tissue inflammation in mice [126]. Conclusively it can be stated that more focused research exploring the toxicity of CNTs is needed to utilize this exceptionally promising nanocarrier system for biomedical applications.

9.10.9.2 Graphene

Graphene (GO) is single layer two-dimensional nanostructured biomaterial with outstanding physicochemical properties such as high surface area and high electrical conductivity. GO and its reduced form rGO have been explored tremendously in several fields including biosensor technology, chemical technology, and biomedical arena. However, their potential biomedical use involving interaction with cells requires extensive investigation and further exploration, as toxicity is a main concern [127].

Survey of literatures on GO and rGO toxicity revealed that graphene is significantly toxic to cells in vitro and in vivo, and it has the potential to affect microbes, mammals, and other animals at a cellular level. A number of reports have been published regarding evaluation of GO and rGO due to their better solubility/dispersibility/stability in aqueous and physiological conditions [128,129].

Zhang et al., in a comparative investigation determining cellular toxicity and cell membrane integrity in neuronal PC12 cells, found that the biological interaction of GO/CNTs was shape dependent [130]. After a 24 h exposure, the metabolic activity of PC12 cells decreased in a dose-dependent manner, with GO generating more cytotoxicity at small concentrations and lower cytotoxicity at larger concentrations than CNTs. The highest concentration of graphene in this study (100 μg/mL) significantly increased LDH release and the generation of reactive oxygen species (ROS). In addition, caspase-3 activation indicated that graphene induced a time-dependent increase in apoptosis at a concentration of 10 μg/mL. The majority of available data matches with the findings of Zhang et al. and reported that GO/rGO are cytotoxic and/or genotoxic.

9.11 Future scope and conclusion

Nanostructured biomaterials have developed in recent time, and our ability to manufacture ever more attractive biomaterials, utilize advanced methodologies, and create safer products by employing nanotechnology will grow in the near future. However, current knowledge about the effects of these innovative nanostructured biomaterials on humans and the environment is limited, requires expansion, and should be documented in relation to their clinical applicability.

Our understanding explicitly indicates that to varying degrees, some or all of the nanostructured biomaterials will present new risks. We must focus on what we are missing and how to balance between novel benefits and potential harms. The availability of many potential nanostructured biomaterials (including gold, silver, silica, selenium, titanium dioxide, zinc oxide, cerium oxide, etc.) makes it significant to conclude and differentiate between toxic and nontoxic nanostructured biomaterials. One common fact about all nanostructured biomaterials is that all of them require well-set protocol for use as biomedical additives, and for that purpose, many serious issues like short-term and long-term toxicity, environmental exposure, methods of entry into the human body, amount and dosage, size, and shape must be addressed in an acceptable

manner. Once a nanomaterial is categorized as nontoxic, it may be considered safe, but if it is proven to be toxic, then suitable approaches (e.g., functionalization) could be developed to reduce/minimize the toxicity to obtain a reasonable benefit-to-risk ratio.

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Conflict of Interest
There is no conflict of interest and disclosures associated with the Chapter.

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