Review

Materials Express. 2022, 12, pp.1–23
2158-5849/2022/12/001/023
doi:10.1166/mex.2022.2161

Toxicological impact of nanoparticles on human health: A review

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ABSTRACT

Nanotechnology is a rapidly growing industry where nanomaterials are used in almost every field, including electronics, cosmetics, engineering, household products, biotechnology and medicine. Nanoparticles (NPs) have unique physical and chemical properties, which may cause potential hazards to human health, especially with constant exposure. Various studies have shown that NPs can enter the human body either through the respiratory tract, dermal absorption or via the gastrointestinal system and have the potential to cause respiratory disorders, behavioral changes, neurological disorders, as well as cancer. This review focuses on the health implications of NPs, specifically gold, silver, silica, titanium dioxide, aluminum, aluminum oxides, metal organic frameworks (MOF), aerosol particles, flame retardants, quantum dots, and carbon nanotubes. Herein, we discuss the routes of exposure and the impact of these nanoparticles on human health. We also summarize *in-vitro* and *in-vivo* studies that analyze the cytotoxicity profile and the associated health impact of these nanoparticles. This study could be utilized to develop well-defined guidelines for setting exposure limits for different NP types as well as a summary of related characteristics such as size, shape, morphology, and surface charge.

Keywords: Nanoparticles, Health Hazard, Physiology, Exposure Limits, Routes of Exposure, Cytotoxicity.

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1. INTRODUCTION

Currently, nanotechnology is one of the most advancing sectors in the industry. Nanomaterials are being utilized for different applications (including biotechnology, aerospace engineering, electronics, cosmetics, and medicine) due to their unique physicochemical and electrical properties. However, the distinctive properties of nanoparticles result in an increased reactivity with biological systems, thus causing potential hazards to human health. Several reports in literature have demonstrated that nanoparticles have a different toxicity profile compared to larger particles [1]. According to the American Society of Testing and Materials, particles in the size range of 1 to 100 nm in two or three dimensions are defined as nanoparticles (NPs). Due to their extremely small sizes, nanoparticles (NPs) can easily cross biological barriers and enter the human body. It is estimated that the half-life of NPs is around 700 days, which increases its threat to the respiratory system.

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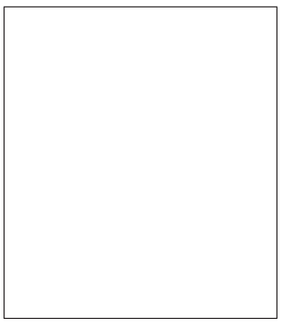

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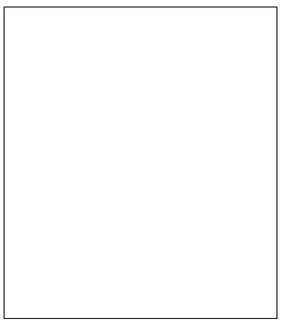

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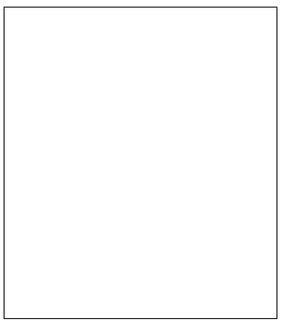

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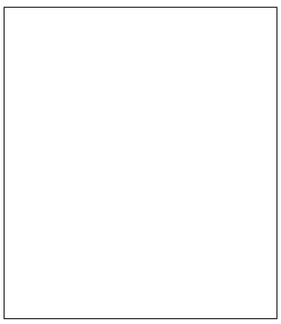

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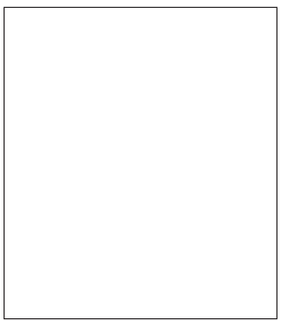

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Comparative studies have also suggested that NPs are more toxic to human health compared to larger particles of the same substance [2].

Recent studies have studied the mechanism behind causing the toxicity of nanomaterials. The most important of these mechanisms is the generation of reactive oxygen species (ROS). ROS can induce oxidative stress impeding the ability of cells to perform normal physiological functions. This can then cause damage to DNA, changes in cell motility, cytotoxicity, apoptosis, and cancer initiation. Some of the critical features which affect the ROS mechanism are the size, shape, particle surface, dissolution, aggregation, mode of interaction and pH of the medium [3].

Human exposure to NPs, whether intentional or unintentional, is inevitable. There are various routes through which nanoparticles can enter the human body. The principal route of entry for airborne particles is via the respiratory system. Studies have shown that ultrafine NPs have the ability to cross the air-blood-barrier in the lungs and reach the liver, spleen and heart. Additionally, inhaled particles can gain access via the olfactory bulb. This is highly hazardous since the particles will gain direct access to the central nervous system through this route. Another route of exposure is the skin, where the nanoparticle can be internalized via dermal absorption and translocation. Various studies have been conducted on particles like titanium dioxide, quantum dots, and fullerenes and their interactions with the skin. Moreover, nanoparticles present in food packaging and additives can enter the bloodstream through gastrointestinal assimilation [4].

The impact of nanoparticles on human health is a critical topic as their use in almost every manufactured item is growing exponentially [5–7]. For example, the global market for Nanomedicine is expected to reach $350.8 billion by 2025 [8]. In this study, a thorough literature review will be conducted to analyze and compare various studies on how certain nanoparticles affect the human body. In this review, gold-, silver-, silica-, titanium dioxide-, aluminum-, aluminum oxides- nanoparticles, metal organic frameworks (MOF), aerosol particles, flame retardants, quantum dots, and carbon nanotubes are investigated in detail along with their routes of exposure to the body and possible adverse health effects. Moreover, this review links the impact of some nanoparticle characteristics such as size and shape to the potential side effects and how it can alter the safety exposure limits. Hence, this review aims to update the safety of NPs and the direction of future research in this area.

2. NANOPARTICLES AND THEIR PHYSIOLOGICAL IMPACT

In recent years, the use of NPs in various applications such as agriculture, textiles, energy, and biomedicine has grown tremendously (Fig. 1). However, this widespread use of NPs means increased exposure to humans on a daily basis as NPs become more ubiquitous in the environment. Figure 2 illustrates the main uptake pathways into the human body. This section summarizes various types of NPs and some of the studies pertaining to their toxicity in the literature. Table I presents examples of recent *in vitro* and *in vivo* toxicity studies of various NPs.

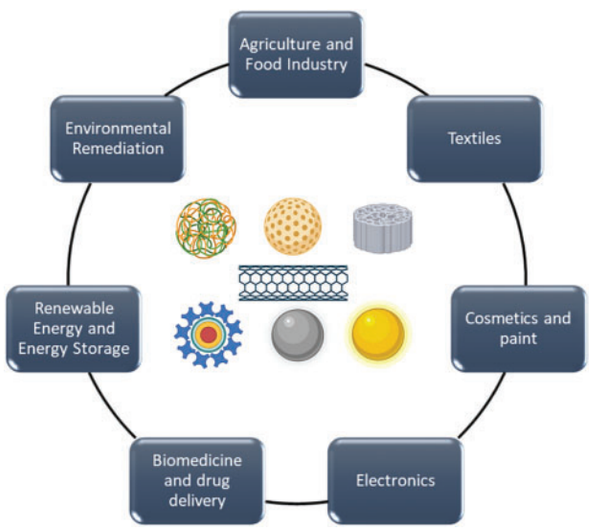

Fig. 1. Applications of nanoparticles.

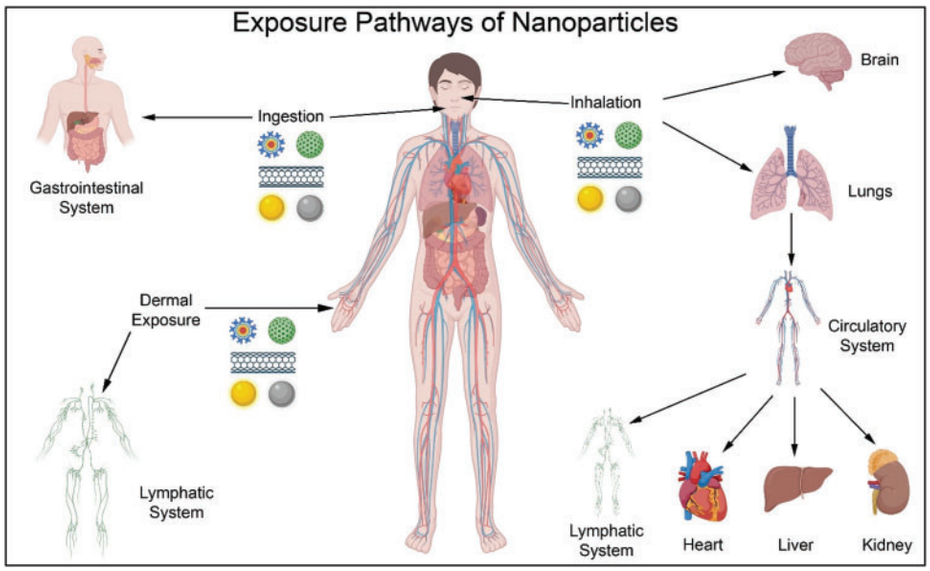

Fig. 2. Overview of the main exposure pathways of nanoparticles.

2.1. Gold Nanoparticles (AuNPs)

Gold is classified as a valuable metal mainly due to its resistance to corrosion, rarity, and aesthetic qualities since ancient times. In drug delivery, gold nanoparticles (AuNPs) are excellent nanovehicles due to their surface chemistry, size, and optical properties. AuNPs are extensively used in nuclear medicine, photothermal therapy, biosensing, drug delivery, imaging, combined cancer therapy, etc. [32–35]. They can be used to transport therapeutic molecules and control the release of drugs triggered by an external stimulus [36]. Extensive research on the biological activity of gold nanoparticles has been reported in the past decade. Most of these studies used particle sizes in the range 3–100 nm, and their effects were mainly studied on bacteria, viruses, and fungi [37]. Some research has shown that gold nanoparticles do not show any cytotoxic effects in human cells. Hence, they are ideal carriers in drug delivery and imaging [38].

A study by De Jong et al. was conducted to understand the particle size distribution of gold nanoparticles in various human body tissues [38]. Metallic AuNP of various sizes 10, 50, 100 and 250 nm were intravenously injected into a group of mice models. The amount of gold was detected using inductively-coupled plasma mass spectrometry (ICP-MS). In the majority of the mice, the elemental gold could be detected 24 hours after injection, and the amount was measured at 588 to 2656 ng/g of blood. It was observed that the majority of the AuNPs were present in the liver and spleen. The distribution of gold nanoparticles proved to depend on the size of the injected particles. The smaller 10 nm particles were present in organ systems, including blood, liver, spleen, kidney, testes, heart, lung, and brain. In contrast, the larger particles were only discovered in the blood, liver, and spleen. This shows that the tissue distribution of gold nanoparticles depends on the size; the smallest nanoparticles show the highest organ distribution.

In 2013, Balasubramanian et al. studied the effect of the inhalation of AuNPs agglomerates on rats [39]. The rats were exposed to AuNP (∼7 and 20 nm in diameters) inhalation for 15 days. The rats were exposed to AuNPs agglomerates 6 hours a day, 5 days a week, for 3 weeks. The fecal and urine excretion in the rats were monitored at six different time points. The results showed the accumulation of gold in 30 different organs. The hippocampus of the brain also revealed a significant accumulation of AuNP. At the end of 15 days, 23% of the organs showed no uptake of the Au, while 30% of organs revealed similar amounts of gold retention. Twenty percent of organs exhibited greater Au accumulation after exposure to the 20 nm agglomerates, compared to the 7 nm particles. However, exposure to both the 7 nm and 20 nm AuNPs revealed a similar trend in excretion. Au was detectable in feces at all six-time points; however, it was not detected in urine. It is interesting to note that the lungs exhibited the highest concentration of AuNP. This is expected since airways are the main portal of entry. It also revealed that a greater fraction of the agglomerates tend to deposit in the alveoli compared to the bronchi and trachea.

Another study was conducted by Kole et al. in which the effect of AuNPs on the adipogenic differentiation process in human mesenchymal stem cells (hMSCs) was investigated [40]. The hMSC's are usually found in various tissues like the bone marrow, muscle, in addition to tissues involved in homeostasis, regeneration and tissue repair. In this study, two different sizes of AuNPs were tested for their effect, i.e., 9 nm and 95 nm. As reported in the literature, these sizes are significant to check if the smaller

Table I. Examples of recent *in vitro* and *in vivo* toxicity studies of various nanoparticles.

NPs	Size	Concentration (Exposure time)	Cell type or animal model (administration route)	Remarks	Reference
AuNPs, AgNPs, CuO, ZnO, TiO_2 NPs	31.99 nm (AuNPS) 7.05 and 31.03 nm (AgNPs) 55.80 nm (CuO) 58.40 nm (ZnO) 27.38 nm (TiO_2)	2–10 μg/ml, (24 hours)	Human colorectal adenocarcinoma (HT-29) cells	Cell viability was significantly reduced for all NPs. Apoptosis induction significantly increased for Ag, ZnO, and TiO_2 NPs. Cellular DNA damage was very low for the tested NPs according to the comet assay.	[9]
AuNPs	10, 30, 60 nm	10 ppm and 10 ppb, (16 and 32 hours)	Human liver cancer (HepG2) and human colorectal adenocarcinoma (HT-29) cells	Cell viability decreased after 16 hours and no significant differences based on the particles' size were detected.	[10]
		0.4 ml/day (8 days)	Wistar rats (Intraperitoneal injection)	Accumulation of NPs was detected in liver, kidney, intestine, spleen, urine and feces. The smallest nanoparticles showed more detrimental effects which was confirmed by their detection in the cell nucleus and the higher DNA damage	[10]
	30, 50, 90 nm	1–25 μg/ml, (24, 48 and 72 hours)	Human leukemia (HL-60) and hepatoma (HepG2) cells	The cytotoxicity was found to be dose and time dependent. The half maximal inhibitory concentration (IC_{50}) from the MTT assay was >15 μg/ml for both cell lines and all particles sizes. HL-60 cells were found to be more sensitive to NPs-induced cytotoxicity than HepG2 cells.	[11]
	6.2, 24.3, 42.5, 61.2 nm (PEG-coated)	0.25, 0.5, 1 mM, (52 hours)	Human hepatoma (HepG2) and Hela cells	Cytotoxicity of the NPs was induced by the generation of reactive oxygen species (ROS) and was influenced by particle size. As particle size decreased, cytotoxicity increased.	[12]
		3 mg/kg, (4 hours to 90 days)	Male Kunming mice (Intravenous injection)	The 42.5 and 61.2 nm PEG-coated NPs accumulated mainly in liver and spleen. The smaller NPs (6.2 and 24.3 nm) distributed in multi major organs.	[12]
	50 nm	– (3 days)	Wistar male rats (Intraperitoneal injection)	Histological examination revealed distribution of the NPs in the testicles, liver, and kidney and mild changes in the examined organs were observed.	[13]
	37.31 nm	5 and 15 ppm (35 days)	Cobb broiler chicks (Drinking water)	Histopathological examination of liver, spleen, thymus and bursa of Fabricius revealed severe alterations at the 15-ppm concentration. Significant decrease in the antibody titer against Newcastle (ND) and avian influenza (AI) viruses. DNA fragmentation and up-regulation of Nrf-2 and IL-6 mRNA levels was detected.	[14]

Table I. Continued.

NPs	Size	Concentration (Exposure time)	Cell type or animal model (administration route)	Remarks	Reference
AuNPs, AgNPs, SiO_2NPs	10 nm (AuNPs and SiO_2NPs), 50 nm (AgNPs)	10 mg/kg for AuNPs, 5 mg/kg for AgNPs and SiO_2NPs) (weekly for 8 weeks)	BALB/c mice (Intravenous injection)	Repeated administration of the NPs did not saturate bioaccumulation in the mice's liver or spleen macrophages. No toxicity was observed with AuNPs and AgNPs after 8 weeks, while some histopathological and serum chemistry changes were observed with SiO_2NPs. No significant changes in the splenocyte population were observed during the study.	[15]
AgNPs	38.4–186.7 nm (in cell proliferation medium) AgNPs coated with various polymeric stabilizers	1–50 mg/L (24 hours)	Murine neural stem cells	The main cellular uptake mechanism for all NPs was determined to be macropinocytosis. Cytotoxicity effects and internalization patterns were dependent on dose and surface coating type. Highest cytotoxicity was determined for the positively charged coating due to the electrostatic attraction with the negatively charged cell surface.	[16]
	18–23 nm	50, 100, 150, 200, 250 ppm (24, 48, 72 hours)	Human dental pulp stem cells (hDPSC)	Cell viability decreased to less than 50% after 24, 48 and 72 hours. The addition of 250 ppm of AgNPs to commercial primes improved the antibacterial effect while preserving the bond strength and the biocompatibility of the dental adhesive used in the study.	[17]
	34.68 nm (AgNPs) 43.87 nm (PEG-AgNPs)	10–150 μg/ml (24 hours)	Human keratinocyte (HaCaT) cells	Cytotoxicity experiments via the MTT assay showed no significant toxicity to the tested cells. The NPs demonstrated antibacterial effects and NPs' concentration range for the antibacterial effect was not toxic to the HaCaT cells.	[18]
	30, 50, 100 nm	20, 40, 60 μM (24 hours)	Human colorectal adenocarcinoma (Caco-2) cells used as model for intestinal epithelial barrier	The AgNPs was exposed to simulated gastrointestinal tract (GIT) fluids and then incubated with Caco-2 cells. The *in vitro* study showed that exposition of AgNPs to fasting-state GIT fluids decreased the cytotoxicity to Caco-2 cells via decreased cellular uptake, while in the fed-state GIT fluid the cellular uptake increased, hence, cytotoxicity of AgNPs in Caco-2 cells increased.	[19]

Table I. Continued.

NPs	Size	Concentration (Exposure time)	Cell type or animal model (administration route)	Remarks	Reference
Cellulose nanofibrils (CNFs) and AgNPs (CNF/AgNP)	10.72 nm (for the AgNPs in the composite)	50, 100, 250, 500, and 1000 μg/ml (24 hours)	Caco-2 and human fetal colon (FHC) cells	Endosomal cellular uptake mechanism was observed for AgNPs. The CNF/AgNP composite did not exhibit toxic effect on the studied cells after 24 hours. The CNF/AgNP exhibited antibacterial effect against two types of foodborne bacteria.	[20]
Citrate-coated AgNPs (cAgNPs)	7.9 nm	0.5, 5 mg/kg (single injection, examination after 7 and 28 days)	New Zealand White rabbits (Intravenous injection through ear vein)	Liver structure and function were disrupted due to AgNPs exposure. The cAgNPs exhibited genotoxic effects in liver tissue after 28 days	[21]
AgNPs	20 nm (with and without polyvinylpyrrolidone (PVP) coating	20–160 μg/ml (24 hours)	Human hepatoma (HepG2) cells	MTT assay results showed significant dose-dependent decrease in cell viability for both NPs (AgNPs and PVP-AgNPs). Both NPs caused dose-dependent genetic toxicological changes on HepG2 cells.	[22]
		10, 50, and 250 mg/kg (daily for 28 days)	ICR mice (Oral gavage)	Bone marrow micronucleus tests revealed limited inhibitory effects, while the effect of chromosome aberration was determined at the highest dose (250 mg/kg).	
AgNPs	4–17 nm	2 mg/kg (single injection on day 19 of gestation, the rats were euthanized after 10 minutes, 1, 6, 12, or 24 hours, respectively)	Female pregnant Wister rats (Intravenous injection)	AgNPs accumulation was quantified by taking samples from maternal blood and tissues such as liver, kidneys, spleen, placenta, besides fetuses, and amniotic fluids. The highest AgNPs level was found in maternal blood (0.523 mg/ml) after 24 hours of administration. Oxidative DNA damage was confirmed by detection of significant levels of 8-hydroxydeoxyguanosine (8-OHdG) in all collected samples from administered rats compared with untreated rats.	[23]
TiO_2 NPs	19 nm	10, 50, 100, and 200 mg/kg (daily for 60 days)	Male Wistar rats (Intragastric administration)	Administration of TiO_2 NPs caused widespread histological alterations and induced significant oxidative stress in the liver tissues. Pretreatment with thymol before NPs administration significantly exhibited protective effects against biochemical and histopathological alterations in a dose-dependent manner.	[24]

Table I. Continued.

NPs	Size	Concentration (Exposure time)	Cell type or animal model (administration route)	Remarks	Reference
TiO_2 NPs in sunscreen	43 nm (from SEM analysis)	138.5 g/testing period (3 days with 2 applications/day)	Human participants, Caucasians, 3 males and 3 females (sunscreen was applied on approximately 80% of the body surface)	Samples were taken from subjects' blood, urine, and exhaled breath condensate (EBC). TiO_2 NPs were detected in the plasma and urine, but not in the EBC, in all sunscreen users, suggesting skin permeability potential of TiO_2 NPs.	[25]
TiO_2 NPs	15–40 nm (via SEM analysis)	0.45, 2.25, 11.25, 56.25 μg/ml (24 hours)	Human umbilical vein endothelial cells (HUVECs)	Cytotoxicity results revealed a decrease in cell viability with increasing exposure concentration. Also, cell exposure to TiO_2 NPs caused cell apoptosis At 56.25 μg/ml exposure concentration, administering Vitamin E was shown to reduce cytotoxicity.	[26]
		4, 20, 100, and 500 mg/kg (daily for 42 days)	BALB/c mice (dermal exposure by dripping NPs solution)	Analysis of mice serum revealed increased levels of ROS as exposure concentrations increased and increased oxidative stress. Administrating Vitamin E demonstrated protective effects.	
Fe-NDC (MOF NP)	230 nm	12.5, 25, 50, 100, and 200 μg/ml (24 hours)	MCF-7 cells	The IC_{50} value was calculated to be 1022 μg/ml. The MOF exhibited small toxicity against the MCF-7 cells. The lowest cell viability was 85.11% at 200 μg/ml.	[27]
MIL-100(Fe) (MOF NP)	102.8 nm	6, 12, 25, 50, 100 and 200 μg/ml	MCF-7 cells	*In vitro* cytotoxicity results showed MIL-100(Fe) exhibited low toxicity, where MCF-7 cells retained about 90% cell viability even when NPs concentration reached up to 200 μg/ml.	[28]
MIL-53(Fe) conjugated with magnetic NaGdF4:Yb/Er NP and functionalized with folic acid (FA)	200 nm, NaGdF4:Yb/Er@ MIL-53(Fe) (based on HRTEM) 245 nm (based on DLS analysis)	0.5, 1, 2.5, and 5 μg/ml (48 hours)	Human Embryonic Kidney cells (HEK293) and murine melanoma cells (B16-F10)	*In vitro* MTT assay showed low cytotoxicity in HEK293 and B16-F10 cells, where cell viability was above 80% up to 5 μg/ml concentration.	[29]
NH_2-Fe-BDC, functionalized with PEG-FA	577 nm (NH_2-Fe-BDC) 461 nm (PEG-FA-NH_2-Fe-BDC	16, 31, 63, 125, 250, 500, and 1000 μg/ml (48 hours)	MCF-7 cells	The functionalized MOF was slightly more cytotoxic than the non-functionalized MOF. The cell viability was >65% at 1000 μg/ml concentration, in the case of NH_2-Fe-BDC, compared to 38% at the same concentration in the case of PEG-FA-NH_2-Fe-BDC	[30]

Table I. Continued.

NPs	Size	Concentration (Exposure time)	Cell type or animal model (administration route)	Remarks	Reference
SiNPs	432 nm (nonporous and mesoporous) 46 nm (nonporous)	Maximum Tolerated Dose (MTD) of SiNPs was as follows: Small non-porous NPs: around 100 mg/kg Large non-porous NPs: around 300 mg/kg Large mesoporous NPs: 40 mg/kg and 95 mg/kg, for female and male mice, respectively (10, 60, and 180 days)	BALB/c mice (Single intravenous injection)	SiNPs exhibited blood toxicity. Histological examination revealed tissue toxicity that was dependent on NPs' size and porosity and exposure time.	[31]

nanoparticles are more toxic than the larger ones. The spherical AuNPs have a citrate shell and are named in this study as GC10 (9 nm) and GC80 (95 nm), respectively. It was observed that the mitochondrial activity of the AuNP-treated cells was similar to the untreated control. The results show that cytotoxicity is induced by the nanoparticles themselves. It was also discovered that GC10 is extremely toxic to hMSCs during adipogenic differentiation at 5.8 l $g \cdot ml^{-1}$. This could be explained due to the surface charge-dependent cytotoxicity of AuNPs, which led to a decrease in mitochondrial activity [40].

Recent *in-vivo* studies of 5 and 50 nm naked and PEG-modified AuNPs on rat models resulted in changes of proinflammatory cytokines expressions and histopathological alterations in the liver and kidneys. Based on particle size and surface modification, the impacts on the rats varied. However, for both types of AuNPs, the larger nanoparticles induced the elevated mRNA expression of cytokines in the liver and kidneys [41]. Similarly, in another investigation, mice models treated with different sizes of AuNPs 5, 20, and 50 nm) were subjected to the immunostaining of IL-1β, IL-6, and TNF-α. From the analysis, 5 nm AuNPs caused minimal proinflammatory cytokines expression in the spleen, whereas 50 nm AuNPs induced intense cytokine expressions [42]. However, in another study, laser-synthesized dextran-coated AuNPs of size 46 nm showed no acute or chronic toxicities in the liver, spleen, and kidneys when tested in mice for 14 days and hence confirmed safe for biomedical applications [43]. Based on the findings of these studies, it can be inferred that the toxicity of AuNPs is dependent on their surface coating and size. However, further studies are required to analyze the safety limits in more detail.

2.2. Silver Nanoparticles (AgNPs)

Nowadays, silver nanoparticles (AgNPs) have the highest rate of commercialization [44] due to the multiple unique properties they offer, including their optical, electrical, thermal, and biological characteristics. The diversity of these properties led to their usage in several areas, including healthcare-related products, antibacterial agents, sensors, cosmetics, pharmaceuticals, diagnostics, and drug delivery [45, 46]. Despite their wide usage, they cause health hazards, toxicity, and risks to humans. Several side effects have been reported upon exposure to AgNPs, including cell death, cancer, oxidative stress, and DNA damage [47]. The increased usage of AgNPs as antimicrobial reagents led to investigating their cytotoxicity on human skin. Samberg et al. researched the impact of different physicochemical properties of AgNPs, including size and surface coating on human epidermal keratinocytes (HEK) [48]. The main finding of this study showed that with a larger size, the severity of the inflammatory response increased, and regardless of the uncoated AgNPs' size, they decreased cell viability. Moreover, this study showed that most AgNPs penetrate skin cells, thus emphasizing the risks of damaged or abraded skin.

Also, using AgNPs as an antibacterial coating has prompted the need to evaluate their impact on the skeletal system. Albers et al. showed that after 21 days, both primary human mesenchymal stem cells (MSC) and osteoblasts (OB) experienced lower cell viability levels and proliferation, thus proving the cytotoxicity of these particles. The toxicity of these particles can severely affect bone metabolism, hence causing abnormalities in bones [49].

The toxicity of silver nanoparticles is even more extreme upon inhalation. Seiffert et al. examined the

pulmonary system of two types of rats: Sprague Dawley and Brown Norway in response to silver nanoparticles (13–16 nm) exposure. The results showed that an inflammatory response was noted upon 24 hours of exposure and continued to increase during the seven-day testing period. Figure 3 shows the lung tissue inflammation scores and eosinophil counts per mm airway length for the two varieties of rats when exposed to Ag nanoparticles for 7 days. It can be concluded that this kind of inflammatory response can cause acute breathing problems, and more risks arise for people with preexisting inflammation, such as asthma. Also, the clearance of AgNPs by macrophages showed low rates that reach 50% within a 7-day period. Hence, AgNPs can severely impair lung functions [50].

The usage of AgNPs in food containers has led to several studies emphasizing the extreme side effects of ingestion. Razavian and Masaimanesh showed that ingestion of AgNPs can alter several physiological parameters of blood [51]. Several AgNPs concentrations were injected into rats and monitored for 6 months, and the analysis of blood showed a decrease in white blood cell count. Moreover, an increase in blood cholesterol was observed, which shows effects on liver functions. Overall, the ingestion of AgNPs can cause high blood pressure, and tissue injury, specifically in liver and endocrine glands. The consequences of AgNPs exposure are even more drastic, as it can damage vision [51].

In addition, *in-vivo* studies of 20 nm AgNPs on male Sprague Dawley rats showed intratracheal changes such as alveolar septal thickening, alveolar deposition of macrophages, mitochondrial cristae disintegration, and mitochondrial swelling. Additionally, AgNPs caused oxidative stress, caspase-3 activation and mitochondrial disintegration [52]. Similarly, AuNPs of size 5–80 nm (tested on Wistar male rats) over 92 days resulted in hepatotoxicity [53]. Johansson et al. [54] demonstrated that AgNPs (20 nm) upon incubation with mouse retina caused elevated levels of immune cells and changed the morphology of the eye retina. Moreover, apoptosis and ROS were detected near the photoreceptor region, hence damaging vision. In summary, the use of AgNPs needs to be evaluated in terms of possible toxicity and exposure limitation.

2.3. Titanium Dioxide (TiO_2) Nanoparticles

Titanium dioxide (TiO_2) is a natural oxide with low toxicity and biocompatibility. This substance exhibits unique

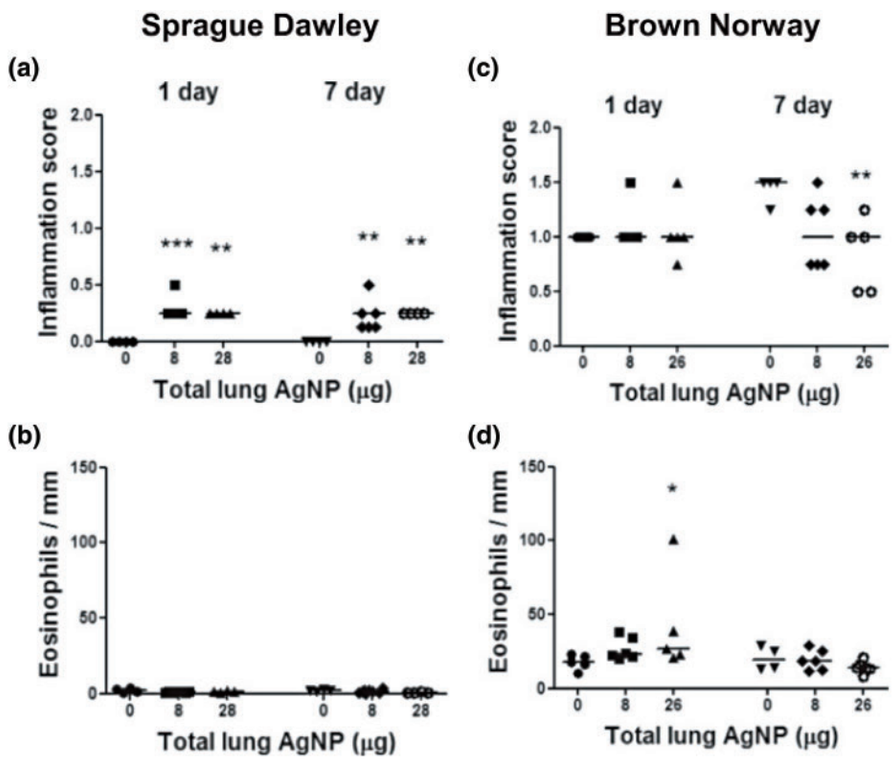

Fig. 3. Lung tissue inflammatory scores and eosinophil counts per mm length of airway wall in Sprague Dawley and Brown Norway rats exposed to silver nanoparticles at 1 and 7 days post inhalation. Reprinted with permission from Ref. [50], Seiffert, J., Buckley, A., Leo, B., Martin, N.G., Zhu, J., Dai, R., Hussain, F., Guo, C., Warren, J., Hodgson, A., Gong, J., Ryan, M.P., Zhang, J.J., Porter, A., Tetley, T.D., Gow, A., Smith, R. and Chung, K.F., **2016**. Pulmonary effects of inhalation of spark-generated silver nanoparticles in Brown-Norway and Sprague–Dawley rats. *Respiratory Research*, *17*(1), p.85. Copyright@Springer Nature.

conductivity, photocatalytic activity, etc. [55]. These properties led to a broad range of applications that vary from usage in food and cosmetics to the pharmaceutical industry [56]; therefore, human exposure is imposed through several routes, namely inhalation, ingestion, and dermal [55]. Although TiO_2 NPs are considered biologically inert, several studies revealed their adverse effects at high concertations and long periods of exposure. Frequent exposure of TiO_2 NPs to humans, even at small doses, can affect the intestinal mucosa, organs like the heart, brain, and other internal organs, and eventually lead to increased health risks like tumors or progression of existing cancer [57].

Zhang and Monteiro-Riviere investigated the effects of TiO_2NPs size on keratinocytes [55]. The impact of six different TiO_2 NPs with different size ranges (10 nm–400 nm) was investigated. All TiO_2 NPs tend to agglomerate in cells upon incubation regardless of the size. The size variation had a significant effect on cell viability and inflammatory response. Moreover, particles with 27.5 nm sizes were more cytotoxic, and the inflammatory response was provoked more with particles of 10 nm and 27.5 nm sizes.

Savi et al. demonstrated that TiO_2 NPs cause an impairment of cells and an increase in cardiac excitability. Moreover, a 25% increase in intracellular damage was observed within a one-hour exposure and a 16% increase in reactive oxygen species (ROS) formation [57]. The significant findings of this study concluded that TiO_2 NPs could significantly decrease the contractility of muscles, thus increasing the possibility of arrhythmic events. Also, the unique physicochemical properties, including size, shape, crystal structure, and surface coating, dictate the biological activity of TiO_2 NPs. In primary rat astrocytes, TiO_2 NPs introduction resulted in enhanced oxidative stress, mitochondrial damage, autophagy, reduction in NLRP3 protein expression, and inflammasome response. Figure 4 represents the difference in DNA damage in control cardiomyocytes (CTRL) versus TiO_2 nanoparticles exposed cardiomyocytes (NP_C) after 1 and 5 hours of exposure, respectively. This was experimentally obtained by examining DNA damage in single, isolated cardiomyocytes using the Comet Assay. The results show that the cardiomyocytes exposed to the TiO_2 NPs showed significantly increased DNA damage compared to the control cardiomyocytes after 1 and 5 hours of exposure [57].

TiO_2 NPs have been extensively used in sunscreens as they can absorb UV light; thus, several studies focused on the impact of TiO_2 NPs on skin. Simon et al. investigated several aspects of keratinocytes' exposure to TiO_2 NPs in terms of cellular distribution, cell proliferation, cell death, and cell differentiation [58]. Cell imaging showed that the particles tend to agglomerate near the nucleus, which indicates that they can drastically affect cells. Cell viability experiments showed that TiO_2 NPs neither induce cell apoptosis nor impact hemostasis elements of cells. Nevertheless, a significant finding is that calcium concentration

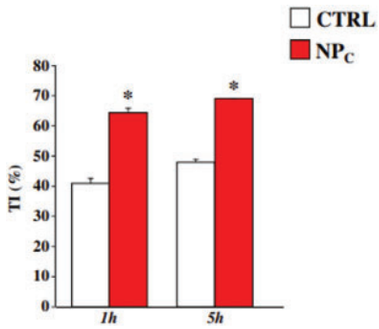

Fig. 4. DNA damage detected in single isolated cardiomyocytes by Comet Assay (pH > 13) in CTRL (white) and NP_C (red) after 1 h and 5 h exposure. Reprinted with permission from Ref. [57], Savi, M., Rossi, S., Bocchi, L., Gennaccaro, L., Cacciani, F., Perotti, A., Amidani, D., Alinovi, R., Goldoni, M., Aliatis, I., Lottici, P.P., Bersani, D., Campanini, M., Pinelli, S., Petyx, M., Frati, C., Gervasi, A., Urbanek, K., Quaini, F., Buschini, A., Stilli, D., Rivetti, C., Macchi, E., Mutti, A., Miragoli, M. and Zaniboni, M., **2014**. Titanium dioxide nanoparticles promote arrhythmias via a direct interaction with rat cardiac tissue. *Particle and Fibre Toxicology, 11*(1), p.63. Copyright@Springer Nature.

increased from $(0.31 \pm 0.02$ mg/g) in a controlled cell up to $(1.19 \pm 0.11$ mg/g) in TiO_2 NPs treated cells. Hence, this variation has several effects, including a decrease in cell proliferation rates, which decreased as low as 93% during a five-day period, and altering actin cytoskeleton organization and cell differentiation.

Inhalation is considered the most significant exposure route for most particles, with the respiratory tract as the primary target [59]. The consequences of TiO_2 NPs $<$50 nm in size on the cardiovascular system can be severe, as, during inhalation, these particles can enter into the bloodstream.When tested in human neuroblastoma (SH-SY5Y) cells, 5-nm TiO_2NPs resulted in a neurotoxic mechanism, where an imbalance of oxidative metabolism pathways was observed. Accordingly, reactive oxygen stress increased ER and led to apoptosis [60].

Wang and Fan established a correlation between lung injury and the cytotoxicity of TiO_2 NPs with different physicochemical characteristics [61]. The study reported that the active crystal form of TiO_2 NPs was more toxic, hence inducing a more inflammatory cell response. Also, coating with silica and alumina can only minimize toxicity to a certain level.

The usage of titanium dioxide nanoparticles as a food additive prompted investigating the biological effects upon ingestion. Chen et al. focused on TiO_2 NPs on the central nervous system entering pathways, particularly the blood–brain barrier (BBB) route [62]. The blood–brain barrier is a critical membrane that selectively transports nutrient materials to the brain and removes metabolic wastes. Thus, a change in BBB permeability can acutely affect the central nervous system functions. The study concluded that TiO_2 NPs were more toxic and had a higher potential for cellular uptake in cerebral cells compared to murine cells.

Overall, the TiO_2 NPs can alter the BBB structure in terms of integrity and tightness, hence possibly harming the central nervous system in the process.

García-Rodríguez et al. concluded that several characteristics of TiO_2 NPs, such as size and shape, can affect their risk potential level and ability to penetrate biological barriers [63]. Three different shapes (nanospheres, nanorods, and nanowires) were investigated upon incubation with colorectal adenocarcinoma cells. An interesting finding of this study is that even though the cellular uptake of nanowires was the slowest compared to others, they showed the most harmful effects. Even though TiO_2 NPs are extensively used in several industries, they have several health risks. There is a need to perform toxicological tests with different parameters to establish reliable risk assessments.

2.4. Aluminum and Aluminum Oxide Nanoparticles (AlNPs, Al_2O_3NPs)

Aluminum and Aluminum oxide nanoparticles (AlNPs, Al_2O_3NPs) have extraordinary physicochemical or structural features such as wear resistance, mechanical stress, optical properties, and porosity [64]. This led to many applications, including municipal wastes, polymers, and pharmaceuticals [65]. As such, AlNPs are present in drinking water, the food industry, as well as agriculture communities [66]. The toxicity of AlNPs, and Al_2O_3NPs have been reported on several cells and organ systems, and Aluminum oxide has been linked to neurotoxicity [66]. Albers et al. reported that Al_2O_3NPs exposure could disturb the central nervous system [49]. The experimental work was performed by intravenous injection of Al_2O_3NPs into rats and assessing their behavioral changes as well as the Al and mineral distribution in their blood. The significant findings of this research showed that although exposure to Al_2O_3NPs had no effect on the general health of rats, it caused drastic changes in behavior and emotional response *in vivo*. This was supported by the elevated plus-maze test, as injected rats spent more time in closed loops. Moreover, an acute decrease in hemostasis mineral elements was observed and thus the possibility of developing ROS [66].

Several characteristics of aluminum nanoparticles can raise their toxicity level, such as size, porosity, shape, etc. Albers et al. showed that the amorphous form of Al_2O_3NPs is more toxic than the crystalline form [49]. That was supported by comparing the response of several cells. Compared to the crystalline form, the amorphous form decreased the number of white blood cells (WBC), increased neutrophils' ratio, and increased inflammatory secretions. Additionally, due to the amorphous particles' low stability, it lowered cell viabilities.

Recently, the oral administration of Al_2O_3NPs on Rattus norvegicus rat models showed significant changes in the antioxidant enzymes in the liver [67]. Similarly, investigations on Wistar male albino rats when treated with Al_2O_3NPs caused hepato- and nephrotoxicities through epigenetic alterations in the gene expression. They resulted in mitochondrial dysfunction, which led to ROS generation and oxidative stress. In addition, changes in antioxidant defense systems led to cytokine production fluctuations and DNA fragmentation, which resulted in accelerated cell death via apoptosis and necrosis. At the same time, combined exposure to Al_2O_3NPs and zinc oxide NPs resulted in a synergistic effect.

Another study analyzed the impact of AlNPs and TiO_2 NPs size variation in human epidermal keratinocytes (HEK) [68]. Upon 24 h exposure to 10 and 50 nm AlNPs, cytotoxicity and inflammatory potential were assessed. Overall, the cell viability studies showed that AlNPs were non-toxic up to 4.0 mg/ml. However, the cytokine data varied, indicating the possibility that AlNPs may have the ability to induce an immune system response. Overall, there is a lack of studies in AlNPs and Al_2O_3NPs mainly due to several difficulties in determining their impact as they interact with assay solutions and tend to agglomerate rapidly.

2.5. Silica Nanoparticles (SiNPs)

Silicosis is a disease caused due to the inhalation of crystalline silicon dioxide or silica particles. It is a global problem but more commonly prevalent in developing countries [69]. This is mainly because silica and silicon dioxide are the most abundant minerals in crystalline and amorphous forms worldwide. The most common free crystalline forms of silica in workplaces are quartz, tridymite, and cristobalite. Various occupations and industries increase human exposure to silica particles like construction, quarrying, drilling, grinding, etc. A number of diseases are caused by direct exposure to silica particles [70].

Coal miners are highly exposed to silica nanoparticles, and these can adversely affect their health. Particle analysis of the dust extracted from the macrophages of the lungs of coal miners has shown the long-term health hazards of exposure to silica dust. Rainey et al. studied three test subjects with long-term exposure to coal mine dust. The particles were studied using high-resolution electron microscopy and chemical micro-analysis and showed that the silica particle structures varied among all three subjects. This indicates that intracellular processes may affect the susceptibility of individuals to silica-induced pneumoconiosis. Two main varieties of morphologies of silica were observed. The first is structurally complex and multiphased, while the second is single-phased and sharply faceted. It was also observed that both forms were predominantly crystalline in the form of alpha quartz. Further analysis of the dust samples from the lungs of the three test subjects gave an idea about the percentage of particles existing as SiO_2 in the macrophages [71].

Extensive research has been carried out since the 1980s to investigate the relationship between crystalline silica

and silicosis in increasing the risk of lung cancer. In 1982, Goldsmith et al. suggested three hypotheses in terms of the relationship between silica/silicosis and lung cancer: (1) silica is a direct carcinogen, (2) silicosis is an intermediate pathological state leading to lung cancer (scar tissue), and (3) silica combined with polycyclic aromatic hydrocarbons (PAHs) impairs lung clearance and causes lung cancer [72]. In addition, a study by Kurihara and Wada in 2004 was conducted where data from epidemiological reports by meta-analysis were summarized to investigate whether crystalline silica nanoparticles increase the risk of lung cancer [73]. Based on findings from 30 different studies, the risk of lung cancer was 1.32%. This indicates that the carcinogenic effect of silica nanoparticles on humans is relatively weak. Currently, many countries have taken measures to prevent silicoses. These measures focus on controlling silica concentration in the work environment and the usage of protective equipment and periodic medical checkups for silica exposed workers.

In addition, a study by Parveen et al. was conducted to investigate the toxicological effects of silica nanoparticles (SiNP) on the frontal cortex (FC), corpus striatum (CS), and hippocampus (HP) regions of rat brains [74]. It is not clear how SiNP can affect brain function, but it is believed that inhaled or injected SiNPs can cross the blood–brain barrier. They enter the central nervous system of the animals and induce oxidative stress. In their study, two SiNP sizes (i.e., 80 nm and 10 nm) at a 150 mg/ml dosage were injected into the animals for 30 days. The results portrayed an increase in peroxide levels and hydrogen peroxide content in different rat brain regions. Furthermore, a decrease in the activities of manganese superoxide dismutase, glutathione reductase, catalase and reduced glutathione in different brain regions was observed. The results also showed a significant increase in silica in the corpus striatum, hippocampus, and frontal cortex of the rat brain. The corpus striatum is responsible for muscular tension, posture, autokinetic stability, and memory. The hippocampus and frontal cortex control learning and long-term memory. Damage to these regions via SiNP can lead to neurodegenerative disorders such as Parkinson's and Alzheimer's diseases.

In-vitro and *in-vivo* evaluations of mesoporous SiNPs within the size range of 100–500 nm were non-toxic and can be used as safe drug delivery carriers [75]. An investigation of the acute and subchronic toxicity of nonporous SiNPs of 50 nm and 500 nm, and mesoporous SiNPs of 500 nm was performed on immune-competent inbred BALB/c mice [31]. For the acute toxicity evaluation, the maximum tolerated dose (MTD) of SiNPs was determined after ten days of intravenous injection. The subchronic toxicity-based MTD of SiNPs was evaluated over 60 and 180 days. Evaluation of SiNPs showed blood toxicity in terms of changes in the mean corpuscular hemoglobin and platelet number for both acute and chronic incubations. Also, depending on the size, dose and exposure time of SiNPs, the major toxic effects observed were cardiac wall fibrosis, lung thrombosis, inflammatory response, brain infarctions, retinal injuries, renal damage and liver lobular inflammation. Moreover, histological examination clearly displayed size, porosity, surface area, and time-dependent tissue toxicity.

Exposure to SiNP can be a possible risk factor for autoimmune diseases such as systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and ANCA-associated vasculitis. Rocha-Parise et al. conducted a study where various markers of the immune activation in individuals exposed to SiNP were studied [76]. These markers included serum levels of soluble IL-2 receptor (sIL-2R), levels of IL-2, other pro- and anti-inflammatory cytokines and lymphoproliferation. The results showed significant alterations in the immune system of silica exposed individuals, as evidenced by increased serum sIL-2R levels, decreased production of IL-2, and increased proinflammatory cytokines. This concludes that individuals exposed to SiNP may have abnormal maintenance of immune homeostasis, which could lead to autoimmune diseases.

2.6. Metal-Organic Frameworks (MOFs)

Metal organic frameworks are hybrid crystalline materials composed of organic units (negatively charged linkers) such as ditopic or polytopic organic carboxylates etc., and inorganic units (metal cations). This crystalline construction offers an open porous structure with high porosity and high surface area to MOFs compared to others such as zeolites and other carbon structures. Typical MOF sizes range from a few nanometers to micrometers and pore sizes of up to 2 nm. A variation of the metal ions or organic ligands can lead to MOFs with larger pore sizes [77]. They have been utilized in various applications such as gas storage, separation, catalysis, sensing, and drug delivery [78]. Studies on the impact of MOFs have recently emerged as new usages of MOFs emerged in the pharmaceutical industry, drug delivery, and imaging. Currently, no exposure limits were declared for MOFs. To analyze the drug delivery potential of these nanoparticles, the *in-vitro* toxicological assessment of an iron-based MOF, MIL-100(Fe) was performed on 2 different cell lines: human normal liver cells (HL-7702) and hepatocellular carcinoma (HepG2). MIL-100(Fe) is produced under hydrothermal conditions using $FeCl_3 \cdot 6H_2O$ and H_3BTC. The nanoporous structure of MIL-100(Fe) is shown in Figure 5. MIL-100(Fe) has been widely investigated due to its high surface area, large drug-loading capability, physiological stability and good porosity. The cytotoxicity analysis by the MTT assay, DAPI staining, LDH releasing rate assay and annexin V assay reported a safe MOF dose at 80 $\mu g \cdot mL^{-1}$, with good biocompatibility, low cytotoxicity, and high cell survival rate $<80\%$ in both cell lines, proving the utility of using MOF as drug delivery vehicles [79].

Ren et al. evaluated the toxicity of zinc-based MOFs on pheochromocytoma of rats' adrenal medulla (PC12 cells) in terms of cell morphology, cytoskeleton, cell viability and neuro signaling proteins [80]. The adverse toxic effects were observed at concentrations above 100 mg/ml, notably in cell morphology, membrane integrity, and viability. Another research group studied the *in-vivo* behavior of MIL-100 NPs upon intravenous administration into rats [81]. This study traced/measured the blood circulating profile and the organ accumulation of the MOF within the first 24 hours. Results showed the immune system's rapid opsonization of the MOFs, as evidenced by the clearance rate of MOFs by the liver and the kidneys 30 minutes after injection. Nevertheless, there were no morphological mutations or alterations to the function of these organs. This demonstrated the utility of using MIL-100 as a drug delivery carrier; however, accumulation and opsonization are still constraints that should be addressed.

Moreover, the diversity of MOFs' structures, shapes, and sizes can lead to different consequences upon injection. Baati et al. investigated three porous iron (III) MOFs with different features (denoted MIL-88A, MIL88B_4CH_3, and MIL-100) [82]. The results showed severe immune system sensitivity with rapid accumulation in the liver and spleen. Remarkably, these organs maintained their functions and no toxicity symptoms were observed. Moreover, the elimination of iron was observed in these organs by analyzing urine and feces. Altogether, these results clearly confirm the wide applications available for non-toxic iron (III) carboxylate MOFs as drug delivery vehicles, with their diverse structures and compositions having no harmful implications.

In addition, Mohamed et al. investigated the impact of iron MOFs MIL-89 and PEGylated MIL-89 (MIL-89 PEG) as suitable carriers for pulmonary arterial hypertension (PAH) drugs [83]. The assessment of their impact included tests on viability and inflammatory responses from a wide range of lung cells, including endothelial cells grown from the blood of donors with/without PAH. Figure 6 portrays the effect of MIL-89 and MIL-89 PEG MOFs on endothelial cell viability (a and b). The outcomes of this study showed that not only MIL-89 and MIL-89 PEG were well tolerated in the lung cells, but also they were anti-inflammatory, thus proving to be a successful candidate for treating PAH [83]. Overall, the past studies validated the potential of MOFs to be utilized as drug carriers or in medical imaging as they have proven to be non-toxic. However, more research needs to be conducted on the impact of the different physiological parameters such as temperature and pH variations on cell viability and proliferation.

2.7. Carbon Nanotubes (CNTs)

A novel nanoparticle system has been introduced known as carbon nanotubes (CNTs) with a wide range of applications. CNTs are cylindrical molecules of hexagonal arrangement made of hybridized carbon atoms. They can either be single-walled (SWCNTs), made by rolling a single sheet of graphene, or multi-walled (MWCNTs) made by rolling multiple graphene sheets. CNTs can act as carriers for therapeutic molecules in drug delivery due to their large surface area and ability to manipulate physical dimensions and surfaces [84].

Various *in-vivo* and *in-vitro* toxicological studies have indicated the health effects of multi-walled carbon

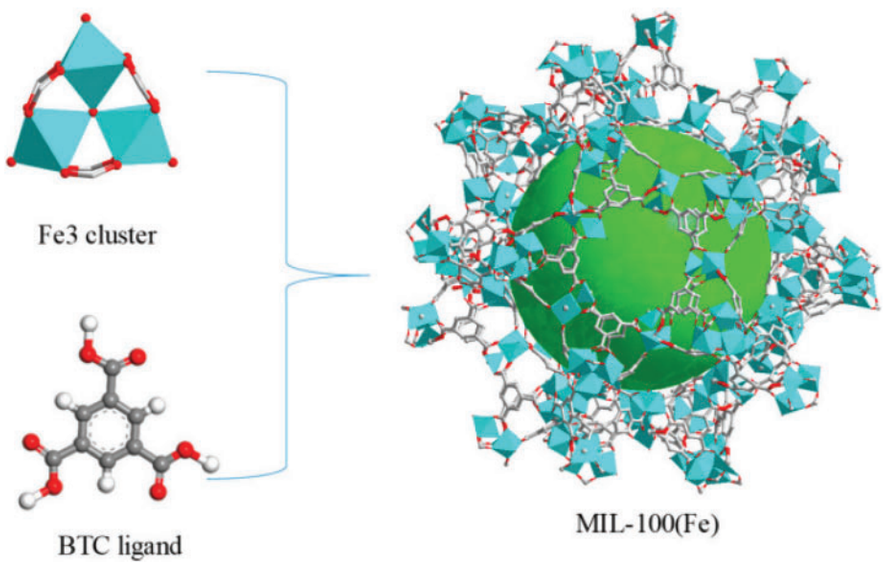

Fig. 5. Schematic illustration of formation of MIL-100(Fe). Reprinted with permission from Ref. [79], Chen, G., Leng, X., Luo, J., You, L., Qu, C., Dong, X., Huang, H., Yin, X. and Ni, J., **2019**. *In Vitro* toxicity study of a porous iron(III) metal–organic framework. *Molecules, 24*(7), p.1211. Copyright@Multidisciplinary Digital Publishing Institute.

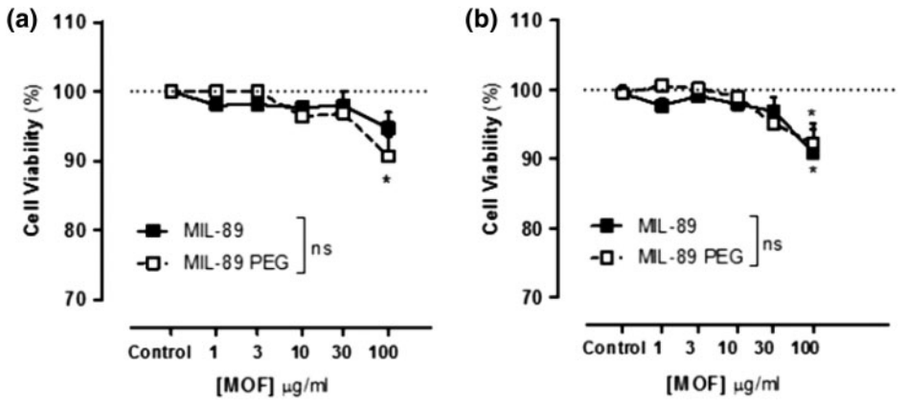

Fig. 6. Effect of MIL-89 and pegylated MIL-89 PEG on endothelial cell viability. Reprinted with permission from Ref. [83], Mohamed, N.A., Davies, R.P., Lickiss, P.D., Ahmetaj-Shala, B., Reed, D.M., Gashaw, H.H., Saleem, H., Freeman, G.R., George, P.M., Wort, S.J., Morales-Cano, D., Barreira, B., Tetley, T.D., Chester, A.H., Yacoub, M.H., Kirkby, N.S., Moreno, L. and Mitchell, J.A., **2017**. Chemical and biological assessment of metal organic frameworks (MOFs) in pulmonary cells and in an acute in vivo model: Relevance to pulmonary arterial hypertension therapy. *Pulmonary Circulation, 7*(3), pp.643–653. Copyright@SAGE Publications Inc.

nanotubes (MWCNTs) on humans [85]. A health surveillance study conducted in the workplace that manufactures MWCNTs included assessing personal and area exposure levels to MWCNTs [86]. Blood samples and exhaled breath condensates (EBCs) were collected from the office and factory workers exposed to MWCNTs. Moreover, a pulmonary function test was also done on these same employees. The results showed worker exposure to elemental carbon to be 6.2–9.3 $mg \cdot m^{-3}$ in the personal samples, and 5.5–7.3 $mg \cdot m^{-3}$ in the area samples. However, hematology, blood biochemistry, and lung function parameters displayed a normal range of values. It was observed that malondialdehyde (MDA), 4-hydroxy-2- hexenal (4-HHE), and n-hexanal levels in the MWCNT factory workers were significantly higher than those who worked in the offices of the same manufacturing plant. Lastly, it was also observed that all the workers showed a normal range of pulmonary function from the pulmonary function test results.

Another investigation tested five different carbon-based nanoparticles: (i) SWCNT, (ii) active carbon (AC), (iii) carbon black (CB), (iv) MWCNT, and (v) carbon graphite (CG) to examine the toxic effects on fibroblast cells. Fibroblast cells synthesize extracellular matrix and collagen and produce the structural framework for animal tissues. This study showed that SWCNT induces the most adverse effects on the cell, including apoptosis and necrosis [87]. Furthermore, an *in-vitro* study was carried out by Yu et al. in 2018 to understand the cytotoxicity of polyethylene glycol-CNTs (PEG-CNTs) on human embryonic kidney cells (293T) and human liver cancer cells (HepG2) [88]. PEG-CNTs are carbon nanotubes modified with PEG to prepare CNTs that are water-soluble. It also improves the CNT biocompatibility, solubility, and drug delivery potential. The effect of the concentration of these PEG-CNTs on the survival rate and activity of cells was studied using the colorimetric assay method after exposure for 24, 48, and 72 hours. In addition, cell mortality after exposure to PEG-CNTs was analyzed using flow cytometry. The results indicated that the toxicity of the cells increases with increasing PEG-CNT concentration. Also, it was concluded that for concentrations of PEG-CNTs less than 100 μg/ml, the toxicity of the PEG-CNTs is non-toxic. However, when concentration was greater than 100 μg/ml but less than 200 μg/ml, PEG-CNTs were mildly toxic. Finally, it was also observed that no significant change in cytotoxicity was discovered after 24 hours of contamination, which indicates that cytotoxicity does not increase with extension of time.

Another investigation was conducted to evaluate the effect of MWCNT in causing pulmonary toxicity upon inhalation by a one-time intratracheal instillation of 11 well-characterized MWCNT in female C57BL/6N Bom-Tac mice. The histological analysis after one year in lung tissue showed short, thin MWCNT as agglomerates and long thick MWCNTs as fibers. The Comet Assay evaluated the genotoxicity in the liver and spleen. However, there was no evidence of MWCNT-induced fibrosis or tumors in the lungs or pleura, but increased DNA degradation levels were observed [89]. In addition, Gaté et al. carried out a comparative study of inhalation and intratracheal instillation to administer two MWCNT [90]. When comparatively tested the influence of intratracheal instillation and inhalation exposure on pulmonary toxicity, both exposures exhibited similar toxicological profiles for the *in-vivo* experiments in terms of inflammation and DNA damage. However, the responses were dose-dependent in both scenarios.

Lastly, a study was conducted to evaluate the neurobehavioral toxicity of SWCNTs and MWCNTs in mice [91].

Different behavioral expressions of locomotion, memory, anxiety, and depression were related to the structure of employed CNTs. The results revealed that CNTs cause behavioral changes like depression and anxiety. It also concluded that MWNTs were more toxic than SWNTs. In addition, brain-derived neurotrophic factor (BDNF) protein and gene expression of CNT-treated mice were studied to understand the toxicity caused by CNTs. BDNF protein is distributed throughout the brain and has many fundamental roles like neuronal growth, plasticity, and maintenance. It was observed that BDNF protein levels were not different in brain tissues of CNTs-treated mice compared to non-treated control mice.

2.8. Quantum Dots (QDs)

Quantum dots (QDs) are new emerging fluorescent nanoparticles (~2–100 nm in diameter), and they exhibit unique properties such as discrete energy levels, semi conduction and luminescence characteristics [92]. QDs are composed of a semiconductor core (e.g., cadmium-selenide, CdSe) located within a shell comprised of a second semi-conductor material (e.g., zinc sulfide, ZnS) [93].

The distinctive properties of quantum dots have led to their applications in several consumer and clinical products. They are currently used in diagnostic imaging, therapeutic purposes (e.g., drug delivery and cancer treatment), and cell tracking in mammals [94]. However, the lack of information on the toxicity and safety of quantum dots hindered their usage in humans. Thus, several studies investigated various aspects of the quantum dots effect *in-vivo* and *in-vitro*.

Roberts et al. assessed the pulmonary toxicity of quantum dots in rats via intratracheal injection [93]. Two functionalized cadmium quantum dots with carboxyl (QD-COOH) and amine (QD-NH_2) terminal groups were evaluated. Histopathological evaluation of the lung tissue after 28 days from intratracheal instillation was observed, as shown in Figure 7, using both types of quantum dots. In Figure 7, "A" depicts lung tissue after saline injection, "B" depicts after instillation of QD-NH_2, while "C" and "D" portray instillation after QD-COOH. It can be observed from "D" that the alveolar tissue contains Type II epithelial cells (indicated by yellow arrows). The results concluded that exposure severity of lung lesions and inflammatory were dependent on the dose, thus empathizing the toxicity of these quantum dots. Regardless of the quantum dot functional group, this research concluded that cadmium dots are cytotoxic and exhibit potential medical hazards, hence may not be suitable for consumer products [93]. In addition, Hauck et al. conducted a toxicity study of CdSe–ZnS core–shell quantum dots in rats [95]. However, QDs did not result in any significant toxicity, which indicated the possibility to use them in biomedical applications.

The clinical usage of quantum dots can be even limited to the gender of the patient. Xu et al. established that QDs exposure could cause toxicity in the reproductive system [96]. They studied the impact of CdSe/ZnS QDs on ovarian functions and the fertilization process. The results showed that ovaries and estrous cycle maintained were invariable. However, drastic implications were observed in the follicle-stimulating hormone receptor (FSHr) and luteinizing hormone receptor (LHr). Both hormones exhibited mRNA downregulations; hence, this can impair the development of follicles and oocytes. Also, fertilization possibility decreased significantly with the high concertation of QDs ($\geq$1.0 pmol).

Graphene quantum dots (GQDs) were tested on female and male ICR mice to evaluate the toxicity effects on reproductive health in mammals [97]. GQDs were introduced to the mice through oral supply or intravenous injection. GQD-exposed mice displayed healthy structural and functional reproductive physiology no accumulation of GQDs in any organs; at the same time, excretion of GQDs via the urine and/or feces was observed. The investigations on the short- and long-term effects of GQD exposure on male mouse sexual behaviors, reproductive activity, and offspring development reveals the potential of GQDs to use for bio applications. Most results displayed the severe implications of Quantum dots; hence more studies need to be directed towards establishing the behavior of the specific organ towards quantum dots exposure.

2.9. Flame Retardants

Flame retardants refer to a class of compounds added to combustible substances and manufactured products such as plastics and textiles to prevent fire from starting or slow the spreading of a fire. Various chemicals with different chemical and molecular structures can act as flame retardants, and these may even be combined to increase effectiveness. A huge variety of flame retardants exist, which can usually be categorized based on chemical structure and properties. The two most commonly used ones are brominated flame retardants and organophosphorus flame retardants. The principal aim of flame retardants is to slow ignition, not completely prevent it. Therefore, their mechanisms are heavily dependent on the retardant's chemical properties and the nature of the substrate. Most halogenated flame retardants are persistent, bioaccumulative, and toxic. Exposure to these flame retardants is widespread and occurs mainly through diet, consumer products, households, workplaces, and house dust [98].

Polybrominated diphenyl ethers (PBDE) are one of the major classes of flame retardants. In 2001, Eriksson et al. performed a study to see the effects of PBDEs on neurological development [99]. Two different PBDE-2,2′,4,4′-tetrabromodiphenyl ether (PBDE 47) and 2,2′,4,4′,5-pentabromodiphenylether (PBDE 99) were used in this study. NMRI mice were used as test subjects. Behavioral tests like spontaneous behavior and swim maze were conducted on the mice after administration of

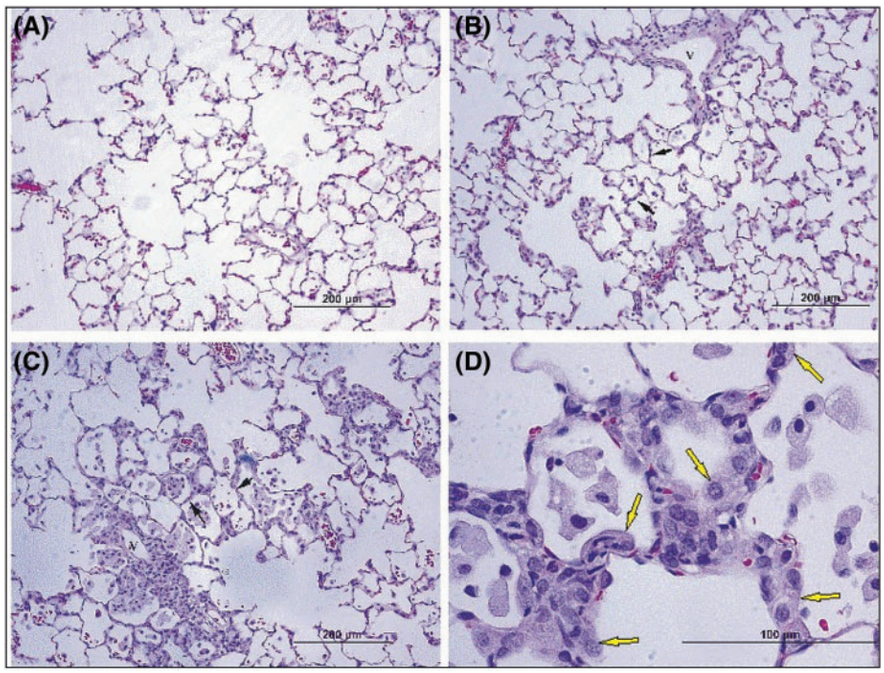

Fig. 7. Micrographs of lung tissue sections from rats 28 days after intratracheal instillation with saline (A), QD-NH_2 (B), and QD-COOH (C & D). Hyperplastic Type II epithelial cells can be found in alveoli (D, yellow arrows). Reprinted with permission from Ref. [93], Roberts, J.R., Antonini, J.M., Porter, D.W., Chapman, R.S., Scabilloni, J.F., Young, S., Schwegler-Berry, D., Castranova, V. and Mercer, R.R., **2013**. Lung toxicity and biodistribution of Cd/Se–ZnS quantum dots with different surface functional groups after pulmonary exposure in rats. *Particle and Fibre Toxicology, 10*(1), p.5. Copyright@BioMed Central Ltd.

the PBDEs. These tests revealed that PBDE 99 was more potent in causing neurotoxic effects than PBDE 47. This shows there is a difference in neurotoxicity among different types of PBDE itself. It was also revealed that neonatal exposure to PBDE 99 and PBDE 47 causes permanent changes in spontaneous behavior.

Another study was conducted by Jarema et al. to investigate the developmental effects of different types of PBDEs in zebrafish [100]. The embryos of wild-type zebrafish were incubated and dosed with flame retardants. The aim of the study was to assess the overall toxicity of each chemical in addition to assessing the developmental neurotoxicity of the chemical. Three of the flame-retardant chemicals: Tetrabromobisphenol A (TBBPA), *t*-butylphenyl diphenyl phosphate (BPDP), and isodecyl diphenyl phosphate (IDDP) did not produce any noticeable developmental effects on locomotor activity. The chemical 2-ethylhexyl diphenyl phosphate (EHDP) produced very weak results. Hyperactivity in the fish was observed on exposure to Tri-*o*-cresyl phosphate (TOCP) and isopropylated phenyl phosphate (IPP). It was observed that every flame retardant produced behavioral effects at a concentration of 10 μm or higher.

The presence of a significant portion of a particular flame-retardant tris(1,3-dichloroisopropyl) phosphate (TDCPP) was reported in human seminal plasma samples in 1981 by Hudec et al. [101]. High doses of flame retardants have been constantly associated with adverse reproductive and neurological systems. Further, it has been proven that household dust commonly carries TDCPP flame retardant [102]. In a study by Meeker and Stapleton, two flame retardants—TDCPP and TPP—found in house dust were investigated to find their association with hormone levels and semen quality among men. From the 50 collected dust samples, TDCPP was detected in 96% of them and TPP was detected in 98%. Figure 8 displays the scatterplot of TDCPP in house dust and serum prolactin; whereas, Figure 9 displays the scatterplot of TPP in house dust and sperm concentration. It was also observed that TPP concentrations were significantly higher than PBDE concentrations from previous studies. It was seen that TPP concentrations were 1.8 mg/g compared to the mere 0.04 mg/g of PBDEs. An inverse association was found between TDCPP concentration and thyroid hormones. Positive relations were found for both TDCPP and TPP with prolactin hormone. This could potentially affect metabolism, homeostasis, osmotic balance, and angiogenesis in humans [102]. In addition, there exists an inverse relation between TPP and sperm concentration [103]. Most flame retardants are toxic reproductive materials that can cause reduced fertility in males. Although evidence of flame retardants on sperm quality and some hormones has

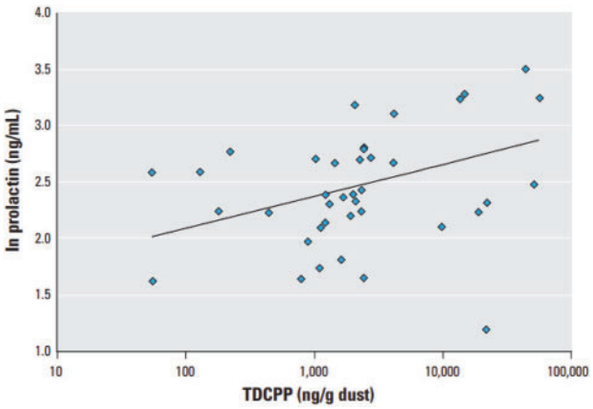

Fig. 8. Scatterplot of TDCPP in house dust and serum prolactin ($n = 38$; $r = 0.43$; $p = 0.0007$). Reprinted with permission from Ref. [102], Meeker, J.D. and Stapleton, H.M., **2010**. House dust concentrations of organophosphate flame retardants in relation to hormone levels and Semen quality parameters. *Environmental Health Perspectives, 118*(3), pp.318–323. Copyright@Environmental Health Perspectives.

been verified, further investigation is needed to determine the extent of these health hazards.

In a study conducted by Xiang et al. in 2017, the effect of TDPP on the human cornea was investigated [104]. The corneal epithelium is the outermost cell layer of the eye and is covered by a tear film to act as a barrier to dust and other particles. However, daily exposure to indoor dust has been associated with increased corneal injury risks. This research investigated the effects of TDCPP on the human cornea by using human cornea epithelial cells (HCECs). Cell viability, morphology, apoptosis, mitochondrial activity, and cellular ATP levels were studied after 24-hour exposure to TDCPP. The results showed that TDCPP did not significantly affect cell viability below concentrations of 68 μg/ml. In addition, TDCPP-exposed cells showed an increase in apoptosis in comparison to control cells. It was seen that TDCPP at 2 mg/ml initiated weak early apoptosis in HCEC. In conclusion, it was observed that TDCP can lead to decreased cell viability and trigger cell apoptosis.

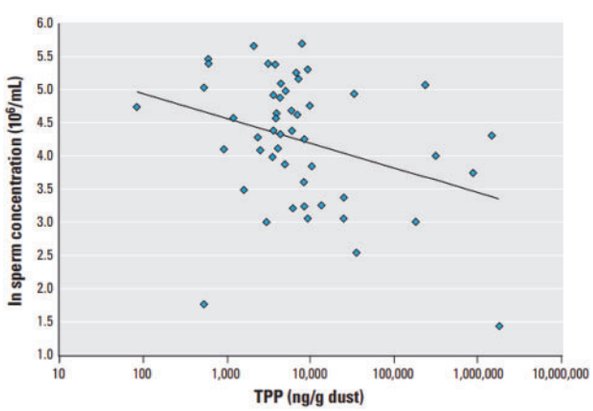

Fig. 9. Scatterplot of TPP in house dust and sperm concentration ($n = 50$, $r = 0.33$, $p = 0.02$). Three samples with sperm concentration of <20 million/mL were excluded from the analysis, and yet the inverse relation remained. Reprinted with permission from Ref. [102], Meeker, J.D. and Stapleton, H.M., **2010**. House dust concentrations of organophosphate flame retardants in relation to hormone levels and semen quality parameters. *Environmental Health Perspectives, 118*(3), pp.318–323. Copyright@Environmental Health Perspectives.

2.10. Aerosol Particles

Aerosol comprises liquid droplets or solid particles uniformly distributed in a fine state of gas, usually air. Aerosol particles exist in sizes that range from a few nanometers to around 1 micrometer. Aerosols can be classified based on their source as natural, such as fog, dust particles, cloud droplets, or anthropogenic such as particulate pollutants in air, smoke, and any household product stored in a pressurized can (e.g., spray paint, hair spry, deodorants, etc.) [105].

A study was conducted to understand the effects of fine particle aerosols less than 2.5 μm, also known as $PM_{2.5}$, on the health of the people of Mumbai city in India in the period 2007–2008 [106]. Mumbai is known as the industrial capital of India, with various factories and ever-increasing vehicles. In this study, the monitoring of air quality was conducted in 4 major areas of the city, representing: control (C), kerb (K), residential (R), and industrial (I). It was observed that the $PM_{2.5}$ concentration at C, K, R, and I were 34–136 $mg \cdot m^{-3}$, 46–180 $mg \cdot m^{-3}$, 33–149 $mg \cdot m^{-3}$ and 48–190 $mg \cdot m^{-3}$ ranges, respectively. These ranges exceeded the Indian Ministry of Environment and Forest (60 $mg \cdot m^{-3}$, 24 h time-weighted average) [106]. In addition, lung cancer data was collected from the Mumbai Cancer Registry for 2007. The study found that increased lung cancer trends, in contrast to previous years, could directly correlate with the increased amount of fine aerosol particles in the atmosphere.

Many of the aerosol products commonly used in households contain various chemicals. To test whether these aerosol particles can adversely affect human health, a study was conducted on healthy adult males and females [107]. They were exposed in a controlled environment to isobutane, propane, fluorocarbon 12 (FC-12, difluorodichloromethane), and fluorocarbon 11 (FC-11, fluorotrichloromethane) at concentrations similar to those permitted in industrial settings. The concentrations used were 250, 500, and 1000 ppm of particles for varied periods of 1 minute to 8 hours. Electrocardiogram (EKG) and other continuous monitoring of modified V5 by telemetry were carried out during exposure. Minor variations in cognitive tests were discovered by male subjects exposed to 1000 ppm of FC-11. However, it is interesting to note that none of the subjects portrayed a decrease in cardiac rhythm or pulmonary function due to this exposure. However, this study does not show the effects of longer-term exposure to identical aerosol particles.

One of the most commonly used pharmaceutical aerosol applications is inhalation therapy. A study by Darquenne in 2012 reviewed the primary mechanism that affects the transport and deposition of inhaled aerosol particles in human lungs [108]. The main mechanisms that affect this are inertial impaction, gravitational sedimentation, and Brownian diffusion. In addition, turbulent flows, interception, and electrostatic perception also play a minor role. For an inhaled drug to be effective to the body, it is essential to deposit sufficient amounts and reach the targeted regions of the lung. This study concluded that particle size plays a significant role in a drug's effectiveness. Larger particles greater than 6 μm were found to deposit in the upper airway. This limited the concentration of drugs that can be delivered to the lung. In contrast, smaller particles that are smaller than 2 μm will deposit principally in the alveolar region. Particles between 2 to 6 μm are appropriate for treating central and smaller airways. These findings can give rise to guidelines for aerosol therapies, which recommend the flow rate of aerosols being delivered to be 30 L/min. Most current inhalers produce a median aerosol diameter of 6 μm or less [108].

3. ORGANIC NANOPARTICLES AS DRUG DELIVERY VEHICLES

In addition to solid nanoparticles, organic nanoparticles are safer and pose fewer health effects. Organic nanoparticles include liposomes, polymeric micelles, and solid lipid nanoparticles. Liposomes are small, spherical-shaped artificial or natural vesicles composed of double phospholipid layers and an internal aqueous/lipophilic cavity, hence possessing the advantage of co-encapsulating both hydrophobic and hydrophilic drugs.

The structural components of liposomes are phospholipids (dioleoylphosphatidylethanolamine, Dipalmitoylphosphatidylcholine), usually synthetic amphiphiles (1, 2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000]) that can be combined with cholesterol to enhance membrane permeability. Because these constituting molecules are either present in the body or resemble lipids that make up the cell member, they are well tolerated by the body, causing little cytotoxicity. They are were among the first nanoparticles to be approved by the FDA (e.g., liposomal DOX or DOXIL was approved in 1995).

Micelles and polymeric micelles are another class of organic nanoparticles. They are usually composed of copolymers (diblock copolymers (e.g., poly(lactic-co-glycolic acid) and triblock copolymers (e.g., Pluronic). Unlike liposomes, these nanovehicles are composed of one layer capable of encapsulating hydrophobic drugs. Polymeric micelles have low cytotoxicity at low concentrations; hence the critical micellar concentration (CMC) is very important. Copolymers that form micelles at lower concentrations are more favorable than polymers with higher CMCs. And yet a third class of organic nanoparticles is solid lipid nanoparticles (SLN). These are composed of lipids and emulsifiers and have low cytotoxicity at low concentrations.

4. CONCLUSION AND FUTURE WORK

Nanoparticles are currently used in diverse industries; their applications are evolving on a daily basis. Areas of utilization include pharmaceuticals, food, medical diagnosis, agriculture, and renewable energy. Human exposure to nanoparticles is inevitable, especially due to the many entry routes to the body, including respiratory, digestion, transdermal, inhalation, and ocular.

Several tissues or organs are affected for each entry route, and in some instances, the whole body is affected. For inhalation, lung tissues and cardiovascular system functions are compromised due to nanoparticles exposure with heart contractibility and lesions in the lung as primary outcomes. Also, dermal exposure alters the proliferation and viability of keratinocytes, leading to skin cancer development due to long-term exposure. In addition, ingestion is the least common route of exposure, yet the most toxic. Ingested nanoparticles can perfuse through many tissue barriers such as the blood–brain barrier and intestine barriers; they can affect key survival needs in the body, causing death in some instances.

Previous research reported that inflammatory response and reactive oxygen species (ROS) are the main risks associated with exposure to nanoparticles. Furthermore, several studies established that nanoparticles characteristics, including size or shape, can drastically affect the exposure limits of TiO_2 NPs, AgNPs, SiNPs, AuNPs, and AlNPs.

Our knowledge of the effects of nanoparticles exposure is still limited. Hence, future work on nanoparticles' toxicity should provide clearly defined guidelines for the exposure limits of each nanoparticle and relate several of their characteristics such as size, shape, morphology, surface charge, and area to potential hazards to toxicity and exposure limits. Also, more *in-vivo* studies should be conducted as literature reports are mostly on *in-vitro* studies. Finally, special attention should be directed to determine whether parameters such as age, gender and weight can vary the behavior of tissues upon nanoparticle exposure, hence the allowable safety limits.

Authors' Contributions

Omnia Mohamed, Saniha Aysha Ajith, Rana Sabouni, Ghaleb Husseini, Abdollah Karami, Renu Geetha Bai.

Omnia Mohamed and Saniha Aysha Ajith: Investigation, Writing-original draft preparation; Rana Sabouni: Conceptualization, Project administration, Supervision, Writing-review and editing; Ghaleb Husseini: Writing-review and editing, Methodology, Resources; Abdollah Karami: Visualization, Writing-review, and editing; Renu Geetha Bai: Writing- review and editing.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgment: The work was supported by the American University of Sharjah via the faculty research grants [Grant Numbers: EFRG18-BBR-CEN-03 and FRG20-M-E84]. The authors acknowledge funding from the Sheikh Hamdan Award for Medical Sciences MRG/18/2020, and Friends of Cancer Patients (FoCP).

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Received: xx xxxx xxxx. Accepted: xx xxxx xxxx.