



Nanomaterials and Their Negative Effects on Human Health

13

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Abstract

Mesostructured silica, dendrimers, and allotropes of carbon were exhaustively used in biomedical, cosmetics, semiconductors, and food industry applications. Considering the huge prospect of nanomaterials, their potential hazards on exposure to humans and their related ecotoxicological effects needs to be summarized. Nanoparticles with size below 100 nm could pass into the lung and then to blood through inhalation, ingestion, and skin contact. As nanotechnology innovation is expected to achieve \$ 2231 million by 2025, humans will be exposed ever increasingly in day-to-day life and in industries. In this review, the latest synthetic methodology of silica, dendrimers, and CNTs, their biological applications (in vitro and in vivo) related to toxicity were discussed. In terms of structured silica, the toxic and non-toxic effect induced by specific templates (cetylpyridinium bromide, cetyltrimethylammonium bromide, dipalmitoylphosphatidylcholine, C16L-tryptophan, C16-L-histidine, and C16-L-poline) that are used to generate mesoporous silica, silica nanoparticle sizes (25, 50, 60, 115, and 500 nm), and silane functionalization (NH_2 and COOH) were discussed. The recent applications of different generations (G3, G4, G5, and G6) of amphiphilic Janus dendrimers were discussed along with toxicity effect of different charged dendrimers (cationic and anionic) and effect of PEGylation. Recent synthesis, advantages, and disadvantages of carbon nanotubes (CNTs) were presented for structures like single walled carbon nanotubes (SWCNTs) and multiwalled

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carbon nanotubes (MWCNTs). The influence of diameter of SWCNTs (linear and short), thickness (thin and thick), effect of oxidation, metal oxide species (TiO_2 , Fe, and Au), and biocompatible polymers (polyethylene glycol, bisphosphonate, and alendronate) were shown in relation to molecular pathways in animal cells.

Keywords

Nanomaterials · Negative effects · Human health · Animal studies · in vitro studies

13.1 Introduction

Nanoparticles applications have expanded from general catalytic applications to biomedical uses and food industry. Nanomedicine represents a set of interdisciplinary research at the interface between biology, physics, and chemistry. In the current scenario, nanomedicine research has been reported using target-oriented drug therapy. Research consideration has been given to develop nanotechnology based therapeutic tools for treating chronic diseases such as cancer, cardiovascular, and diabetics. Structured silica nanoplateforms (MCM-41, SBA-15, MCM-48), carbon nanotubes (single walled and multiwalled), polymers (Chitosan, liposomes, dendrimers) are most widely reported for theranostic applications. The nanoparticle utilization has evolved from the monotonous role of drug delivery system to multi-functional role of labeling, drug and gene transportations, detection of pathogens and proteins, as RNA and DNA probe, optical imaging enhancer, tissue designing, biomolecules and cell isolation, and as tumor destructor. Though they are best available drug carriers, they are still marred by certain critical issues like toxicity at high dose level, passivation due to multiple inorganics, and low pH sensitive. In order to reduce the toxicity, several modifications like using biocompatible polymers are reported. The benefit over conventional drug supply includes high stability, solubility, slow metabolization, less excretion of drug, and specific target oriented (Hare et al. 2017). This type of cargos is reported to be effective for several recently developed biomolecules based drugs such as proteins, peptides, oligonucleotides that showed poor biocompatibility (Hoffmann et al. 2018).

13.2 Silica Nanomaterial

Recently, the different types of nano-sized silicas such as graphitized/mesoporous carbon, MOFs and metal oxides are very attractive due to their ordered atomic layers, high surface area, ordered pore size distributions and therefore used in drug delivery and diagnostic applications. Silicalite, the silica form of ZSM-5 nanozeolite has been widely used as adsorbent in industrial relevant process. The structure of silicalite is composed of MFI three-dimensional structure with a diameter of

0.56 nm. The unique properties of such silicalite include (1) high crystallinity, (2) homogeneous structure with high degree of silanol domain, (3) high ability for surface functional groups mobilization, and (4) less structural defects. The surface area is contributed by both internal and external surface area with MFI pore system. The chosen silicalite has 3D porous network, which can provide extensive diffusional access to drug molecules. The other added advantage of such kind support involves the presence of high number of silanol groups relevant for surface functionalization and ability to modification to meso form using several templates such as CTAB, F127 to high surface area support (up to 1100 m²/g) with large pore volume (1 cc/g) and pore diameter (4 nm). Overall, the ability to expand the pore system using mesoporous templates such as CTAB, brij-56, F127, and P123 and create combination of high surface area and ordered pores with uniform pore size distributions makes them attractive for the applications in nanomedicine. In particular, the high adsorption and desorption capacity of external and internal surface hydroxyl groups are expected to be the perfect host (cargo)/drug carriers in drug delivery study.

The attention is usually related to the superior textural characteristics such as high surface area, tunable pore sizes, and high chemical stability. Conventional microporous zeolites (such as ZSM-5) were prepared through sol-gel technique using tetrapropyl ammonium templates. The pores range between 0.5 and 2 nm. The micropores are reported to be in narrow size distribution with slightly high specific surface area between 100 and 500 m²/g, and pore volume and adsorption capacity for gaseous or liquid adsorption. Silicalite, the silica form of ZSM-5 nanozeolite has been widely used as adsorbent in industrial relevant process. The chosen silicalite has 3D porous network, which can provide extensive diffusional access to drug molecules. The other added advantage of such kind support involves the presence of high number of silanol groups relevant for surface functionalization and ability to modification to meso form using several templates such as CTAB, F127 to high surface area support (up to 1100 m²/g) with large pore volume (1 cc/g) and pore diameter (4 nm).

Due to nanotechnology revelation (nano biomedical technology), there is a renewed interest in the therapeutic and diagnostic utilization of structured silicas. The application of diagnostic nanosilicas has been used as new transfecting agents (Tieu et al. 2019) and immunoassay (Banerjee and Jaiswal 2018). The role of diagnostic nanosilica drug carrier is to respond to external field and thereby assist bioimaging, magnetic targeting agent to carry drug and delivery (Tiwari et al. 2018). For example, the magnetic nanosilicas have already been shown to have the potential to develop cancer-based drug on commercial basis. The material has shown positive success in animal study and in clinical trials (Rainone et al. 2017).

Cisplatin/hierarchical mesosilicalite nanoformulation (IAUM-56) has been developed. The basic nanocarrier has been derived from silicalite, a zeotype material. The micropores of silicalite were turned into hierarchical pores through template mediated dissolution technique (top-down approach) The formation of micro- and mesopores (hierarchy) was established through several characterization techniques such as X-ray diffraction, BET surface area analysis, and transmission electron microscope. The cytotoxic effect of the designed in-house nanoformulation

IAUM-56 against HeLa cells and MCF-7 cells exhibited a drastic reduction in cell proliferation. Drug cisplatin showed high toxicity against normal fibroblast cells, while IAUM-56 showed a lesser toxicity (Jermy et al. 2018). SPIONs/SBA-16 silica composite functionalized with silane and cisplatin has been reported (Jermy et al. 2019). The MTT cell viability assay shows that HeLa cells were most sensitive towards cisplatin bound with silane/SPIONs/SBA-16 nanoformulation. The LC50 value shows that the formulation is 2.9 times more effective on HeLa cells compared to HCT 116 and HEK 293.

Multifunctional nanocomposite silica was reported involving natural antioxidant curcumin and polyethylene glycol. The textural features of mesoporous silica as analyzed by transmission electron microscope and dynamic light scattering techniques show monodispersed spherical silica with particle size of about 185 nm with polydispersity index value of 0.52. Zeta potential analysis of silica indicated positive surface charge of 38.3 ± 6.09 mV. The loading of curcumin over silica reduced the surface charge positivity to 36.2 ± 3 mV. With polyethylene glycol coating, further decrease in charge occurs to 20.8 ± 4.28 mV. However, the presence of such negative potential increases the stability in between the particles. The release study of nanoformulation involving mesoporous silica, curcumin, and polyethylene was measured at tumor pH value of 5.5 and normal physiological pH condition of 7.4. The nanoformulation showed a controlled release, beginning with slow release of curcumin (<1%) until 192 h in normal pH of 7.4. In case of tumor pH 5.5, the polyethylene glycol disintegrates and followingly curcumin release was accelerated to 52%. The release efficiency was reciprocated in in vitro study, where the formulation exerted significant cytotoxicity against HeLa and HepG2 cells. The prime reason was attributed to the cell cycle arrest at G2/M (Elbially et al. 2020).

13.2.1 Silica toxicity

The emergence of nano-revolution sparked a wave in interdisciplinary field of research from material to medicine. The market of nanotech and smart pill is expected to grow 125 billion US dollar and 650 million US dollar by the year 2025. Nevertheless, the health benefit of stable in humans remains an apprehensive and intimidating. In particular, the nanoparticle seems to affect the reproductive organ and lungs more severe followed by liver and skin (Elalfy et al. 2018). In case of silica nanoparticle (Fig. 13.1), the exposure route was reported to exert several kinds of toxicity (Shi et al. 2013; Missaoui et al. 2018; Inoue and Takano 2011).

In cell regulation, protein kinase B (serine/threonine) plays an important role in cellular functions like survival of cells, multiplication, cellular moments, proinflammatory cytokines expressions (Szymonowicz et al. 2018). In molecular signaling pathway, Phosphoinositide 3-kinases (PI3Ks) enzyme is present in cell membrane. Tyrosine kinases are the cell surface receptors, it activates the PI3K and produces the phosphatidylinositol 3-phosphate (PI3P), which is a lipid mediator. In parallel, PI3P and Akt binding activate proteins lead to Akt activation by two phosphorylated amino acids. Various substrates were recognized by AKT. In cell cycle function,

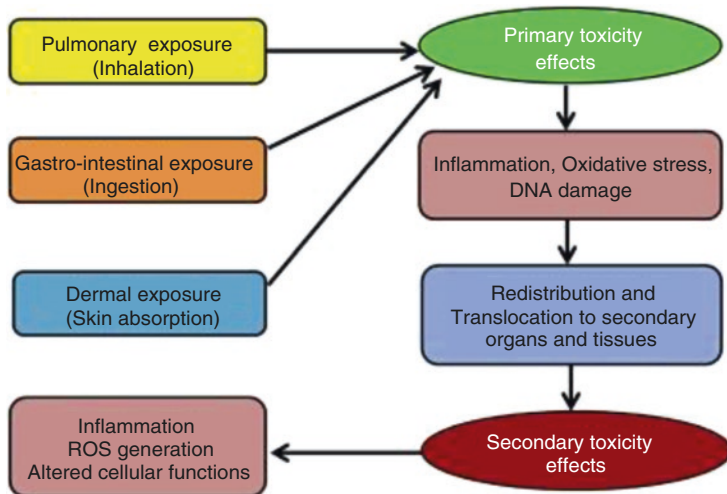


Fig. 13.1 Silica nanoparticle toxicity at different human body exposed sites (Shi et al. 2013; Missaoui et al. 2018; Inoue and Takano 2011)

proliferation and apoptosis occur with balance. Pro-apoptosis proteins (BAD, BAX) involved in the for Akt kinase activity as substrate (Koh et al. 2000). The biological effect of nanosized silica exhibited high internalization, elevates the inflammatory responses, initiates autophagy through PI3k/Akt/mTOR pathway (Duan et al. 2014). In addition, silica nanoparticle induced apoptotic pathway is reported to generate reactive oxygen species. This generated free radicals causes the stress and stimulates TNF α and TNFR1 which leads to stimulation of FADD–procaspase-8–Caspase-8–BID resulted program cell death. The BCL-2 protein then shifts to mitochondria and activates the mitochondrial pathway related protein Caspase-3, -6, -7 leading to mitochondrial apoptosis (Asweto et al. 2017). Silica nanoparticle 30 (SNP30) induces reactive oxygen species production in KUP5 cells. P2X7 receptor is simulated by SNP30 and releases ATP. Increasing the reactive oxygen species simulates the inflammation pathway through caspase-1-dependent pathway (Kojima et al. 2014). The toxic effect of nanomaterial was studied using 3D human liver microtissue model. In vivo study involving nanomaterial dose at lower concentration for 3 weeks with liver's recovery tenure of 2 weeks was studied. Investigation revealed that cytokine profile involving IL6, IL8, IL10, TNF-alpha is effective in analyzing recovery period in pro-inflammatory response reduction (Kermanizadeh et al. 2019). Chen et al. (2018) have reviewed and reported that toxicity due to silica nanoparticle involves generation of reactive oxygen species and autophagy are critical mechanistic pathway to affect immune system (Fig. 13.2).

The different dose effect of mesoporous silica prepared using cetylpyridinium bromide as template, tetraethylorthosilicate as silica source was studied for heart and lung toxicity. The in vivo study was conducted by varying the dose of nanoparticle between 25 and 200 mg per kg body weight for the period of one month.

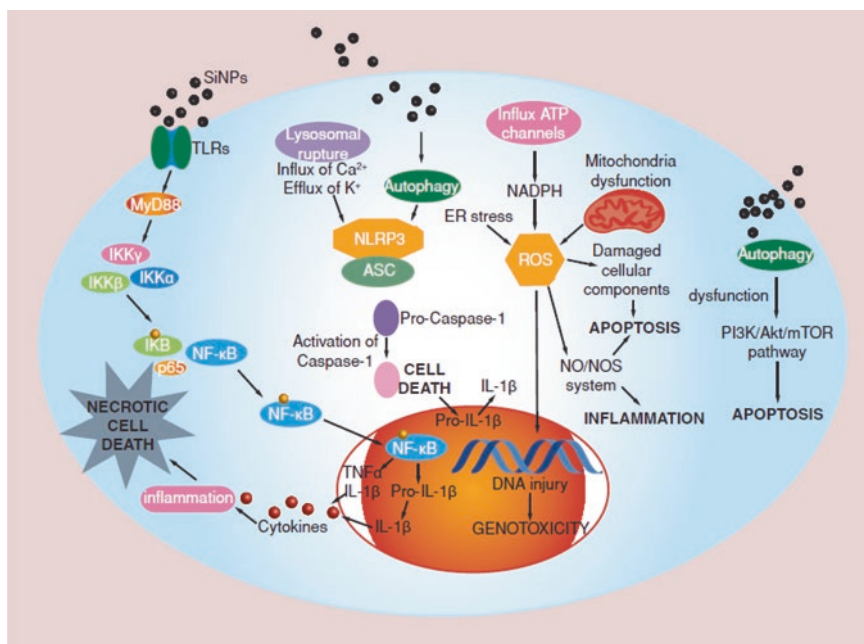


Fig. 13.2 Silica nanoparticle induced toxicity (Chen et al. 2018)

The study revealed that silica nanoparticle elevated the cardiac makers, tumor necrosis factor alpha (TNF α), and cholesterol. Mesoporous nanoparticles administered rats showed abnormalities in hematological indices due to elevated levels of reactive oxygen species. Antioxidant levels were reduced leading to toxicity in cardiac and lungs. It was confirmed by histopathological examinations. Conclusively MSNs affect the cardiac, respiratory, hematological, and tissue (Hozayen et al. 2019).

Li et al. (2019c) explored the inhalation toxicity of silica nanoparticle in the presence and absence of surfactant dipalmitoylphosphatidylcholine. In vitro study indicated that at dose level of 128 microgram/milliliter, the nanoparticle without template exerted cytotoxicity in 16HBE human bronchial epithelial cells. However, the presence of template reduced the toxicity. In case of A549 adenocarcinomic cells, such toxicity of silica was not observed. The main cause of such adverse effect was found to be due to internalization effect and generation of reactive oxygen species. In 16HBE cells, ABC transporter (Calcein) plays a key role, induced by silica at high dose. Inhibitor of transporter (MK571) elevates the silica toxicity in 16HBE and A549 cells.

The biocompatibility, degradation, and toxic effect of silica mesoporous nanoparticles synthesized from sodium silicate (silica source) have been reported. The study indicated a less toxic effect of such nanoparticles. At normal blood pH condition, the silica determined to be degraded within 6 days to silicic acid form. In addition, nanoparticle found to be biocompatible (90% cell viability) with different cell lines (HEK-293, Caco-2, HepG2, and 3 T3). The silica concentration can be as high as

200 microgram per milliliter. Hematological and biochemical assays showed that mice have well tolerance level (40 mg/kg) and excreted as silicic acid (20 mg/kg) in 4 days (Bhavsar et al. 2019).

Silica nanoparticle toxic effect for particle size of 50 nm (small) and 500 nm (large) was explored through intravenous administration, single dose in male and female immune-competent inbred BALB/c mice. The particles were prepared following Stober synthesis using cetyltrimethylammonium bromide (template), ammonia (catalyst), ethanol (solvent), and tetraethylorthosilicate (silica source) at room temperature. The maximum tolerance dose study showed that nanoparticle with 50 nm size induces cytotoxicity for female of 103 ± 11 mg/kg and male of 100 ± 6 mg/kg. The toxic effect found to reduce with increase in particle size. However, the sex related toxicity reported to increase with large particle silica (40 ± 2 mg/kg for male; 95 ± 2 mg/kg for female) (Mohammadpour et al. 2019).

Toxic effect of three types of mesoporous silica was reported using three different types of heterocyclic amino acid-based templates such as C16-L-tryptophan, C16-L-histidine, and C16-L-poline, respectively. The *in vitro* and *in vivo* study were studied evaluating the silica particle bioavailability, disintegration, which are primarily based on their wettability. The silica was reported to disintegrate within 2–13 weeks under simulated physiological condition. The study showed that silica synthesized with C16-L-tryptophan template contains largest hydroxyl groups and tends to disintegrate quickly due to high wettability. However, severe hemolysis and cell cycle arrest were observed. Therefore, caution must be taken by choosing the silica with apt wettability property (Li et al. 2019).

The nanoshell containing silica alone and iron-silica (Fe-SiO₂) with size ranging between 497 and 455 nm was synthesized using tetramethyl orthosilicate (silica), iron ethoxide (iron source), and amino polystyrene (template). The thickness of shell involving silica was found to be about 33 nm, while Fe-SiO₂ of about 27 nm, respectively. The single dose acute toxicity study using 10–20 mg per kg dose showed that only very less amount of silica was present inside the body after 10 weeks and then nanoformulation showed no chronic toxicity (Mendez et al. 2017).

Lung inflammation in *in vitro* using human lung cancer epithelial cell line (A549), and *in vivo* using C57BL/6 mice was assessed using silica prepared by Stober method and silane functionalized silica (3-aminopropyltriethoxysilane). The nanoparticle in the absence and presence of silane group found to exhibit a less lethal effect at a concentration of 200 µg/ml. Respiratory toxicity study was reported by introduction of two types of silica directly into trachea (intratracheal instillation). Surprisingly, silica alone induced an elevated level of inflammation compared to silane functionalized silica. Each mouse treated with two doses of silica (0.1 and 0.5 mg) showed an increased the level of leukocyte and protein level indicating the responses to infections. However, silane functionalized silica reduces lung infection and improves the bioavailability of silica (Morris et al. 2016).

Silica nanoparticle with sizes of 25 nm, 60 nm, and 115 nm, along with amino and carboxylic acid functionalized silica was studied for embryotoxic effect. Each animal was intravenously treated with dose concentration of 200 microgram at three gestational periods (5.5, 12.5, and 16.5 dpc). At gestational period of 5.5 and 12.5 dpc,

silica with particle size of 25 and 60 nm was observed in conceptuses. In later part, three nanoparticles were observed in placenta due to high permeability factor. At 5.5 dpc, silica particle with 25 nm with positive charge density ($+30 \pm 5$ mV) and –COOH functionalized silica with 60 nm (-44 ± 5 mV) were observed in conceptuses. In stage of 12.5 dpc, both species were observed in placenta and fetuses. At 16.5 dpc, silica irrespective of particle sizes with positive charge was found to be accumulated in placentas. However, with negatively charged silica particles, 60 nm and 115 nm were observed in fetuses. The study conclusively determines that silica with 60 nm with negative charge density of -44 ± 5 mV was able to cross placenta and reach conceptus. Except silane functionalized with 25 nm size silica, other particles of different charge density were found to be non-toxic and safe for placental development (Pietrojusti et al. 2018). Silica nanoparticle induced an elevated level of oxidative degradation of lipids and inflammatory cytokines. Ultrafine silica particles were excreted in urine (Hong et al. 2017). Pure silica induced oxidative stress and toxicity in vitro lung cell line (A549) and animal model studies cells through the oxidant generation such as reactive oxygen generation and lipid peroxidation (18).

13.3 Dendrimers

Dendrimers are supramolecular structured branched polymers. Branching of polymers occurs from perfect dendrimers and expands from dendrons layers in an ordered precise pattern. The assembly of chemical species is driven by phase separation leading to spatially arranged supramolecular domain (e.g., surfactant templates-based micelles, vesicles, and rods). The repeating layers were known as generation (G). The structure depends on the initiator core that can lead to helical tubules, supramolecular hydrogels, and spherical aggregates. Initiator core can be cystamine, ammonia, or ethylenediamine. Methyl acrylate addition to core followed by amidation leads to expand dendrimers. Based on the elements of organics (carbon, phosphorus, and nitrogen) in core and number of branching polymers, over 100 dendrimer families were prepared. Dendrimers at lower generations display open structure due to less branching patterns, while the surface density increases with branching leading to globular form. With each generation, an increase in the particle size occurs to about 1 nm. Precise control leads to formation of monodispersed dendrimers. The presence of active functional groups at the external end site promotes further functionalities.

Dendritic units containing hydrophilic and hydrophobic groups are used to prepare supramolecular structure known as amphiphilic Janus dendrimers. Controlling the chemical functionalities of such dendrimers in water leads to different structured morphologies known as dendrimersomes. Recently, a series of hybrid types of Janus dendrimers based on fluorinated, hydrogenated, and combination of both chemical components were reported by Xiao et al. (2017). Moreover, Ohta et al. (2019) have reported the Janus diblock hyperbranched copolyimide. The morphological structure of Janus dendrimers tuned from spherical aggregated to cylindrical and then to

dendritic shape with aqueous solution temperature variation from 25 °C to 50 °C and to 70 °C. Onion shaped Janus dendrimers have been reported to be influenced by the enthalpy rather than concentration that leads to lamellar, micelles, and vesicles (Hu et al. 2019). Dendrons are attached with one or two cell adherence motifs. Scaffolds coated with linear peptide coating (L-lysine) showed improved colonization of scaffold surface by human bladder smooth muscle cells. Dendrimersomes can be an effective drug delivery system due to their unique physical characteristics such as high stability in biological media, monodisperse and can load both hydrophobic and hydrophilic type of drugs.

siRNA delivery using disulfide containing Janus dendrimer was reported by Du et al. (2018). The reported redox sensitive delivery system with particle size of about 40 nm and distribution of size value of 0.20 (polydispersity index) was constructed in aqueous solution using cationic polymer with hydrophilic head group and disulfide group containing hydrophobic dendron. Redox property was imbedded using hydrating thin film technique. Zeta potential measurement indicated the positive surface charge of about 47 mV, which effectively allows the binding of siRNA with negative charge. The siRNA release study showed advantage of disulfide containing dendrimer with high percentage of siRNA release of about 67% within 5 min and attains to maximum of about 97% in 4 h. Redox based dendrimer also reported effective for simultaneous drug and gene delivery. Diaminobutane core (DAB) based generation 3 dendrimer (diaminobutyric polypropylenimine) with particle size ranging between 150 and 200 nm coupled with polyethylene glycol and camptothecin (anticancer drug) was reported to be effective for delivering DNA along with drug to cancer cells (Laskar et al. 2019). Somani et al. (2018) have investigated generation 3- and 4- DAB based dendrimer for gene delivery. Polyethylene glycated (PEG ~2 kDa) DAB exhibited high gene expression on treatment with B16F10-Luc cells. The toxicity induced by DAB on B16F10-Luc cells was reduced significantly by three-fold compared to dendrimer without modifications and therefore effective for gene delivery and transfection efficacy. Nile Red encapsulated Janus dendrimers are reported using copper-based click reaction for drug release of propranolol. Morphological characterization using transmission electron microscope and dynamic light scattering techniques showed the formation of uni- to multilamellar dendrimersomes in size ranging between 90 and 200 nm suitable for biomedical uses (Nummelin et al. 2017).

In case of dendrimers, the cytotoxicity depends on the type of dendrimers used in biomedical applications. There are reports suggesting that cationic dendrimers exhibit toxicity compared to anionic (Morris et al. 2017) and non-ionic dendrimers. The prime reason is attributed to the effective electrostatic interactions positively charged dendrimer with negatively charged cell membranes (Malik et al. 2000; Janaszewska et al. 2019). Dendrimers with primary amines at the terminal site like PAMAM and PPI were reported to exert dose dependent toxic effect (Mendes et al. 2017). Dendrimers with neutral or anionic terminal group showed less toxic effect (for example, carbosilane-poly(ethylene oxide)). The generation-based cytotoxicity induced by PAMAM was found to generate reactive oxygen species, enhance

lysosomal activity, apoptosis, and DNA disintegration (Mukherjee et al. 2010). PAMAM inhibited the growth of microbes significantly than G3 and G2. PPI with diaminobutane or diaminoethane core, poly(ethylene oxide) (PEO)-grafted carbosilane (CSi-PEO), and polyether dendrimers and surface functionalities were studied in *in vitro*. Li et al. (2009) have reported a molecular mechanistic based study about the PAMAM based dendrimer (Starburst polyamidoamine) effect in lung injury. *In vivo* study revealed that the nanoformulation triggers autophagic cell death by deregulating Akt-TSC2-mTOR signaling pathway. PAMAM induced lung injury can be suppressed by the addition of 3-methyladenine (autophagy inhibitor). Wang et al. indicated that cationic type of PAMAM dendrimers studied in human glioma cells promoted both cytotoxicity and autophagic degradation activity (autophagic flux). The autophagy was found to be initiated partly by intracellular reactive oxygen species and occur through Akt/mTOR pathway. Ultrastructural analysis clearly showed the accumulation of autophagic vacuoles caused by dendrimers. In addition, the Western blot analysis showed critical influence of dendrimers leading to autophagic flux effect at different PAMAM concentration for 20 h (Wang et al. 2014). It has been further reported that anionic PAMAM and CNTs remains as non-toxic and induce no toxic effect in mice. Whereas cationic PAMAM found to directly interact with angiotensin converting enzyme 2 (ACE2) leading to dysregulation of renin angiotensin system by reducing the activity and downregulation of its expression in lung tissue (Sun et al. 2015). It has been shown that modification of terminal surface of cationic dendrimer with less toxic anionic or neutral group can reduce the toxicity. Functionalization with biocompatible polymers such as polyethylene glycol and pyrrolidone can decrease the cytotoxicity (Fig. 13.3).

13.4 Carbon Nanotubes

Carbon nanotubes (CNTs) belong to the carbon allotropes and are cylindrical in shape with hexagonal arrangements of carbon atoms. The CNTs were as strong as steel but thin like human hair. Based on their sidewalls and spatial arrangements, they are further differentiated as multiwalled carbon nanotubes (MWCNTs) and single walled carbon nanotubes (SWCNTs). Key advances in nanotechnology led CNTs into a wide variety of applications in electronics to energy sectors. Unique physico-chemical properties of CNTs are found to be an attractive material for drug and gene delivery applications. Numerous applications have been reported using CNTs as drug delivery system in chronic diseases. The transportation of CNTs was reported to occur by lymphatic circulation. SWCNTs and MWCNTs have been debated over toxicity due to their ability to interact with body organs. In particular, SWCNTs due to their dispersive and hydrophobic character reported to inflict more toxicity leading to apoptosis compared to MWCNTs (Cui et al. 2005). Inhalation of CNTs induces more toxicity than other mode of administration such as injection, dermal, and oral. Inside the body, the nanoparticle interaction occurs

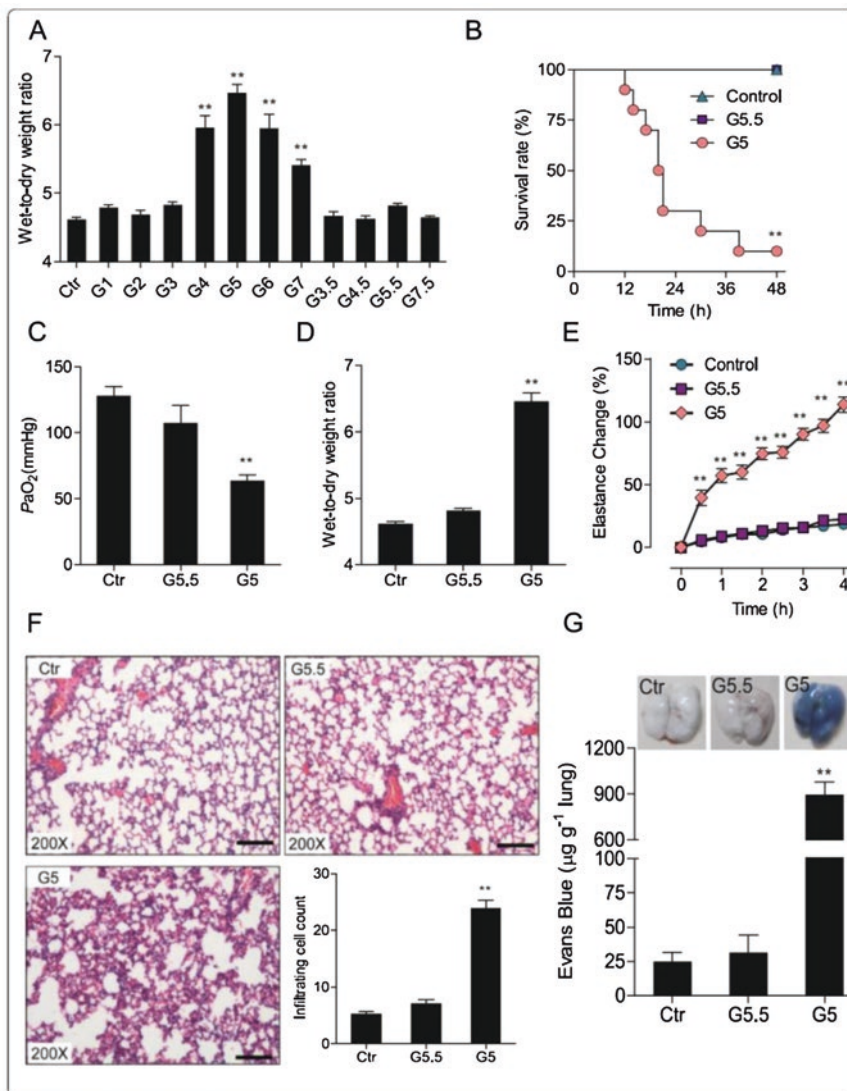


Fig. 13.3 G5 PAMAM dendrimers toxicity in lung (Sun et al. 2015)

with cells leading to distributions of particles to various organs and either remains localized or excreted depending on the chemical functionality. Importantly, the textural characteristics such as functional moieties and crystal size tend to play vital role in inducing toxicity. It has been proposed that toxicity occurs mainly due to extracellular matrix protein signaling leading to apoptosis.

13.4.1 Lungs Toxicity

SWCNTs were shown to exert respiratory toxicity of inflammation and cytotoxicity in rats through intratracheal deposition at the tissue walls and in alveolar leading to formation of different colored spots including black, brown, and gray (Honda et al. 2017). Particle transition of CNTs as clumps occurs during such deposition and then eventually transforms to tumor formation. SWCNT functionalized with carboxyl group treated animals showed respiratory embolization in lung. Also, inflammation was observed in lung histological examination. Due to oxidative stress and lung toxicity, a pro-inflammatory cytokines activation occurs and cause strong inflammation. This indicates that macrophage fails to phagocytize SWCNT and causes lung toxicity (Mohanta et al. 2019).

13.4.2 Liver Toxicity

Liver is one of the vital organs in the body, metabolic pathway is regulated by liver. Drug metabolization involves various enzymatic actions. An *in vivo* study using SWCNTs was evaluated to analyze the efficient bioavailability. SWCNTs were administrated for nine weeks. SWCNTs accumulation increases the uncontrolled cell growth, elevated the enzymatic action and inflammation (Principi et al. 2016). Aspartate aminotransferase, alanine aminotransferase, and bilirubin levels were elevated due to the liver toxic, which was evaluated by serum liver marker assays. Also, histopathological evaluation of SWCNT treated CD1 mice showed tissue inflammation and infiltration. Therefore, exposing CNTs without functionalization for long duration even with less dose imparts undesirable side effects such as inflammation and toxicity in liver.

Oxidized MWCNT nanomaterial was administrated in mice model. It leads to liver toxic and it was confirmed by serum liver function test such as aspartate aminotransferase and alanine aminotransferase. When it was treated by simvastatin, the toxic effect was reduced, and normal functions were restored (Qi et al. 2017). To evaluate the cytotoxic of Mitsui-7- MWCNTs, a studied was reported using various cells. Human alveolar type II epithelial cells A549 cells, the THP-1 The MRC-5 lung fibroblast cell line (ATCC CCL-171) were treated with different concentration of Mitsui-7- MWCNTs and exposed with different time durations. The exposure of MWCNTs to 24 h stimulates the proinflammatory response. Long term exposure leads to elevate profibrotic mediators but not in correlation with production of collagen or cell regulation (Chortarea et al. 2019). The cytotoxicity effect of various functionalized CNTs was studied in cell line of Caucasian colon adenocarcinoma grade II carcinoma (HT29). HT29 was used as experimental cell model in 2D (monolayer) and 3D (spheroid) system, along with *in vitro* 2D and 3D cancer cells (*in vitro*) and mice model (Balb2/c). Doxorubicin (DOX) was found to be effectively functionalized on the CNT surface and release in a controlled manner due to disintegration of peptide bonds with CNT surface. The DOX/CNT composite

showed less cytotoxic effect compared to unmodified DOX. Liver marker enzyme ALT, AST, ALP Albumin, and total protein and blood profile confirmed the role of CNT in drug delivery. It reduces the DOX liver damage and other related complications (Perepelytsina et al. 2018). The effect of thin bundles (CNT-1) and thick bundles of SWCNTs (CNT-2) was studied for pulmonary toxicity. In vitro and in vivo study was conducted. CNT-1 and CNT-2 were administrated and tested for lung toxicity. The MIP-1 α protein, bronchoalveolar lavage fluid (BALF), and histotechnique indicated an inflammation in pulmonary cells caused by CNT-1. However, the toxicity induced by CNT-1 managed to recover in slow phase, while CNT-2 exerted significant acute toxicity in lung. In molecular level, various genes were altered by CNT-2 after treatment of 1 day. CNT-2 induces the reactive oxygen species (ROS), suppresses cell multiplications, while CNT-1 did not exert significant adverse effect. The study showed CNTs with thin bundle inflict less inflammation than thick shaped CNT-2 (Fujita et al. 2015).

Zhang et al. (2019) reported the engineering of MWCNT functionalized with thermosensitive block copolymer that act as gatekeeper for DOX. Based on the pH conditions, the release of drug is manipulated (tri-stimuli). A composite involving MWCNT and mesoporous silica grafted with Schiff base linked with DOX has been reported to be active against Hela cells with concentration less than 10 microgram/ml. The nanoformulation without DOX shown to be less toxic, while DOX loading with maximum capacity of 51.8% showed increased toxicity inside cancer cells.

Karthika et al. (2018) used de-toxification of MWCNT using metal oxide nanoparticles such as titanium dioxide along with gold. The coating over MWCNT was carried out using solvothermal technique. The bark extract of *Guazuma ulmifolia* Lam that belongs to Sterculiaceae family was used as reducing agent. DOX was used as anticancer drug with concentration of 0.5 mg/ml. The study showed that the presence of high surface area of CNT, enable the loading of TiO₂ and Au and increase the biocompatibility of nanoformulation. The linkage of DOX with CNT was attributed to the presence of hydrogen bonds and π - π stacking. The presence of such bonding seems to control the pH based DOX release of about 90% at cancer condition (pH 5.5) and of about 11% normal condition (pH 7.4) for a period of 10 h, respectively. In vivo study on Zebrafish embryos showed that nanoformulation involving TiO₂-Au-MWCNT had reduced the toxicity not affecting the hatching of embryos. CNTs with iron metal residue have shown to generate hydroxyl radicals and their dissolution in biological media tends to affect biological targets (Ge et al. 2012; Fig. 13.4).

The cytotoxicity study of MWCNT has been studied with residual iron and iron extracted pure form of MWCNT (heat treated) in A549 human lung epithelial cells. Interestingly, the cytotoxic effect found to depend on the lack of surface defects of MWCNT caused by heat treatment due to free radical generation and interference inside the cell cycle. The presence of residual iron exerted less toxicity (Requardt et al. 2019).

The drug delivery application of Buckypapers and aggregated forms of CNT was reported using different kinds of drugs (acidic and basic characters). The study

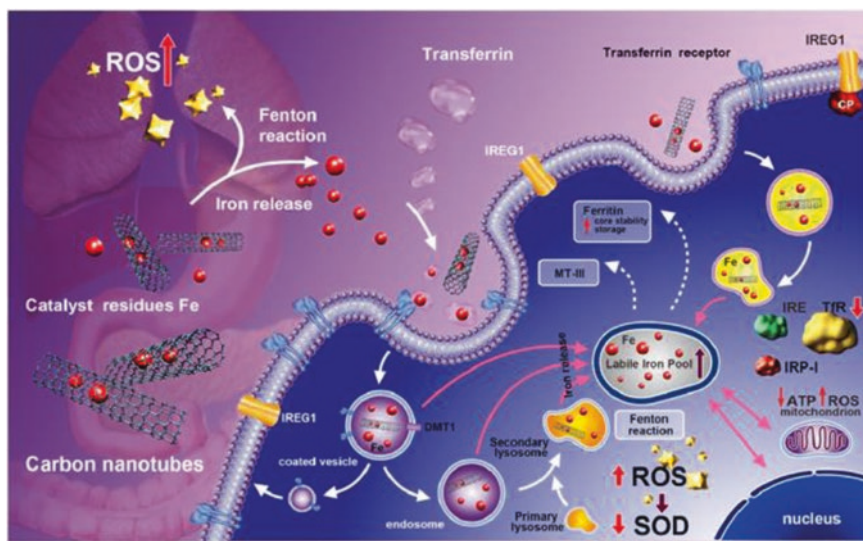


Fig. 13.4 Transport pathway, cellular and molecular mechanisms of toxicity associated with cellular exposure to carbon nanotubes and leached metal (Ge et al. 2012)

reveals the sonication effectiveness for conductive property and drug release experiments. The drug release pattern (passive) was found to depend on the non-covalent bonding. The release can be accelerated or decreased by adjusting the predetermined voltage or current of required polarity (Schwengber et al. 2017).

Modified CNTs were reported by functionalizing with biocompatible polymer polyethylene glycol and bone targeting groups (bisphosphonate and alendronate) for organ specific DOX drug delivery application. The nanocomposite was reported to be effective for DOX loading (35% wt/wt) and release ability (about 51% after 2 days). Biocompatibility of nanoformulation was proved with dispersibility (neoplastic transformation), chromosomal aberration, and cytotoxicity assays. In vivo study showed that compared to free DOX, DOX bound functionalized CNTs (PEG-dMWCNTs and BT-PEG-dMWCNTs) effectively decrease the tumor size and increase the survival period of mice (Falank et al. 2019).

Bisphosphonates were used as effective drugs against osteoporosis. It has been reported that MWCNTs can be functionalized with bisphosphonates such as neridronate, pamidronate, and alendronate. The effective conjugation of bisphosphonates with oxidized MWCNTs was established using thionyl chloride-DMF mixture solution under refluxing condition. After washing with THF, the prepared bisphosphonate along with glucosamine in THF was added and again refluxed. After conjugation, the release of neridronate was studied at three different pH conditions 1.2, 5.5, and 7.4. The high neridronate release at low pH 1.2 than pH 5.5 and pH 7.4 shows the important influence of amine protonation with subsequent dissociation of hydrogen bonding leading to controlled release (Dlamini et al. 2019).

Multifunctional CNT (Fe) in composite with hydroxyapatite was synthesized using chemical vapor deposition technique for pH responsive DOX release. The formulation showed magnetic saturation value of 0.88 emu/g. The composite was fabricated with biocompatible polymer such as chitosan using acid treatment of CNT in the presence of sulfuric acid/nitric acid mixture. Folic acid was further functionalized using EDC chemistry (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC).HCl). In the presence of π - π stacking and folic acid, high adsorption of DOX was reported (up to 130 wt%). In addition, pH sensitive DOX release (52 wt%) was observed at tumor acidic condition of pH 5.5 after 3 days. The formulation showed very less drug release of about 8 wt% at normal pH condition (pH 7.4) (Li et al. 2019).

Nervous necrosis virus attacks the protected central nervous system (CNS) of fish leading to mass mortality. The presence of barrier blood cerebral spinal fluid in CNS limits the conventional drugs reaching the target site and therefore reduces the therapeutic efficiency against infection such as necrosis and vacuolation. Single walled carbon nanotubes are (SWCNTs) reported to be an effective nanocarrier for tsoprinosine that contains inosine acedoben dimepranol active for antiviral effect. The drug activates T-helper cells to kill infected cells. The study shows an enhanced antiviral effect of SWCNTs functionalized isoprinosine with low concentration of 200 mg per liter for period of 3 and 5 days than pure form of Isoprinosine (Zhu et al. 2019). Graphene, allotrope of carbon was reported to simulate macrophages functions (Th1/Th2 cytokines) (Zhou et al. 2012; Fig. 13.5).

13.5 Conclusion

Structured silica, dendrimers, and carbon nanotubes were important nanomaterials that are expected to play a major component in future biomedical relevant appliances. The review shows that templates, solvents, silica source, functionalization silanes, and synthesis conditions of nanoparticles play a critical role in inducing lung inflammation. Mesoporous silica synthesized using sodium silicate as silica source, nanoshell based Fe-SiO₂, C₁₆-L-tryptophan template-based silica, dipalmitoyl phosphatidylcholine template-based silica were reported to be non-toxic and effectively disintegrate in biological medium. Silica nanoparticle synthesized using templates like cetylpyridinium bromide and heterocyclic amino acid-based templates such as C₁₆-L-histidine and C16-L-poline were reported to be toxic. Mesoporous silica prepared by Stober method in the presence of template cetyltrimethylammonium bromide was reported to be toxic, while in the absence of template led to non-toxic silica nanoparticle. Non-porous silica prepared by Stober method in the presence of silanes exhibited reduced toxicity in lungs compared to unmodified silica. Dendrimers can be an effective nanocarrier by controlling the surface charge density of cationic dendrimers or using anionic or non-ionic dendrimers. The biocompatible can be improvised using polymers like polyethylene glycol and components like bisphosphonate and alendronate. In case of single

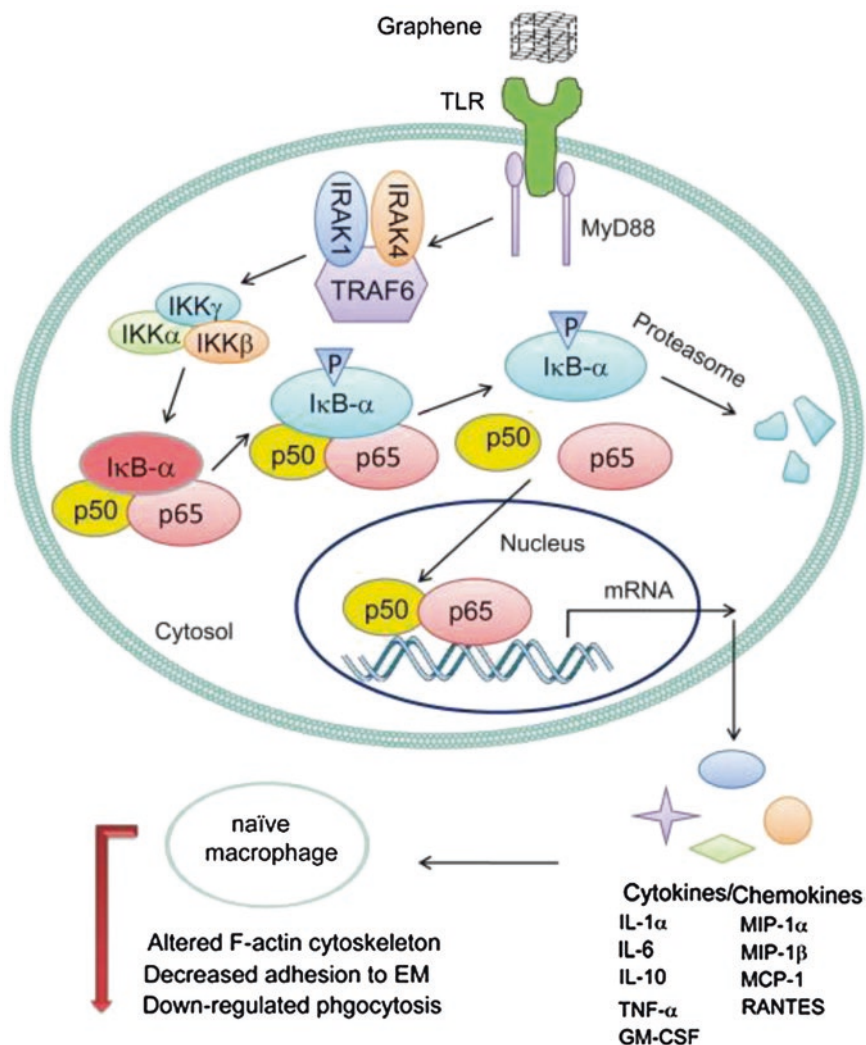


Fig. 13.5 Graphene induced activation of macrophage signaling pathway (Zhou et al. 2012)

walled carbon nanotubes (SWCNTs), short and long form of SWCNTs are reported to induce inflammation and respiratory toxicity, though no genotoxicity was observed. Multiwalled carbon nanotubes (MWCNTs) have shown to induce proinflammatory response and elevate profibrotic mediators. However, the cytotoxicity of carbon nanotubes in lungs can be reduced significantly by using biocompatible polymers such as polyethylene glycol, chitosan, insertion of metal oxides (iron, TiO₂, Au), oxidized form of nanotube with drug like Simvastatin, and by using thin bundles CNTs (Table 13.1).

Table 13.1 Impact of nanomaterials on organs/cells/tissues

Sl. No	Material	Material source	Study type	Organ toxicity	Biocompatibility	References
	<i>Silica</i>					
1.	MSN	Cetylpyridinium bromide (template), urea, cyclohexane, isopropanol, tetraethylorthosilicate	Albino Wistar rats	Reactive oxygen species generation in heart and lung, inflammation, anemia, thrombocytopenia	–	Hozayen et al. (2019)
2.	MSN	Silica obtained from Nanjing XFNANO Materials Tech Co., Ltd. (prepared using Stober method)	A549 adenocarcinomic cells and 16HBE human bronchial epithelial cells	Without template-dipalmitoyl phosphatidylcholine exhibits toxicity in 16HBE human bronchial epithelial cells	With template-dipalmitoyl phosphatidylcholine induces less toxicity and high compatibility	Li et al. (2019)
3.	MSN	Cetyltrimethylammonium bromide (CTAB), Na ₂ SiO ₃ (silica source), ethyl acetate	HEK-293, Caco-2, HepG2, 3 T3	–	Exhibits high biocompatible (90% cell viability) with different cell lines (HEK-293, Caco-2, HepG2, and 3 T3). Degraded within 6 days	Bhavsar et al. (2019)
4.	MSN-50 nm (size) MSN-500 nm	Cetyltrimethylammonium bromide (template), ammonia (catalyst), ethanol (solvent) and tetraethylorthosilicate (silica source)-Stober method	Intravenous administration, single dose in male and female immune-competent inbred BALB/c mice	Cytotoxicity exhibited by both size nanoparticles under acute conditions	Exhibits less subchronic toxicity compared to non-porous silica on 60 and 180 days	Mohammadpour et al. (2019)

(continued)

Table 13.1 (continued)

Sl. No	Material	Material source	Study type	Organ toxicity	Biocompatibility	References
5.	MSN	Different types of heterocyclic amino acid-based templates such as C16-L-tryptophan, C16-L-histidine, and C16-L-polline, respectively	In vitro and in vivo study	Severe hemolysis and cell cycle arrest were observed	Silica synthesized with C16-L-tryptophan disintegrates quickly due to high wettability, reduce toxicity	Li et al. (2019)
6.	Nanoshell SiO ₂ and Fe-SiO ₂	Using tetramethyl orthosilicate (silica), iron ethoxide (iron source) and amino polystyrene (template)	Single dose acute toxicity study using 10–20 mg per kg dose	–	Trace amount SiO ₂ nanoparticles observed in lung and no inflammatory response observed in lungs	Mendez et al. (2017)
7.	MSN	Cetyltrimethylammonium bromide (template), ammonia (catalyst), ethanol (solvent), and tetraethylorthosilicate (silica source)	Lung inflammation in in vitro using human lung cancer epithelial cell line (A549), and in vivo using C57BL/6 mice	Respiratory toxicity	–	Morris et al. (2016)
8.	MSN-Silane	Non-porous silica, no template used, ammonia (catalyst), ethanol (solvent), and tetraethylorthosilicate (silica source) 3-aminopropyltriethoxysilane	Lung inflammation in in vitro using human lung cancer epithelial cell line (A549) and in vivo using C57BL/6 mice	–	Amine functionalized silica showed reduced toxicity, less reactive oxygen species in lungs compared to unmodified silica	Morris et al. (2016)

9.	Silica -25 nm, 60 nm, and 115 nm	NH ₂ and COOH functionalized silica nanoparticles	Embryotoxic effect In vitro lung cell line (A549) and animal model	Silica-25 nm size silica 3-aminopropyltriethoxysilane Oxidative stress and toxicity studies cells through the oxidant generation such as reactive oxygen generation and lipid peroxidation	Silica 60 nm and 115 nm Non-toxic and safe for placental development	Pietroiusti et al. (2018)
10.	Ultrafine silica	Silica nano and silica microscale obtained from Zhejiang Hongshen Material Tech. Ltd. Company, China	In vitro lung cell line (A549) and animal model	Generation such as reactive oxygen generation and lipid peroxidation	–	Hong et al. (2017)
<i>Dendrimers</i>						
1.	Diaminobutane core (DAB) based generation 3, 4, and 5 dendrimer (diaminobutyric polypropylenimine) for gene delivery	Diaminobutyric polypropylenimine (3-, 4-, and 5-), methoxy PEG (~2 kDa) succinimidyl carboxymethyl esters	Bioware PC-3 M-luc-C6 human prostate adenocarcinoma, bioware B16F10-Luc cells, A431 human epidermoid carcinoma, T98G human glioblastoma, DU145 human prostate carcinoma	–	PEGylated G3 and G4-DAB reduced cytotoxicity of dendrimer. G4-DAB with PEG (2 and 5 kDa) reduced toxicity of dendrimer at lower dose of 20 µg/ml	Somani et al. (2018)
2.	Cationic dendrimers polyamidoamine dendrimers G4, G5, and G6 (PAMAM)	Ethylenediamine core based polyamidoamine dendrimers G4 (14,215 Da), G5 (28,826 Da), and G6 (58,048 Da)	HaCaT cells, SW480 cells	Dendrimer charge density is correlated to chronic responses. Hormetic response at lower concentration, while toxicity observed at higher concentration	Adenocarcinoma of colon most sensitive to toxicity induced by dendrimers	Mukherjee et al. (2010)

(continued)

Table 13.1 (continued)

Sl. No	Material	Material source	Study type	Organ toxicity	Biocompatibility	References
3.	Cationic type of PAMAM dendrimers	PAMAM G5 obtained from Sigma-Aldrich. Methanol removed and dissolved in PBS 7.4 (10 mg/ml)	Human glioma cells (U87MG, U118, U251MG, A172)	Cationic dendrimer induced cytotoxicity and autophagic degradation activity (autophagic flux)	–	Wang et al. (2014)
4.	Cationic PAMAM	PAMAM obtained from Sigma-Aldrich, methanol removed and mixed with PBS	C57BL/6 J mice	Dysregulation of renin angiotensin system Downregulation of its expression in lung tissue	–	Sun et al. (2015)
5.	Anionic PAMAM	PAMAM 1.5 (2935 Mw of Na salt) PAMAM 3.5 (12,931 Mw of Na salt) PAMAM 5.5 (52,901 Mw of Na salt)	Rat	–	Non-toxic, exhibited high biocompatibility, can be effective drug nanocarrier	Morris et al. (2017)
<i>Carbon nanotubes</i>						
1.	SWCNTs	SWCNTs (carbon nanotechnologies, Inc)	Human embryonic kidney 293 cells (HEK 293)	SWCNTs upregulate apoptosis associated genes (p16, Rb, and p53)	–	Cui et al. (2005)
2.	SWCNTs (short and linear type)	SWCNTS with 8.6 and 0.55 µm, ten fold diluted in PBS containing 1% salmon serum deoxyribonucleic acid	F344/DuCrjCrij male rats	Long SWCNTs deposited at terminal bronchioles, short SWCNTs in alveolus, respiratory toxicity, inflammation	No genotoxicity was observed in lungs	Honda et al. (2017)
3.	SWCNTs	Crude SWCNTS/DMEM/10%(vol/vol) FBS	MITO-Luc and CD1 mice	Induces uncontrolled cell growth, elevated the enzymatic action and inflammation, liver toxic	–	Principi et al. (2016)

4.	Oxidized MWCNT	MWCNTs treated with 3 mol/L HNO ₃ /calcined at 450 °C	Kunming mice (female)			Simvastatin reduce toxic effect of oMWCNTs	(Qi et al. 2017)
5.	Mitsui-7-MWCNTs	MWCNTs/bovine serum albumin (1 mg/ml in H ₂ O)	Human alveolar type II epithelial cells A549 cells, the THP-1 the MRC-5 lung fibroblast cell line (ATCC CCL-171)	Exhibits proinflammatory response, elevates profibrotic mediators		–	Chortarea et al. (2019)
6.	Doxorubicin/fluorescein/CNTs	Oxidized CNTs/DOX-N-cytohetyl-N'-(2 morpholinoethyl) carbodiimide metho-o-toluenesulfonate/FITC/ultrasonic treatment in PBS	Cell line of Caucasian colon adenocarcinoma grade II carcinoma (HT29) in 2D (monolayer) and 3D (spheroid) system in vitro and mice model (Balb2/c)	–		DOX/fluorescein/CNT exhibits less cytotoxic effect compared to unmodified DOX	Perepelytsina et al. (2018)
7.	Thin bundles (CNT-1) And thick bundles of SWCNTs (CNT-2)	SWCNTs/bovine serum albumin (1 mg/ml; 10 mg/ml)	In vitro and in vivo study	Lung toxicity CNT-2 exerted significant acute toxicity in lung		CNT-1 toxicity managed to recover in slow phase	Fujita et al. (2015)
8.	DOX, MWCNT functionalized with thermosensitive block copolymer	MWCNT@MSN-s-s-g-PNIPAM-b-PFBEMA-DOX	In vitro, Hela cells	Cytotoxicity, DOX loading with a maximum capacity of 51.8% showed increased toxicity inside cancer cells		Biocompatible nanocarrier	Zhang et al. (2019)

(continued)

Table 13.1 (continued)

Sl. No	Material	Material source	Study type	Organ toxicity	Biocompatibility	References
9.	DOX, MWCNT, titanium dioxide, gold	MWCNTs/TiO ₂ /Au (bark extract) (1:1 and 1:3)	In vivo study on Zebrafish embryos	-	TiO ₂ and Au increase the biocompatibility of MWCNT, toxicity not affecting the hatching of embryos	Karthika et al. (2018)
10.	Iron and iron extracted pure form of MWCNT	MWCNTs obtained from cyclohexane precursor, ferrocene as catalyst	A549 human lung epithelial cells and HepG2 cells	Iron extracted pure form of MWCNT showed cytotoxicity	Residual iron exerted less CNT toxicity	Requardt et al. (2019)
11.	DOX, CNTs, polyethylene glycol, bisphosphonate, and alendronate	Discrete MWCNTs, DMF, thionyl chloride, PEGylation, NHS, EDC, alendronate, Cy5, DMSO, DOTA label	In vivo study CD-1 mice	-	DOX bound functionalized CNTs (PEG-dMWCNTs and BT-PEG-dMWCNTs) effectively decrease the tumor size and increase the survival period of mice	Falank et al. (2019)

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