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A Review on Nanoparticles Toxicity

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ABSTRACT:

A number of thousands of distinct nanoparticles are known to exist today, but there are currently no clear guidelines for assessing their possible toxicity and managing their exposure. These guidelines cover the introduction of nanoparticles as well as their characteristics, including chemistry, chemical composition, size, shape or morphology, surface charge, and location can affect their biological impacts and activities. Either a safe particle or a harmful one can arise from a particular feature. Because of their small size, nanoparticles can enter the body by a number of different routes, enter the bloodstream and lymphatic system, reach organs and tissue, and only interact with biological structures. hence impairing their regular processes in various ways. A synopsis of the toxicology knowledge pertaining to the specificity of nanoparticles, whether they are ambient contaminants or technological instruments, is given in this paper. The objective is to draw attention to their possible risk and to give a fair assessment of all the significant issues and areas that require immediate attention.

Keywords: Nanoparticles, Toxicity

1. INTRODUCTION:

The prefix "nano" in the word "nanoparticle" (NP) is derived from the ancient Greek language and means "dwarf," meaning that the particle is much smaller than most particles, with a diameter of less than 100 nanometres (10^{-9}m), ranging from 1 to 100nm [1-5].

The most notable of these are heavy metals like nickel, cadmium, manganese, zinc, titanium, gold, antimony, silicon and their metal oxides, carbon, and others that can be engineered or accidentally released into the environment. However, a wide range of chemicals with various shapes and characteristics can be categorized as nanomaterials. Incidental nanoparticles (NPs) can originate from many industrial processes and are present in the surrounding ecosystems. They are mostly produced by coal, natural gas, and oil power plants. Incidental nanoparticles (NPs) can originate from many industrial processes and are present in the surrounding ecosystems. They are mostly produced by coal, natural gas, and oil power plants. Designed and manufactured NPs have been used in a variety of biomedical sectors, mostly to enhance therapeutic treatments and diagnostic instruments.

Fossil fuel burning, solid waste incineration, and traffic emissions can all produce nanoparticles. In these situations, NPs may consist of a complicated blend of several chemical compositions.

A complex NPs mixture could also be formed in the armed forces shooting ranges as a result of the explosion of bombs developing very higher temperatures; adhering to this, surrounding materials may be pulverized, to the rocks to the soil, and easily transported as a fine suspension not only in air as well as in water. The resulting inorganic and metallic powders are frequently insoluble and nonbiodegradable particles; because of their small size, they can be released into

the environment and remain there indefinitely. The primary anthropogenic sources of NP exposure, their release into the environment and workplace, and the ensuing occupational or public exposure through a variety of entry and translocation pathways into the human body are all detailed in Fig. (1). The focus on the NPs peculiarity originates from their nanoscale size that leads to a very high surface given to all distinct reactions. Although several created nanoparticles have shown great promise in a number of disciplines, a number of negative impacts have emerged that have raised concerns. Indeed, there may be some similarities between accidently released NPs and designed NPs.

may have a number of detrimental consequences on human health in common. NPs can infiltrate the human body and build up as foreign substances in organs and tissues regardless of their usage or source. Because of this, a new field of study called nanotoxicology was recently established with the goal of examining the harmful consequences of nanomaterials on the environment and human health [6,7].

This review attempts to assess the special characteristics of particles with nanoscale dimensions, which should be considered in order to shed light on their harmful consequences. This summary of the toxicology of NPs, whether they are environmental pollutants or technological instruments, aims to characterize their possible hazard and offer a fair update on all the significant subjects pertaining to their numerous applications.

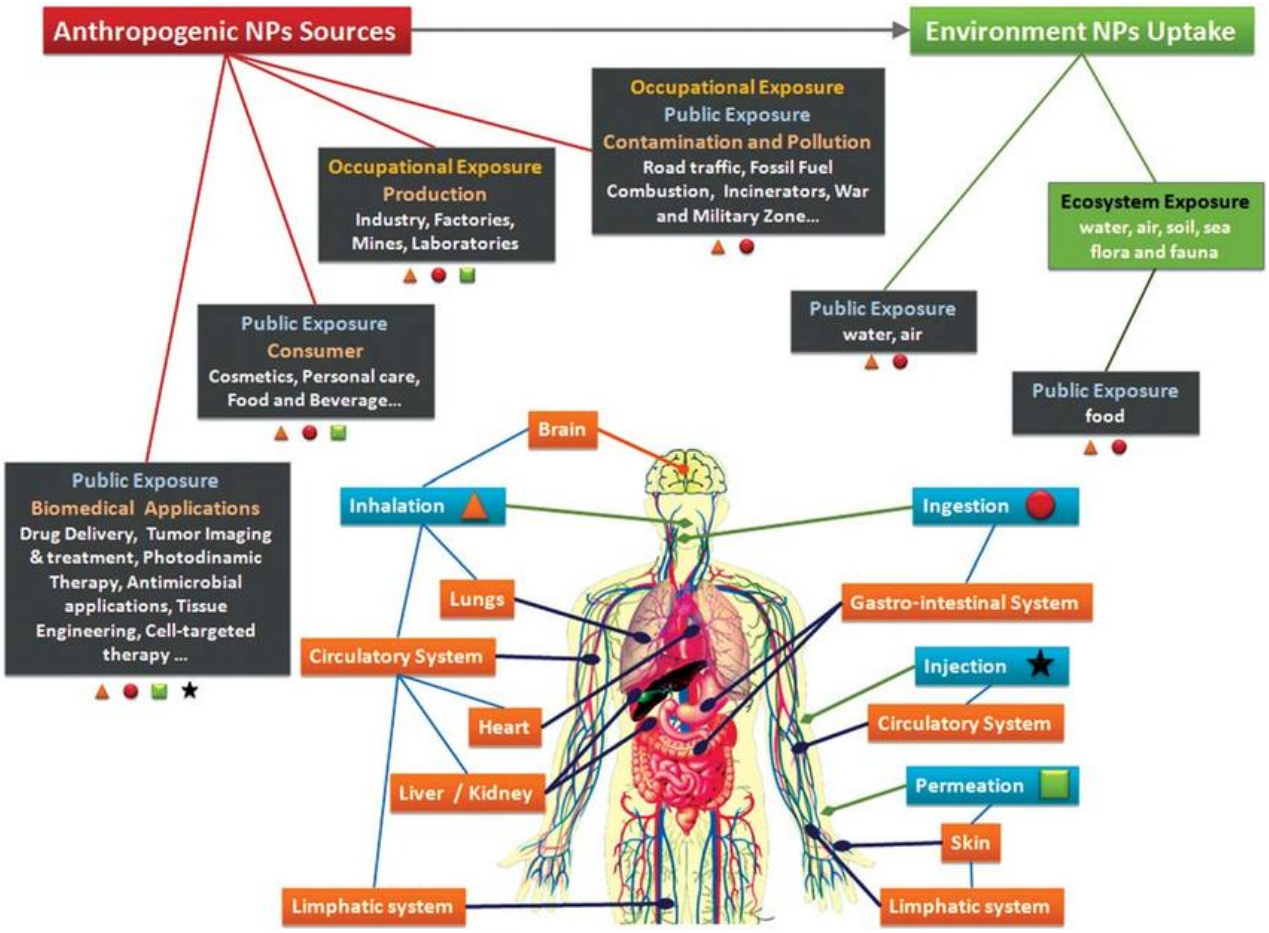

Fig. (1). Human exposure to NPs. Main anthropogenic sources of NPs, their release in the work place and environment, the subsequent occupational or public exposure through several ways of entry and translocation into human body [146].

Particle Aspect Connected to their Activity:

It is now widely acknowledged that the mechanisms behind the uptake, translocation, biological, and toxicological effects of nanoparticles (NPs) are heavily influenced by their physical characteristics. To obtain reliable studies, it is essential to first characterize the NPs' size, shape, surface charge and surface area, hydrophilicity, agglomerate and aggregate formation, as well as their solubility, chemical, and geometrical properties. The size plays a significant role in influencing the reactivity since it affects the surface area. In actuality, it can either increase or decrease the area involved in the particular effect: the smaller the particles, the higher the surface to volume ratio and, often, the more noticeable their reactivity.

There are numerous cases to support that. For example, after intravenous treatment in rats, the bigger gold nanoparticles, ranging in size from 50 to 250 nm, were discovered primarily in the liver, spleen, and blood, while the smaller ones, measuring 10 nm, were widely dispersed throughout many organs. This indicates that the tissue distribution of gold nanoparticles is size dependent. [8]

Along with their water solubility, nickel particles' carcinogenic potential has been continuously linked to their size. Larger particles are phagocytized by macrophages, while particles smaller than 200 nm are likely to infiltrate the epithelial cells. The fate of these particles is also determined by their surface charge: In contrast to crystalline nickel sulphide (NiS) and sub sulphide (Ni3S2) particles, which are negatively surface charged, amorphous positively charged surface particles do not penetrate cells. Through phagocytosis, y surface charges infiltrate cells [9] **(Fig. 2).**

The acidic pH of endocytic vacuoles can then dissolve them. By doing this, a steady supply of Ni2+ ions is made available, which can then enter the nuclear components of cells and, through direct or indirect mechanisms, induce a variety of nuclear damage. These include promutagenic DNA damage, disruption of the DNA repair system, and epigenetic effects in chromatin, particularly on histone acetylation and methylation. All of these mechanisms may contribute to the known carcinogenic potential of Ni (II) particles [10–25].

Nanotoxicology:

Since any inherent properties of particles will likely be emphasized with the increase in surface area per unit mass [149,150], research now shows that harmless bulk materials have the opinion that the smaller the particles, the more reactive and toxic are their effects. This is one of the main factors that may make nanotechnology potentially dangerous to human health, even though it is what makes it so useful in industry and medicine. However, the distinct kind of toxicity brought on by surface alteration is the particular worry with nanotechnology. It has been demonstrated that the surface chemistry (coating) of nanoparticles and in vivo surface changes play a major role in enhanced endocytosis, which includes the possibility of inflammatory and prooxidant activities [151, 149]. Increased pulmonary toxicity (granuloma development, inflammation, etc.) Cell death may arise from oxidative stress brought on by free radicals produced when particles contact with cells. Following nanoparticle endocytosis, evidence of mitochondrial distribution and oxidative stress response was seen. Because of their small size, nanoparticles may act as haptens to change the structure of proteins, changing their function or making them antigenic, which could increase the likelihood of autoimmune reactions [152].

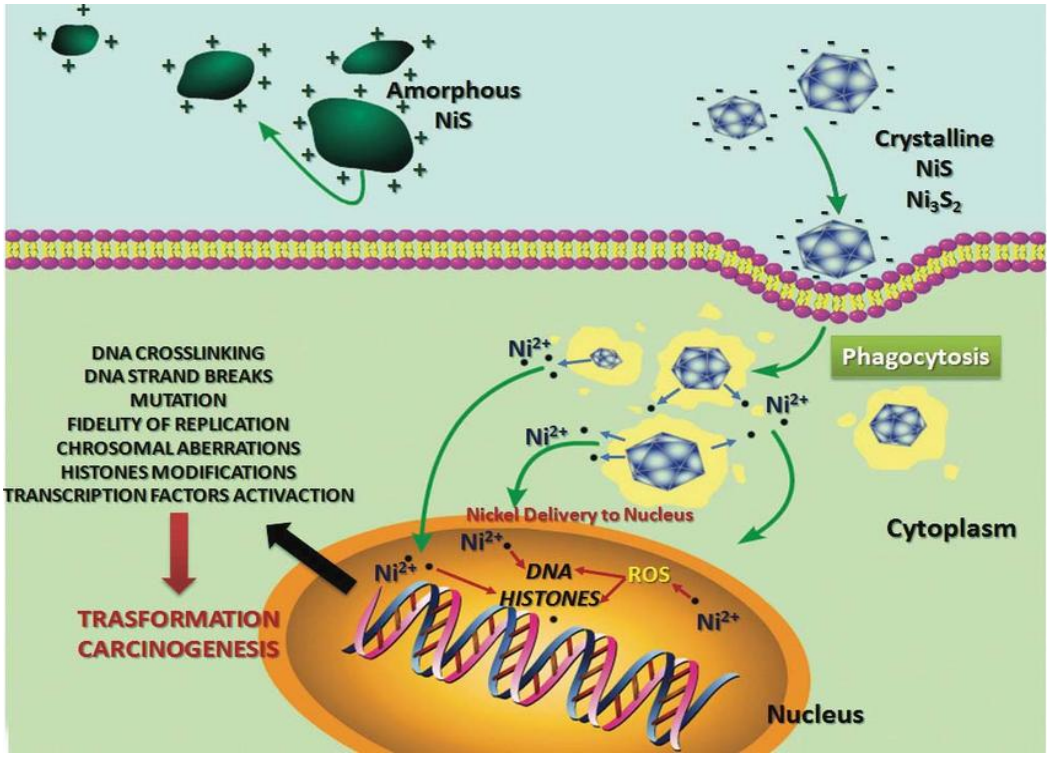

Fig. (2). Model of phagocytosis mechanism and intracellular dissolution of nickel sulphide particles into cells and the potential cellular nuclear damages. Crystalline nickel sulphide particles were selectively phagocytized by the cells, while amorphous NiS particles were not. Afterwards, phagocytized nickel sulphide particles were dissolved in the cytoplasm by the acidification of cellular vacuoles and the nickel ions released produced selective damage in heterochromatin. Adapted from [16]

The genome destroying capacity of both metal and metal oxide NPs that have been modified has been examined, oxidative DNA mechanisms along with impairments of gene expression and strand breaks have been reported based on in vitro experiments [27]. Moreover, charged gold NPs of 1.5 nm size cause cell death by apoptosis, while neutral gold NPs lead to necrosis in HaCaT cell lines [26]. Therefore, it seems that the particle surface may also play an important role concerning toxicity, as it determines the initial direct contact with living things and cell surface and aspects. NPs might not make it to the cellular nucleus in this scenario, but [28–31].

The following **Table 1** from [32] lists the most prevalent biological consequences associated with the physical and chemical characteristics of nanoparticles:

The geometrical and structural forms that give NPs their belt, tube, wire, sphere, and fiber appearances **(Fig. 3)** are crucial in assessing their harmful bioactivity, and it appears that the long wire or fiber is the shape that should be of the most concern. The fibers cannot be eliminated by the normal clearing procedures of the alveolar macrophages, which are supposed to be in charge of eliminating inhaled pollutants.

For instance, even though TiO2 NPs with a size of 200 nm are thought to be comparatively biologically inert material in vivo and in vitro, but TiO2 nano-belts longer than 15 m are extremely toxic particles that cannot be sequestered inside the cells into a lysosome, which makes them persistent in the lung where they can cause an inflammatory reaction and release of inflammatory cytokines [56] with potentially harmful consequences. The same effect is seen with various forms of asbestos and silica, and it has been reported that certain types of carbon nanotubes can also cause asbestos-like pathologies in mice [57]. Therefore, the size and form of the material appear to be the determinant factor in causing inflammation in vivo, instead of its chemical composition. Long-term exposure to manufactured asbestos-like wiring can cause fatal illnesses like lung fibrosis fibres.

Translocation and Entry methods:

Particles' physical and chemical characteristics influence their capacity to enter the body through particular pathways as well as their likelihood of being retained or otherwise moving through the body to various organs or tissues. NPs can enter the body in a variety of ways **(Fig. 4)**, but the three primary pathways are ingestion through the digestive tract, skin penetration, and inhalation through the respiratory tract.

Inhalation:

One of the most frequent ways that people get exposed is thought to be by inhalation. The size of the particles appears to be the primary determinant of how much dust and other airborne particles enter, deposit, or eventually go to other locations.

Permeation:

The risk of NPs dermal exposure is a topic of scientific debate and concern, and the findings around this are still up for debate. Since the skin acts as a protective barrier and NPs can only pass through the top layers of the epidermis before penetrating the area near the hair follicles, the majority of research on the uptake, delivery, and distribution of NPs in and through the skin indicates that the associated toxicity appears to be negligible.

Table (1). Toxicokinetic findings and biological effects due to physicochemical properties of NPs. Reprinted with permission from Elsevier [32].

Physicochemical Property		Toxicokinetic Findings	Biological Effects	Ref.
Size	15 nm gold nanoparticles (NPs)	Most widespread organ distribution including blood, liver, lung, spleen, kidney, brain, heart, stomach in mice	Biodistribution of the nanoparticles	[33]
	15 and 50 nm gold NPs	Pass blood–brain barrier (BBB) in mice	Blood Brain Barrier (BBB) permeability	[33]
	40–50 nm gold NPs	Activation of membrane receptors in SK-BR-3 cells		[34]
	50 nm gold NPs	Maximum uptake by Hela cells		[35]
	50 nm quantum dots	Efficient receptor-mediated endocytosis in Hela cells		[36]
	1–10 nm silver NPs		Exclusively attach to HIV-1	[37]
	1–10 nm silver NPs	Penetrate inside the bacteria		[38]

Physicochemical Property		Toxicokinetic Findings	Biological Effects	Ref.
Shape	Open-ended Single-walled carbon nanotubes (SWNTs)	Efficient blocking of ion channels in CHO cells	Spherical shaped close-ended SWNTs are comparatively less reactive	[39]
	Spherical gold NPs	Higher uptake by Hela cells	Rod-shaped gold NPs showed less uptake	[35]
	Carbon particles, except C60CS	Stimulated human platelet aggregation *in vitro* and accelerated the rate of vascular thrombosis in rat carotid arteries	Biological reactivity: mixed carbon nanoparticles (MCNs) single-walled carbon nanotubes (SWNTs) > multiwalled carbon nanotubes (MWNTs)	[40]
	Filomicelles (Filamentous micelles)		More efficient for drug delivery than their spherical counterparts in rats and mice	[41]
Surface area/volume ratio	TiO_2 (300 cm^2 surface area)	Increased lymph-node burdens and Inflammation	More reactive in rats as compared to $BaSO_4$ (200 cm^2 surface area)	[42]
	TiO_2 and $BaSO_4$ with same surface area	Inflammatory effects were similar	Inflammation	[42]
	Ultrafine carbon black particles (270 m^2/g surface area)	Cause greater pulmonary toxicity in rats	Increased reactivity in comparison with larger-sized carbon black particles (22 m^2/g surface area)	[43, 44]
Chemical composition	Incorporation of 1% (w/w) manganese doping into titania particles	Increase in UVA absorption and reduction in free radical generation *via* surface reactions		[45]

Physicochemical Property		Toxicokinetic Findings	Biological Effects	Ref.
	Carbon nanomaterials	Different geometric structures exhibit quite different cytotoxicity *in vitro*	The cytotoxicity follows a sequence order: SWNTs > MWNTs > quartz > C_{60} on alveolar macrophages isolated from guinea pigs	[46]
	Metal traces associated with the commercial carbon nano-tubes	A dose- and time-dependent increase of intracellular reactive oxygen spe-cies and a decrease of the mitochondrial membrane potential in rat macrophages (NR8383) and human A549 lung cells	More reactive as compared to purified carbon nanotubes	[47]

However, the skin is porous to nanomaterials, and hair follicles and glands provide holes on the skin surface that can act as channels of entry, particularly for ultra-fine materials [104]. In fact, it has been shown that several NPs can pass through the derma and enter the systemic vascular system through lymph nodes. Millions of people use a variety of cosmetics and personal care products that contain nanoparticles on a daily basis, including shampoo, toothpaste, deodorant, soap, sunscreen, cream, foundation, face powder, perfume, and eye shadow, to mention a few. As a result, 33 million Americans use sunscreen products every day, and many more occasionally [135]. Changes to the skin may improve the uptake of NPs because they may act as entry points for both bigger and finer particles [145].

Physicochemical Property		Toxicokinetic Findings	Biological Effects	Ref.
	Quantum dots core metalloid complexes of Cadmium, Cd	Can cross the blood–brain barrier and placenta, and are systemically distributed to all bodily tissues, with liver and kidney being target organs of toxicity	A probable carcinogen	[48]
	Quantum dots core metalloid complexes of Selenium, Se		A marked impact on the local ecosystem resulted from elevated environmental	[48]

Physicochemical Property		Toxicokinetic Findings	Biological Effects	Ref.
			concentrations of Se	
	Ag, MoO_3, Fe_3O_4, Al, MnO_2 and W (Tungsten)	Ag was highly toxic whereas, MoO_3 moderately toxic and Fe_3O_4, Al, MnO_2 and W (Tungsten) displayed less or no toxicity at the doses tested on *in vitro* rat liver derived cell line (BRL 3A)	Reduced cell proliferation and death	[49]
	$La_{0.7}Sr_{0.3}MnO_3$ (LSMO) nanoparticles doped with cerium ($La_{0.7-x}Ce_xSr_{0.3}MnO_3$ were 0 x 0.7) and $La_ySr_yMnO_3$ nanoparticles with different values of y (La/Sr ratio)	Low cytotoxicity in Ce-doped samples as well as in samples with reduced La/Sr ratio as revealed by *in vitro* studies on HT-1080 (human fibrosarcoma) and A431 (human skin/carcinoma) cells	Improved cell proliferation upon Ce doping	[50]
Surface charge	Neutral NPs and low concentration anionic NPs		Drug delivery applications to brain in rats	[51]
	Cationic NPs		Toxic effect at the blood brain barrier in rats	[51]
	Anionic NPs at lower concentrations		Superior uptake rates as compared to neutral or cationic NPs at the same concentrations in rats	[51]
	Positive surface charged poly(amidoamine) dendrimers	Deposition into tissues is higher than neutral surface dendrimers in B16	Higher deposition in tissues	[52]

Physicochemical Property		Toxicokinetic Findings	Biological Effects	Ref.
		melanoma and DU145 human prostate cancer mouse tumor model		
	Coating of respirable quartz surface with aluminium lactate or polyvinyl-pyridine-*N*-oxide (PVNO)	Inhibits DNA strand breakage and formation of 8-hydroxy-deoxyguanosine in human lung epithelial cells	Reduction in toxicity	[53]
Aggregation state	Rope-like agglomerates of carbon nanotubes	Induced more pronounced cytotoxic effects than well dispersed carbon nanotubes in human MSTO-211H cells	Cytotoxicity	[54]

The majority of the particles are typically deposited in the nose, mouth, and larynx, but the smallest grains can either reach the bronchial tree, where they can be retained and cause their harmful effects, or they can translocate to other different sites. Epidemiological studies conducted on miners and refinery workers exposed to metal particles have shown a correlation between exposure and the incidence of cancer to the respiratory tract (lung and nasal cancer) [58]. The tendency of nickel workers exposed to nickel-containing dusts to develop cancers of the nasal cavities was first reported in 1933. The pattern of negative effects on the retention sites seems specific to a particular particle; for instance, asbestos fibres deposit primarily on airways bifurcations and cause fibrosis "spots" following acute exposure; they manifest as fibrotic nodules in chronic beryllium disease and emphysema in "coal workers" via lymphatic pathways along the airways [59–61].

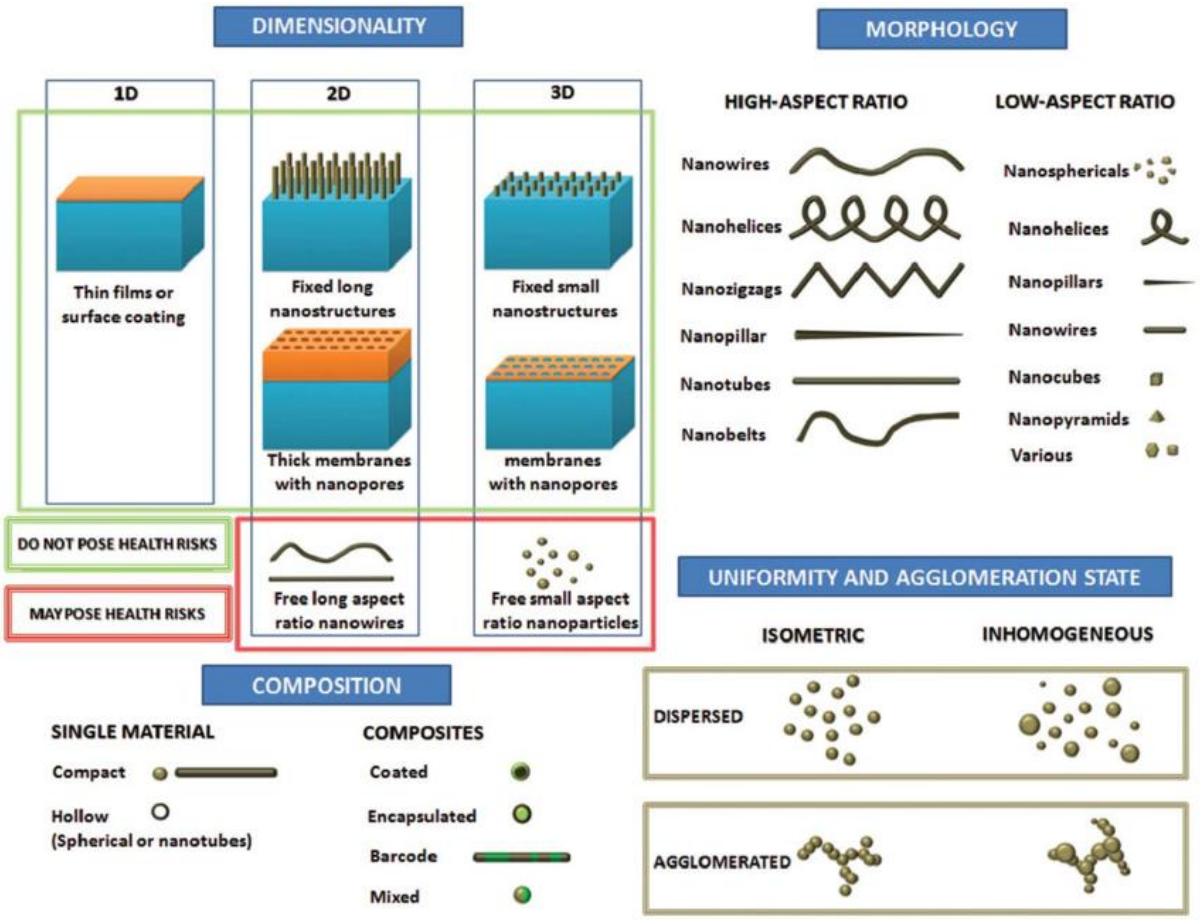

Fig. (3). The classification of NPs based on shape or morphology, size, composition and agglomeration state. Adapted from [55]

In any event, as **Table 2** [62] summarizes, the locations of retention have inflammatory and detrimental consequences on cellular targets and metabolic activity. The smallest particles, particularly ultrafine ones, can go to different organs and tissues after being inhaled. According to multiple studies, nanoparticles (NPs) from ultra-fine dusts and aerosols provide the greatest risk following inhalation exposure [89–92].

According to reports, the primary mechanism for the translocation is alveolar epithelial cell endocytosis [93]. Numerous studies have been conducted on the translocation of ultra-fine particles, including carbon, zinc, iridium, manganese, manganese oxide, and others, to various organs [89,90,94-98].

Animal studies have demonstrated the short-term transfer of metal nanoparticles from the lungs into the bloodstream and to target organs. For instance, ultra-fine radiolabelled iridium particles, which are around 20 nm in size, have been discovered in numerous extra-pulmonary organs, primarily the kidneys, liver, spleen, heart, and brain, one week after rats were exposed for one hour through inhalation [99]. Large amounts of intratracheally administered gold nanoparticles (approximately 30 nm in size) and TiO2 (about 20 nm in size) were discovered in the platelets inside the pulmonary capillaries of rats within 30 minutes of exposure [20]. Because of this characteristic, it is hypothesized that nanoparticles cause platelets to aggregate, which in turn causes blood clots to develop.

After 12 weeks of inhalation in rats, 20 nm titanium dioxide nanoparticles demonstrated a greater translocation to the interstitial locations and a longer retention duration in the lungs compared to bigger nanoparticles (250 nm) with the same crystalline structure [100].

Debris of micro and nanoparticles was found in the organs and blood of patients with metallic orthopedic implants [101, 102] or worn dental prosthesis [103] using scanning electron, environmental scanning electron microscopy, and X-ray-micro evaluated with an energy dispersive system technique.

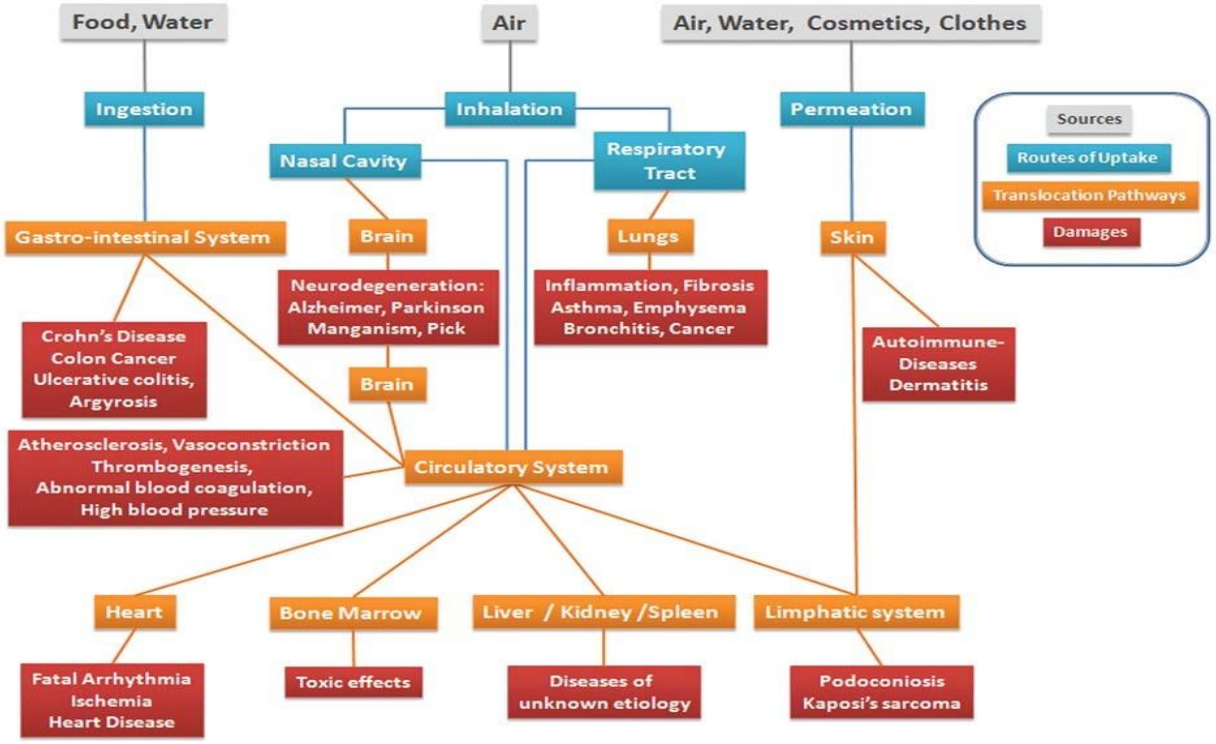

Fig. (4). The main pathways for NP exposure, absorption, transport, and possible hazards. The orange boxes show possible translocation channels, the red boxes show possible harm, the blue boxes show the main uptake routes, and the grey boxes show the source of NPs exposure [147]

It is important to highlight that there are notable differences between metallic and non-metallic species in terms of particle chemistry [104-106]. Actually, following inhalation, in contrast to non-metallic nanoparticles sized between 4 and 200 nm, which move very little or hardly at all, metallic nanoparticles smaller than 30 nm enter the blood circulatory system quickly in instillation trials conducted on healthy animals [107,108].

The process by which NPs are transported from the pulmonary site to the brain, the most vulnerable organ, following inhalation exposure has received a lot of attention lately.

Professional groups at risk of occupational exposure to metal NPs include, among others, manganese mining, welding, and manufacturing personnel, as well as welders in stainless steel facilities exposed to fumes and dusts. Manganese NPs were observed to be transported from the nasal epithelium to the brain's olfactory bulb and a progressive along the axons of olfactory neurons in these instances harm to the central nervous system's ability to function has been proven. [89,90,91-98, 109-117]

According to Oberholster et al., rats exposed for seven days by inhalation had 30 nm-sized MnO2 NPs moved from the lungs to the olfactory organ [104], from whence they might enter the brain [6,89]. Reactive oxygen species are created when MnO2 NPs are inhaled, and this leads to oxidative stress in the brain. Studies conducted on biopsies from city dwellers have also shown the potential role of ambient air NPs in neurological disorders [118].

Interestingly, whereas bulk TiO2 is thought to be innocuous, the effects of fine dusts of bio persistent TiO2 nanoparticles appear to be comparable to the long-term inflammatory processes associated with asbestos fibre inhalation [119].

TiO2 is widely used to give opaqueness or brightness to a wide range of items, including toothpaste, paints, colorants, plastics, papers, foods, and many more. To improve defense against UV rays, TiO2 NPs are also utilized in sunblock's, skin care products, and cosmetics. Recently, an intriguing evaluation was released that summarizes the risk assessment for nanoproducts' carcinogenic potential [120]. Despite conflicting findings and a lack of comprehensive and definitive epidemiological research on carcinogenesis, some data support the possibility that nanoparticles can cause tumours: in sensitive animal models, high concentrations of carbon nanotubes (CNTs) in various forms, as well as fine (<2.5 m) and ultrafine (<100 nm) TiO2 particles, can cause cancer of the respiratory tract.

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Table (2). summarizes the in vitro and in vivo assessments of NPs' toxicity with an emphasis on experimental targets for the liver, brain, skin, and lungs. Reprinted from Elsevier with permission [61].

Target	NPs	Concentration (time/size)/route of administration	Cellular target	Animal target	Major outcomes	Ref.
Lung	**SWCNT**	1.56-800 g/mL (24 h)	A549 human lung cancer cells		Low acute cytotoxicity was further reduced by dispersion of SWCNTs in serum.	[63]
	SWCNT	47 mg on days 0 and 7 (follow-up: 4 months) Intravenous infusion		Nude mice	No significant inflammatory changes were observed, however, particle deposition in liver macrophages was observed.	[64]
	MWCNT	0.5, 2 or 5 mg/animal (3 and 15 days) Intratracheal instillation		Sprague-Dawley rats	Dose-dependent increase in inflammatory markers post-BAL. Dose-dependent fibrotic change and interstitial granuloma formation.	[65]
	Silica NP	10-100 g/mL (24 h, 48 h and 72 h)	A549 human lung cancer cells		Dose- and time-dependent decrease in cell viability: up to 50% reduction at highest dosage after 72 h. Oxidative stress indicated as mechanism of cytotoxicity.	[66]

Target	NPs	Concentration (time/size)/route of administration	Cellular target	Animal target	Major outcomes	Ref.
	Silica NP	25 g/mL (24 h)	A549 human lung cancer cells HepG2 cells RPMI 2650 human nasal septal epithelial cells N2a mouse neuroblast cells		Nuclear protein aggregation and subsequent interference with gene expression resulting in inhibition of replication, transcription and cell proliferation.	[67]
	Silica NP	33-47 g/cm^2 (small NP), 89-254 g/cm^2 (larger NP) (24 h)	EAHY926 endothelial cells		Size-dependent reduction in viability with smaller particles in the nanoscale exhibiting higher toxicity compared to particles >100 nm.	[68]
	Silica NP	20 mg/animal (1 or 2 months) Intratracheal instillation		Wistar rats	Nano-sized silica particles produced relatively lower pulmonary fibrosis compared to micro-sized silica particles. This is thought to be due to the translocation of ultrafine Nano silica away from the lung parenchyma.	[69]
	Silver NP	515 g/m^3 (6 h/day, 5 days/week for 13 weeks) Inhalation		Sprague-Dawley rats	Dose- and time-dependent increase in blood Ag nanoparticle concentration was observed along with correlating increases in alveolar inflammation and small granulomatous lesions.	[70]

Target	NPs	Concentration (time/size)/route of administration	Cellular target	Animal target	Major outcomes	Ref.
Dermal	**Silver NP**	0.76-50 g/mL (24 h)	A431 (human skin carcinoma)		No evidence for cellular damage up to a concentration of 6.25 g/mL. Morphology changes at concentrations between 6.25 and 50 g/mL with concomitant rise in GSH, SOD and lipid peroxidation. DNA fragmentation suggests cell death by apoptosis.	[71]
	Silver NP	0-1.7 g/mL (24 h)	HEK cells		Significant dose-dependent decrease in cell viability at a critical concentration of 1.7 g/mL with concomitant rise in inflammatory cytokines (IL-1, IL-6, IL-8, and TNF-).	[72]
	Silver NP	Silver-coated wound dressing ‘Acticoat’ (1 week)		Human burns patient	Reversible hepatotoxicity and argyria-like discoloration of treated area of skin, elevated plasma and urine silver concentrations and increased liver enzymes.	[73]

Target	NPs	Concentration (time/size)/route of administration	Cellular target	Animal target	Major outcomes	Ref.
	TiO_2 NP	15 g/cm^2 (24 h)	HaCaT (keratinocyte cell line), human dermal fibroblasts, human immortalized sebaceous		Cytotoxicity was observed affecting cellular functions such as cell proliferation, differentiation and mobility resulting in apoptosis.	[74]

			gland cell line (SZ95)			
	TiO_2 NP	NP containing sunscreen		Human volunteers	Increased skin permeation of NP when sunscreen was applied at hairy skin of human volunteered.	[75]
	Silica NP	70, 300 and 1000 nm in size	XS52 (murine Langerhans cells)		Size-related toxicity with faster cellular uptake of smaller particles and concomitant higher toxicity.	[76]
	Silica NP	30-300 g/mL (48 h)	CHK (human keratinocytes)		Reduced cell viability.	[77]
	Gold NP	95, 142 and 190 g/mL (13 nm) 13, 20 and 26 g/mL (45 nm) (3 or 6 days)	CF-31 (human dermal fibroblasts)		Cytotoxicity was size- and dose-dependent. Larger particles (45 nm) exhibited greater toxicity at smaller doses (10 g/mL) compared to smaller ones (13 nm) which only exhibited cytotoxicity at a concentration of 75 g/mL.	[78]
	Gold NP	0.8-15 nm in size (48 h)	SK-Mel-28 (melanoma cells), L929 mouse fibroblasts		Maximum cytotoxicity with smaller NP (1.4 nm) characterized by apoptosis and necrosis.	[79]
Liver	**Gold NP**	8 mg/kg/week (3-100 nm in size) (4 weeks) Intraperitoneal		BALB/C mice	Naked NP: severe adverse effects with resultant death with particles ranging from 8 to 37 nm in diameter. Microscopically, Kupffer cell activation in the liver and lung parenchymal destruction was observed. Surface modified NP: elicited increased host immune response and improved cytocompatibility.	[80]

	Gold NP	0.17, 0.85 and 4.26 mg/kg body weight (13 nm in size) (30 min after injection for 7 days) Intravenous		BALB/C mice	NPs were found to accumulate in liver and spleen. Significant upregulation of inflammatory cytokines (IL-1, 6, 10 and TNF-) with subsequent apoptosis of hepatocytes at highest concentrations (4.26 mg/kg). No significant changes in the liver at lower doses.	[81]
	Silica NP	50 mg/kg (50, 100 or 200 nm in size) (12, 24, 48 and 72 h, 7 days) Intravenous		BALB/C mice	Size-dependent hepatic toxicity with inflammatory cell infiltrates. Macrophage- mediated frustrated phagocytosis of larger NP (100 and 200 nm) resulted in release of pro-inflammatory cytokines and cell infiltrates within hepatic parenchyma.	[82]
	Silica NP	2 mg/kg (20-25 nm in size) (24 h) Intravenous		Nude mice	Greatest accumulation of NP in liver, spleen and intestines but no pathological changes were observed with small NP (<25 nm). Near-total excretion of NP via the hepatobiliary system.	[83]
	CdSe QD	62.5, 250 and 1000 g/mL (24 h)	Primary rat hepatocytes		Cytotoxicity was thought to be due to the release of free cadmium ions which could not be fully eliminated by ZnS coating of the OD core.	[84]

Target	NPs	Concentration (time/size)/route of administration	Cellular target	Animal target	Major outcomes	Ref.
	CdSe QD	62.5, 100 and 250 g/mL (24, 48 or 72 h)	HepG2 cells		Dose-dependent cytotoxicity. In extreme conditions (250 g/mL for 72 h) a reduce-in cell viability of almost 40% was observed which correlated with an increase in free cadmium ion concentration of 1.51 ppm.	[85]
Brain	**Gold NP**	(12.5 nm in size) (40, 200 or 400 g/kg/day for 8 days) Intraperitoneal		C57/BL6 mice	Small amounts of NP were able to cross the BBB but did not induce evident neurotoxicity.	[86]
	Silver NP	30, 300 or 1000 mg/kg/day for 28 days (60 nm in size) Per oral		Sprague-Dawley rats	Dose-dependent accumulation of NP was observed in the brain and other organs suggesting systemic distribution after oral administration. ALP and cholesterol in-creased significantly in high-dose group (1000 mg/kg/day) indicating hepatotoxicity.	[87]
	CdSe QD	0.68 mg containing 50 nmol Cd (13.5 nm in size) (6 h) Intraperitoneal		ICR mice	Relatively high amounts of Cd ions found in brain tissue but no signs of inflammation or parenchymal damage were observed.	[88]

There is proof of clot formation and inflammatory cell activation from in vitro investigations on the effects of several NPs of varying sizes and sources on the host response [127]. Nickel, antimony, and silver nanoparticles have also been shown to increase platelet aggregation, fibrin polymerization, and its cross-linking. Cobalt, titanium, and iron nanoparticles have been shown to activate macrophage phenotypes that secrete larger quantities of tumour necrosis factor, a member of a class of cytokines that trigger the acute phase reaction and contribute to systemic inflammation. Furthermore, SEM research revealed that these particles' translocation seemed to have a negative impact on important organs, particularly the cardiovascular system.

Engineered nanoparticles are made to have extremely specific characteristics, and current work has been done to explore ways to increase their activity in the industrial and medicinal fields. Silver nanoparticles for their antimicrobial properties in surgical instruments, bone prostheses, and contraceptive devices; quantum dots, semiconductor nanocrystals, for in vivo imaging and diagnostics and cell labelling; carbon and gold nanoparticles for inhaled and oral drug delivery, frequently as chemotherapeutic agents; and zinc and titanium oxide for creams and sunscreen preparations.

Despite all of these examples, studies testing the potential negative effects of manufactured nanoparticles have been ongoing recently, and a number of issues regarding their use have been brought up.

The available in vitro and in vivo data following the assessment of the effects of engineered nanoparticles are compiled in Table 2. Depending on the target organs (liver, brain, derma, lung), the concentration, size, timing, and mode of administration of the NPs, as well as the cellular, animal targets (mice, rats), or human volunteers, the main results have been gathered. It is obvious that there are discrepancies between the data from in vitro and in vivo trials, and extrapolating findings from cell culture research to humans can result in misunderstandings and perhaps unwarranted anxiety.

It is also evident that adopting a unifying protocol is essential first in order to obtain more realistic data. Furthermore, the dosage and method of administering NPs must be extremely carefully considered, and in particular, long-term exposure should be assessed in order to extrapolate data on humans.

In fact, among other findings from in vivo research, especially using rat and mouse models, 30 nm-sized gold nanoparticles are delivered and localized in the alveolar epithelium in rats following interstitial instillation; in experimental mice, 10 nm-sized quantum dots were discovered in the liver, lymph, and bone marrow. They have been shown to cause an inflammatory reaction when placed in the alveolar tract, and they take two months in rats and roughly two years in humans.

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After inhaling ultrafine silver nanoparticles, a significant amount of silver was found in the rat brain [128-131]. Silver nanoparticles, which are 4–10 nm in size, reach the circulatory system after 30 minutes of rat inhalation trials and have been discovered in the liver, kidney, and heart a day later. After a week [105], they were subsequently removed from these organs. They have been transported from the liver into the small intestine through the biliary system.

Some new compounds, such as cerium and cerium oxides (CeO2), which are specifically utilized as diesel fuel additives to lower fuel consumption, CO2 emissions, and to catalyse the burning of particles, provide an intriguing case study.

Initially regarded as a safe substance, recent findings have proved disputed. As only low absorption has been seen in the lungs of people occupationally exposed to cerium, it has been claimed that the usage of nanosized cerium oxide is unlikely to cause health harm [132, 133].

But according to a study on the possible impact of nanosized CeO2 particles on lung damage, male Spaghetti rats exposed to the particles by tracheal instillation showed cytotoxicity and alveolar macrophage apoptosis, which may lead

to lung fibrosis following inflammation and pulmonary stress. Lung tissue showed aggregates of cerium needles or fine granules ranging in length from 30 to 60 nm, with longer needles after four weeks of exposure [134].

Protein-Nanoparticle Interactions:

Within the medical device community, it is now well accepted that material surfaces are modified by the adsorption of biomolecules such as proteins in a biological environment [135, 136], and there is some consensus that cellular responses to materials in a biological medium reflect the adsorbed biomolecule layer, rather than the material itself. However, the importance of the adsorbed protein layer in mediating interactions with living systems has been slower to emerge in the case of nanoparticle protein interactions. The key role of protein-nanoparticle interactions in nanomedicine and nanotoxicity has begun to emerge recently with the development of the idea of the nanoparticle-protein “corona”. When this dynamic layer of proteins (and other biomolecules) comes into touch with living systems, it instantly adsorbs on the surfaces of the nanoparticles. The quantities of the more than 3700 proteins in plasma [137] and the kinetic on and off rates (also known as equilibrium binding constants) of each protein for the specific nanoparticle will dictate the protein corona's makeup at any given time. This corona might not appear right away.

attain balance while in contact with a biological fluid. The surface of the nanoparticle will initially be occupied by proteins with high concentrations and high association rate constants, but these proteins may also dissociate rapidly to be replaced by proteins with lower concentrations, slower exchange, and higher affinity. Since the protein corona is what the cell "sees" and interacts with, it is the biological identity of a nanoparticle. Another way that especially small nanoparticles, with their huge surface area as a binding interface, may cause protein mal-functioning that could result in pathogenesis and negative health effects is through functional alterations of the proteins of such complexes [138]. According to a review of the literature on nanoparticle-protein binding, apolipoproteins are bound by the great majority of nanoparticle types that have been investigated thus far [136].

Therefore, nanoparticles containing surface-adsorbed apolipoproteins may be able to penetrate cells by taking advantage of the many receptors for apolipoprotein complexes at cell surfaces [139]. Apolipoprotein E has been shown to bind to certain nanoparticles, which is pertinent if we take into account the problems of nanoparticle transport and fate in both humans and animals [135]. Since apolipoprotein E is known to be important in trafficking to the brain, this could have major effects on neurotoxicity and the development of neurotherapies [139].

Proteins adsorbed to nanoparticles are now directly influencing biology, according to the first reports of this phenomenon. It has been demonstrated that 10 nm amorphous silica coated with albumin and single-walled carbon nanotubes (SWNTs) cause anti-inflammatory reactions in macrophages, as evidenced by the inhibition of cyclooxygenase-2- (Cox-2) activation by lipopolysaccharide in serum-free circumstances [140]. Precoating the nanoparticles with a non-ionic surfactant (Pluronic F127) prevents albumin from adhering to them, which also prevents the nanoparticles' anti-inflammatory effects. These findings imply that the adsorbed proteins play a significant part in regulating the toxicity and absorption of SWNTs and nanosized amorphous silica [140].

It is unknown, nevertheless, whether albumin would stay attached to nanoparticles in competitive binding circumstances, such those found in plasma or a cellular milieu, because these investigations were carried out in a serum-free environment. When bare CdS QDs interact with human adult hemoglobin (Hb), the shape of Hb is drastically changed, and the secondary structure's α-helix content drops from 72.5% to 60.8%. The sulphur atoms of the cysteine residues establish direct bonds on the surface of the CdS QDs, according to the results of Raman spectra [141]. Controlling how nanoparticles interact with proteins is becoming more and more common through the functionalization of nanoparticle surfaces with peptides [137].

Discussion:

The biokinetic assessment of artificial nanostructures and nanodevices is known as nanotoxicology. The rapid growth of nanotechnology, which has been extensively employed in the pharmaceutical, medical, and engineering sectors over the past 20 years, made this field of study necessary [142, 143]. The genesis of nanotoxicological concepts can be traced back to particle toxicology and the ensuing harmful health effects of coal dust and asbestos fibres. The most frequent targets of nanoparticles are tumours, endothelium, which are thin, specialized epithelial cells that line the inside surface of lymph and blood vessels and act as gatekeepers to control the flow of materials together, and macrophages, which are specialized host defense cells. The balance between the generation of reactive oxygen species (ROS) and the biological system's capacity to detoxify or repair itself is upset when nanoparticles within these biological targets promote the formation of prooxidants, particularly when exposed to light, UV light, or transition metals [142, 143]. The NADPH oxidase in phagocytic cells, which is the goal of nanoparticle devices, can also create ROS. Both cellular redox signalling and mitochondrial function can be altered by nanoparticles. By upregulating redox-sensitive transcription factors such as nuclear factor kappa B (NFkB), activating protein (AP-1), extracellular signal regulator kinases (ERK) C-Jun, N-terminal kinases JNK, and p38 mitogen-activated protein kinases pathways, oxidative stress brought on by nanoparticles has been shown to exacerbate inflammation. The most significant documented harmful consequences of the therapeutically utilized nanoparticles examined in this paper are compiled in **(Fig. 5).**

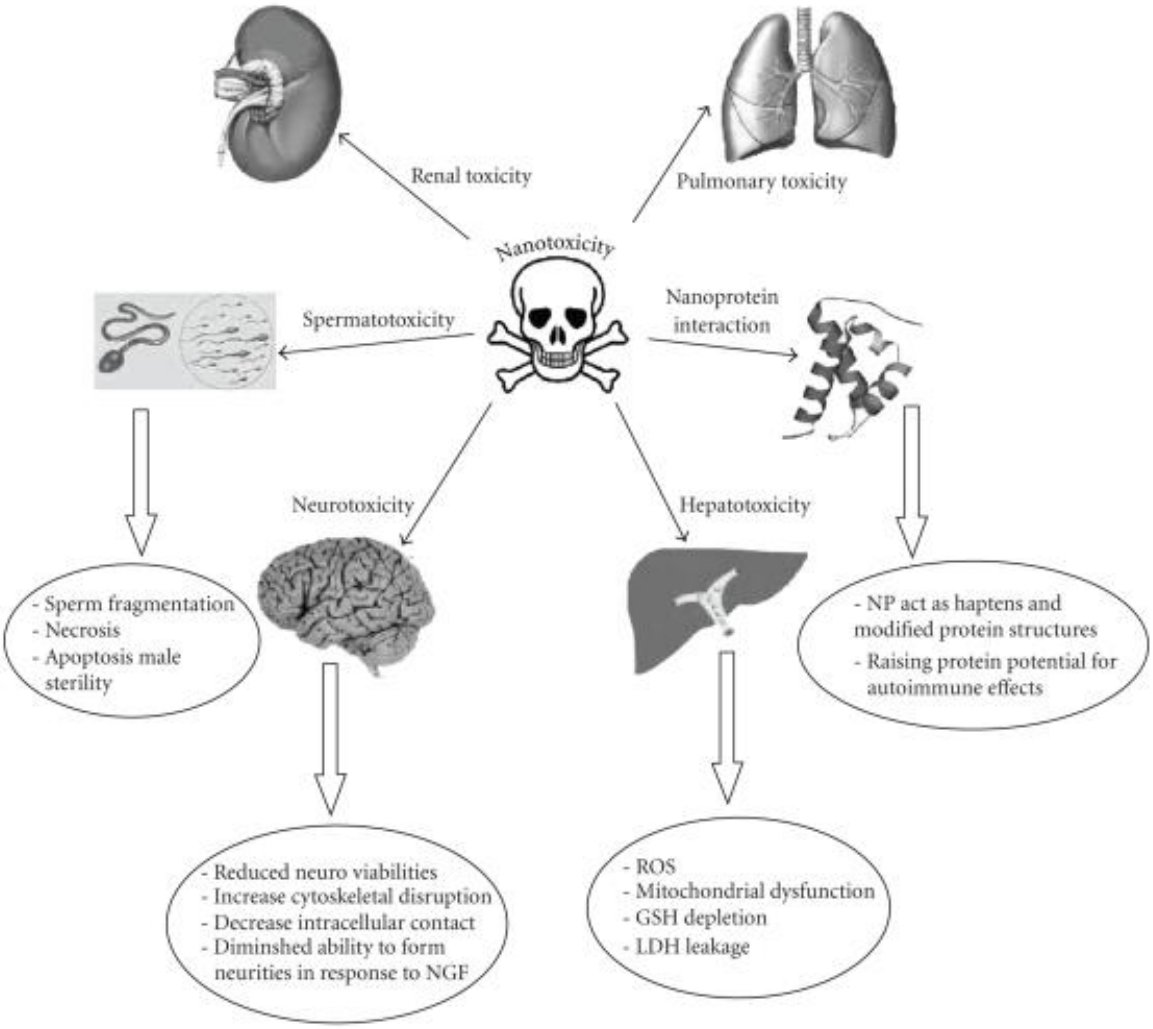

Fig. (5): An overview of the most significant documented harmful consequences of the medicinal nanoparticles examined in this work [148].

CONCLUSION:

Nanotechnology is a rapidly developing field of study whose potential is still up for dispute. In fact, a new field of study called nanotoxicology has been established specifically to investigate the potential negative health effects of materials with nanoscale dimensions. Numerous studies have been conducted recently to examine the potential actions of NPs, and a number of issues about their utilization have been brought up.

Numerous investigations have examined the toxicity of nanoparticles, with the most serious issue pertaining to their carcinogenic potential, which has been linked to both their chemistry and physical characteristics. Size, shape, and surface appear to be more significant in all other indirect mechanisms that underpin cancer, while chemistry was thought to be particularly relevant for oxidative DNA damage and the production of reactive oxygen species (ROS) engaged via direct mechanisms.

By considering all the fascinating and intricate aspects of materials of nano size that underlie their interactions with biological materials, a more accurate risk assessment can be determined. In conclusion, it is hoped that the increased ongoing studies on nanotechnology and nanotoxicology will result in a greater awareness and understanding. As a result, more caution and attention should be paid in the use, as well as in the manipulation and manufacturing of engineered as well as unintentionally released NPs. In the end, chemistry, medicine, and biology should collaborate to shed light on all the intricate molecular processes involved in toxicology related to the unique realm of nanoparticle.

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