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Review Article

Nanotechnology to Nanotoxicology: An Esplanade to Explore

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Nanomaterials have become an inevitable part of common daily life endeavors, therefore research on nanotoxicity is gaining attention. The most extensively used nanomaterials comprise metallic nanoparticles which impede cellular pathways by producing Reactive Oxygen Species (ROS) leading to enzyme malfunction and ultimately to death of the cell. The inexorable exposure of metal oxide nanomaterials escort reduced cell viability, mitochondrial dysfunction, enhanced oxidative stress and altered protein expression on the molecular level. The nanotoxicity of carbon-based nanomaterial is accounted for the generation of ROS which harasses the homeostasis of the intracellular milieu and also induces genotoxicity. The exposure of quantum dots, which are a prime tool in advancing biomedical applications, has chances for the generation of reduced forms of ions like cadmium which are fatal to cells. These nanomaterials can make their way to enter the body intentionally or unintentionally via various routes. It is earmarked for addressing the toxicological activity of nanoparticles and their derived products to ascertain if or the extent they may constitute a threat to the environment and human health and define the mechanism of nanotoxicity posed by these nanostructures on biological systems. Therefore, this review aims to summarize the toxicological effects of nanomaterials based on research studies of various In-silico, In-vitro and In-vivo assays for nanotoxicity. Therefore, these studies can be the basis for designing and engineering safe nanomaterials and their product directing their use in nanomedical sciences.

Introduction

Nanoscience focuses on building up composite materials and structures with precise control over matter in nanoscopic range [1]. The techniques required for synthesis, characterization and use of properties of nanomaterials in different applications are collectively called Nanotechnology [2]. Over the past ten years, nanoscience has risen up to the point that that it has moved from being a scientific benchmark to a technological application. At present, there exists ample varieties of commercial goods such as electronic apparatus, sport-tools, cosmetics such as sunscreen that utilizes nanomaterials along with promising biomedical applications [1,3]. At nanoscale, optical, thermal, mechanical, electrical, magnetic, dynamic properties of material change. New properties can be utilized in diverse applications entailing different fields. Nanomaterials show different properties as compared to bulk material (table 1). The force of attraction appears to be very weak on larger scale but on a nanoscale, these are strong [4]. One reason that accounts here is the surface area to volume ratio. In commercial applications, nanomaterials are used increasingly viz- opacifiers, fillers, water filtration, catalysts, semiconductors, microelectronics, cosmetics, etc. (figure 1) accounting for direct as well as indirect exposure in humans [5]. Besides the exploitation of nanomaterials for consumer products, numerous applications are being recounted in the biomedical field, especially as biosensors, drug-delivery agents, or imaging contrast agents [6-7].

Nanoparticles can be intentionally injected and consumed directly into the body for medical purposes. Nanomaterials having applications in drug administration and imaging are often purposely coated with biological entities like proteins and nucleic acids for targeting specific cell [8]. Materials within nano-range approach the length scale at which some definite environmental associations can arise [9]. Besides this, owing to their extraordinarily minute dimensions, nanomaterials exhibit tremendously enhenced

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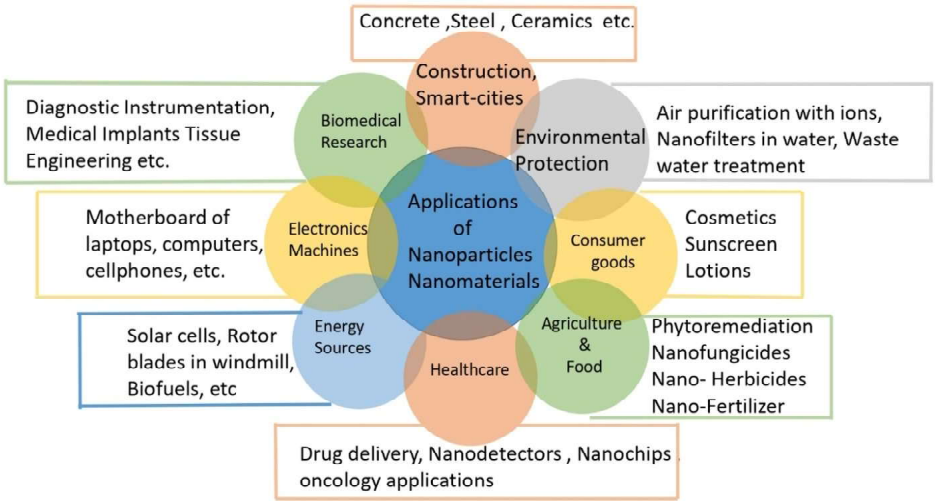

Figure 1: Applications of nanomaterials in various sectors

surface area volume ratio with therefore rendering these minute entities exceedingly reactive. Greater reactivity is potentially toxic while interacting with physiological systems and with the environment in a harmful way [10]. Nanotoxicology encompasses physico-chemical characterization, path of exposure and distribution inside the body pertaining to genotoxicity, cytotoxicity etc. While in-vivo studies scrutinize health effects, in vitro studies elucidate toxicity mechanism without influence of toxicokinetics and toxicodynamics. Nanoparticles have dose-dependent and time-dependent causes on cytotoxicity [11].

The necessity for well-structured investigations addressing the risks and possibilities of toxicity posed by NPs has intensified over the past few years as stress about the toxicological effects of these structures on human has grown [12]. These minute particles penetrate the physiological barriers entering the body accidentally (naturally) or purposely (artificially) through the skin, lungs, and digestive tracts. They then travel through the circulation and accumulate in various organs, where they may have negative biological effects. Considering the routes of exposure is essential for comprehending the health impacts of NPs, there won't be any risks if there is no exposure. This requirement paved the door for the current investigation, in which the impact of MO-NPs was examined on a variety of cell lines that represent numerous major and primary organs.

However, ingestion, inhalation and intravenous injection, most importantly skin contacts are pre-dominant routes of exposure in case of humans. Available in-vivo data were largely gathered from inhalation as well as from intra tracheal instillation in model such as rats, including the data stating bulk toxicity for Gold, Carbon, Cadmium Oxide, Iron, Manganese oxide, Nickel, Titanium Oxide, and carbon nanotubes [13]. When nanostructures take entry into the physiology of the body, these are absorbed through the interactivity with biological machinery such as proteins and cells. Post-distribution into various tissues or organs, they either retain the same structure or become altered (metabolized) [14]. Nanostructures that are orally administered do not appear to be radically absorbed or sequestered infaeces [15].

The chemical as well as physical properties of NPs, like the shape, size, catalytic activity, specific surface area, surface charge, and the presence of active groups on the surface, all have a significant role in how poisonous they are. These NPs are being circulated by blood as well as lymph to various tissues of organ systems and they can either be translocated into cells through trans-cytosis procedures or merely diffuse into them through the plasma membrane due to their small size, which enables them to pass through endothelial and epithelial barriers by lymph and blood [16]. Nanomaterials also promote increased access to the blood stream all the way via ingestion [17].

Characterization of nanoparticles is crucial in nanotoxicity studies as properties of these particles have probability to manipulate toxic outcomes. Due to the distinctive features of nanoparticles, such as their small size (100 nm), it was believed that they would have more profound biological impacts than their corresponding micro-sized particles. Assuming equal particle mass, as particle size decreases the surface area of particles increases dramatically. Nanoparticles possess higher bioreactivity for a given mass when compared to micro scale particles. The properties can be utilized for biomedical applications such as contrast enhanced MRI agent molecular image,[18] and drug delivery [19].

In contrast, increased specific surface area impose higher oxidative stress, immune response, damage of intracellular molecules and cell death. Material composition also affects toxicity. Multiple studies investigating NPs of different material composition supports this statement pointing to diverse toxic response. In the present study toxicity assessment of metal-based nanoparticle was done on the basis of NPs metal composition. Each NPs type show its activity

Table 1: Properties change in the nanoscopic range

Material	Macromolecule	Nanoscale
Gold	Yellow (Golden) Solid at room temperature	Orange or Green Liquid at room temperature
Platinum	Inert	Catalytic
Aluminium	Stable	Combustible
Silicon	Insulator	Conductor
Copper	Opaque	Transparent
Iron/ Cobalt/Nickel	Ferromagnetic	Superparamagnetic

with different behavior in biological media, depending on its size and morphology [3].

Nanoscience and Nanotechnology

Nanotechnology as a disciple was unfolded in the 1980s as it occurred through junction of Drexler's conceptual and non-private work, that grew and endowed popularity to a visionary scheme for nanotechnology, as well as high-resolution experimental breakthrough which fetched auxiliary comprehensive consideration to the prospects of atomic control of matter. In the 1980s, some major quantum leaps sparked the growth of nanotechnology in modern times. The invention of SEM (scanning electron microscope) yielded unequalled visualization of individual atoms and bonds in 1981. It was successfully used to manipulate individual atoms in 1989. The microscope's developers Heinrich Rohrer and Gerd Binnig at IBM Zurich Research Laboratory received a Noble Prize in Physics in the year 1986. Binnig, Quate and Gerber also lead to the invention of the analogous atomic force microscope in the same year.

Nanomaterials & Classification

Nanomaterials are the basic and pivotal elements in nanotechnology research. These are defined as the materials that have at least one dimension not exceeding 100 nm size [2]. This means that they have quite a small size comparing with that of corresponding bulk materials. The nanomaterials possess different physicochemical characteristics than the corresponding bulk particles, which intrinsically depends on their shape and size [13]. Amazingly these materials bestow a peculiar nature with novel characteristics and capabilities with modification of the shape and size at the nanoscale [20].

On basis of dimension, Nanomaterials can be of following types,

Nanoparticle – If all three external dimensions of that material are on the nanoscale range, the material is said to be a nanoparticle. These are also called Zero dimensional Nanomaterials [2].

Nanofiber – When two external dimensions are on the nanoscale range, the material is known as Nanofiber. These can be nanotubes or nanorods. Nanotubes are hollow nanofibers whereas nanorods are solid nanofibers. Nanofibers are also called One dimensional Nanomaterials [9].

Nanoplate – A nanomaterial is said to be a nanoplate if it has only one dimension on the nanoscale. These are also called Two dimensional nanomaterials [21].

However, there is also the existence of bulk nanomaterials (3-Dimensional). The perimeter of any dimension of these nanomaterials does not lie in the nanoscopic range meaning that in three arbitrarily dimensions they are >100 nm scale. These are categorized based on their forms (phases) of matter –

Nanocomposite – This class entails solids that contain at least one physically or chemically distinct region with at least one dimension in the nanoscopic range [22].

Nanofoam – This is solid or liquid matrix, filled with the gaseous phase, where among the two phases, one has dimension on the nanoscale [23].

Nanoporous material – Nanoporous materials are solids comprising nanopores, cavities with dimensions on the nanoscale [24].

Nanocrystalline materials –These are materials that have a significant fraction of crystal grains on a nano scale [25].

Nanotechnology has attracted a huge amount of interest owing to the essentiality and implementations of nanomaterials in ample sectors of human activities sectors viz- industry [26], agriculture [27], business [28], medicine and public health [29]. Because nanomaterials have become an inevitable part of our daily life endeavors, environmental exposure to nanomaterials is unavoidable and consequently research on nanotoxicity is gaining attention [30].

Evaluation of Nanotoxicity

Nanotoxicity encompasses the latent adverse health effects posed due to engineered nanomaterials exposure. The alarm for latent toxicological impacts of these NPs on human body has augmented during recent years and the requirement for befitting studies commercializing with risks associated with nanoparticles rise constantly. These nanoparticles possess ability to enter the living system naturally (unintentionally) or induced artificially (intentionally) via the lungs, skin, intestinal tracts, which further transport through blood and deposits in several organs, may cause numerous adverse biological effects [31]. Thus, fundamental for the study of health effects from NPs is to comprehend the routes of exposure. If there is no exposure, there will be no risks. This requisite passed the way for the present study, in which the effect of NPs on model organism was being investigated.

In vitro assays for nanotoxicity

The in-vitro assays are idyllic in nanotoxicity research as they yield reproducible outcomes swiftly and cost-effectively eliminating the exploitation of animals. Simple in-vitro methods that produce quantitative and specific dimensions of toxicity are intensely relevant for initially evaluating the expected biocompatibility of new nanoparticles. Enormously cited examples are the LDH assay of cell membrane integrity, the MTT assay of assessing the mitochondrial activity, and immunochemistry markers molecules for apoptosis and necrosis [32-33]. However, these methods provide not much information on the mechanism of cellular toxicity and death of the cell. Recent studies have shown little correlation between the in-vitro and in-vivo toxicity of some nanomaterials.

To evaluate the reliability of screening strategies involved in in-vitro methods, studies put forward to envisage In-vivo pulmonary toxicity. Rats exposed to a variety of NPs, including iron, crystalline and amorphous silica, and zinc oxide, showed pulmonary toxicity in vivo. When in-vivo and in-vitro measurements were compared, there was negligible correlation between the groups [34]. Thus, the primary application of in-vitro systems is to identify specific properties of nanomaterials that should be used as markers of nanotoxicity. To investigate topics like toxicokinetic in the body, or ADME, which stands for absorption, distribution, metabolism, and elimination, animal models would be especially useful [35]. These in-vivo tests are costly, time-consuming, and fraught with moral dilemmas. The carcinogenicity, pulmonary, cutaneous, and gastro-intestinal toxicities associated with the first deposition of nanomaterials by diverse routes of exposure can, however, be learned from these investigations only [13].

In silico assays for nanotoxicity

In-silico methods for envisaging the nanotoxicity of several nanostructures complement or displace some expensive and chronophagus assays particularly early in the design process of new materials. Quantitative Structure Activity Relationship (QSARs) are theoretical models used to envisage the physio-chemical and biological properties of molecules. Toxicological techniques In-

silico are cost-efficient and rapid alternative to bioassays for identification of toxic effects of NPs [36]. In research, QSAR method was used to extend mathematical models to forecast cellular membrane damage resulting from several nanoparticle physicochemical features. It was found that the size, concentration, and zeta-potential of particles in ultra-pure aqueous medium are among the most influential factors on cytoplasmic leaking [13].

To vaticinate the toxicity of 17 distinct metal oxides, another team of researchers used nano-QSAR. They were able to explain the association between nanoparticle structure and cyto-toxicity to E. coli cells employing theoretical models and experimental data. It is crucial to use in-silico approaches since they may be used with both in-vivo as well as in-vitro data. The precision of the model is nonetheless limited by the ambiguity of the in-vivo data [37].

In vivo Assay for nanotoxicity

Many bulk materials can be adequately studied using in-vitro as well as in-silico methodologies for acute toxicity, but the in-vivo interaction of NPs with the biological systems is highly complex and dynamic. Additionally, the utility of these procedures is limited in the absence of adequate in-vivo data to cite correlation with the in-vitro and in-silico studies. Following delivery in the numerous model organisms via several routes, including intravenous, inhalation, transdermal, intra-peritoneal, subcutaneous, and oral, the toxicity of nanoparticles by in-vivo assay can be assessed [37-39].

Although the most common routes of contact for humans are ingestion, inhalation, skin contact, and also intravenous injection, the bulk toxicity data for metals like gold, carbon, cadmium oxide, iron, manganese oxide, nickel, titanium oxide, and carbon nanotubes were mostly assembled from inhalation along with intra tracheal instillation in model rodents[40].The oral and intravenous modes of administration, which are more pertinent for most interesting NPs in nanomedicine, are the subject of a dearth of investigation. Nanostructures can be absorbed into the body through interactions with biological elements including cells and proteins. These can allocate (distribute) into various tissues where they can retain their original structure or undergo transformation or metabolization. Then, they expel themselves from the body. Nanostructures taken orally fail to be appreciably absorbed or retrieved in stools [35].

To comprehend NPs' behavior and potential toxicity, an extensive study of their pharmacokinetics (PK) is needed. Nanostructures are absorbed, distributed, metabolized, and excreted in PK, which provides quantitative data pertaining to how they behave in biological systems. The fetched information can lead to :-

- Improvement in lattice of NPs for theranostic applications
- A better perception of nanostructures, non-specificity towards tissue and cell types.
- Assessment of basic ADME clearance that serves as model in assessing their toxicity and the associated future investigative direction [41].

The majority of nanomaterials require compatibility of blood for their in-vivo dynamics. Lack of blood compatibility causes coagulation to occur by causing platelet adhesion, plasma protein adsorption, and activation of the complement pathway's cascade events. Certainly, NPs coagulate under thermodynamic pressure to reduce the interaction surface of hydrophobic domains within the aqueous surroundings. To ensure their safety, NPs' blood contact qualities should be assessed before being used in clinical settings. The principal method for determining the toxicity of nanoparticles is the hemolysis test exploiting mammalian erythrocytes because nanoparticles in contact with blood can cause hemolysis, thrombocyte aggregation, or blood coagulation [42].

Red blood corpuscles are the foremost hematocytes in the blood that play a crucial part in transportation of oxygen and carbon-dioxide. These corpuscles are at wide risk of nanotoxicity with agglutination; deformation as well as membrane damage [43]. Nanoparticles toil hemolytic effectvia several mechanisms, such as changes in rheological properties, enzymatic modification, oxidative damage to plasma membrane, alteration in osmotic stability. Some carbon-based nanoparticles and microparticles are capable of activating platelets and enhance vascular thrombosis. Urban dust that contains engineered carbon based with exception of C60CS, vitalized thrombocytes agglomeration and compute for the increased rate of vascular thrombosis in carotid arteries of modal rodent with similar grade of efficacy [42].

In brief words, it can be stated that during the past two decenniums, the NPs use and exposure to humans has enormously extended and led to the establishment of nanotoxicology, which is led by a general goal i.e.- to formulate the rules of safe synthesis of NPs which summons for an extensive and organized approach for inspection of the toxic characteristics of NPs and their consequent impact on various cells, tissues, organs, and the body as a whole. There are two standard perspectives for studying the impacts of various entities on living systems that also apply to nanotoxicity: in vitro procedures on model cell lines and in vivo experiments on model organisms (laboratory complex animals). The third possible approach, computer simulation is not much considered for estimating nanotoxicity, as the pathways and their mechanisms involving the toxic impacts of NPs are not popular enough for a computer system to predict the outcomes of interactions between NPs and living matter for a wide range of nanomaterials with sufficient reliability. Both in vivo and in-vitro approaches when thrilled for studying the toxicity of nanomaterials, have their specific advantages and limitations. The cell culture allows cavernous perception into the mechanisms associated with toxicity at molecular level and recognition of the prime targets of NPs; nevertheless, the patterns of the allocation of these nanomaterials in the body and their transportation to different tissues and cells in the body are not taken into consideration. The study of nanotoxicity in animal experiments permits the delayed effects of action of these nano-

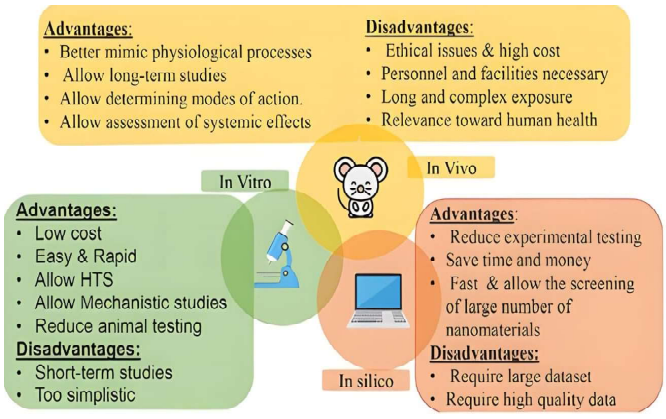

Figure 2: Advantages and disadvantages of methods involved in nanotoxicity evaluation

Table2: Potential routes of Nanoparticle mediated drug administration

Route of drug delivery	Advantages	Disadvantages	References
Intravenous	Minimally invasive Prompt Response Complete bioavailability	Risk of systematic toxicity	[16,56]
Inhaled	Non-invasive Large Surface Area	Susceptibility to pulmonary clearance	[57]
Intramyocardial	Direct delivery of drugs, Polymeric scaffolds and stem cells.	Highly invasive	[58]
Oral	Non-invasive Good patient compliance	Intestinal barrier First pass metabolism	[59]
Intraperitoneal	Large Surface Area Rapid absorption	Highly invasive	[60]

sized entities in vivo to be estimated. Though, the common pattern of toxicity expression is made so complex that it is not possible to distinguish the primary root of the inference effect from its consequences. Advantages and disadvantages of various methods involved in nanotoxicity evaluation are given in figure 2.

Mechanism of Nanotoxicity

From the above text, rapid growing and promising fields of nanoscience and nanotechnology possess substantial impacts in environment and medical healthcare etc. Moreover, it is also indicated that these entities induce cytotoxicity particularly genotoxicity, oxidative stress, and inflammatory responses. Various mechanisms can promote nanotoxicity in the body but majorly it occurs from the excessive generation of ROS (Reactive Oxygen Species). A mechanism of oxidative stress posed by NPs come about in course of the dissolution of Fe based nanoparticles, that catalyze the generation of ROS and formation of OH^- and OOH radicals from hydrogen peroxide (H_2O_2) through the series of step called the Fenton mechanism[44].Furthermore, some inert nanomaterial rarely foster unsolicited generation of ROS yet, have potential for inducing production of ROS under physiological condition, based on ability of nanostructures in targeting Mitochondria [45]. ROS are both potentially destructive and physiologically essential. Numerous cellular activities, including signal transduction, gene expression, the proliferative response, and also protein redox regulation, are modulated in particular ways by moderate amount of ROS[46].The elevated level of ROS are a sign of oxidative stress, which can harm cells by peroxidation of lipids, altering proteins, disrupting DNA, interfering with signaling, and modulating gene transcription ultimately leading to cancer, renal disease, cardiovascular disease, neurodegeneration and pulmonary disease. ROS deplete lipids in the plasma membrane by fetching electrons, causing decline in physiological activity and function accounting for cell death [47].

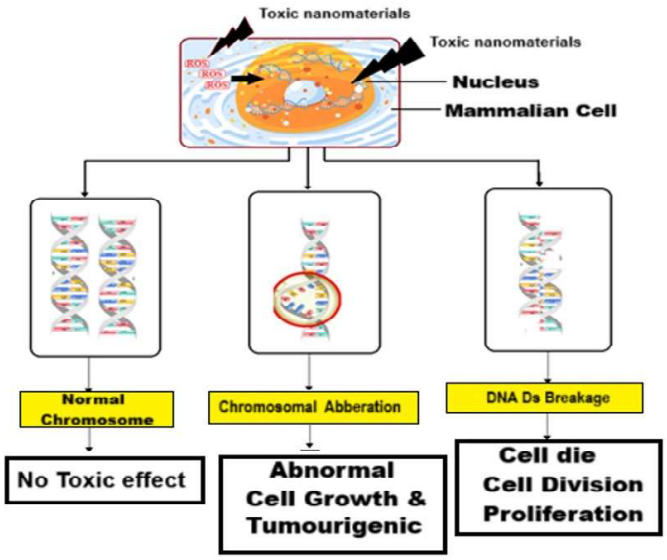

Figure 3: Schematic representation of the different mechanisms of Induction of Genotoxicity by Nanomaterial induced ROS

Toxicity generated by ROS should be more pronounced with reference to the central nervous system (CNS) because of excessive amount of MUFA (Monounsaturated fatty acid) and PUFA (Polyunsaturated fatty acid), that are at open risk of peroxidation. ROS also plays a part in the development of vasculopathies, which include those that elucidate atherosclerosis, restenosis and hypertension following angioplasty. Accumulation of nanoparticles in Reticuloendothelial system (RES) plus the acceptance of numerous phagocytes, results in disproportion of ROS homeostasis and antioxidant defenses, which make the spleen as well as the liver target of oxidative stress [48]. Schematic representation of the different mechanisms of Induction of Genotoxicity by Nanomaterial induced ROS is given in figure 3.

Oxidative stress induced by nanoparticles has an impact on cell signaling in three stages. A small level of oxidative stress is associated with increased transcriptional rate of some genes via nrf2, a transcription factor. However, oxidative stress of a higher-level triggers inflammation signaling, and ultrahigh levels are associated with activation of apoptosis and also due to necrotic pathways [44].

Various processes and assays can be accessed in the disciple of nanotoxicology and now it turns to an important move to certify the toxicity profile of any nanomaterial before it is subjected to any application in the nanomedical or other fields. Thus, the study can serve as a basis for accessing the toxicity of any nanomaterial, engineering safe nanomaterials and certified their direct use in various fields.

Health Hazards Associated with Nanomaterials

Engineered nanoparticles (NPs) are commercially synthesized materials that exhibit at least one dimension in the nanoscopic range of 1-100 nm.[49] Nanotechnology has fetched a great revolution in the industrial area. On account of their unique elemental, electrical as well as physicochemical properties, nanomaterials have attracted considerable attention in the areas of electronics [50], biotechnology [51], and aerospace engineering [52]. As far as medicinal field is concerned, Nanoparticles are employable tool in novel drug delivery system via various routes (table 2) for drugs [8], proteins [52], DNA [53], and monoclonal antibodies [54]. So far, these nano-sized entities have been manufactured from metal and their oxides or other salts, non-metallic structures, polymeric materials or bio-ceramics [55]. The NPs that have application in medicine are dendrimers, polyethylene glycol, and liposomes.

Humans encounter direct exposure to various nanomaterials and the novel budding sector of nanotechnology has attained new peril to human life. Because of the minute size, NPs direct their path nimbly to seek entry into the human body [61] and overpower variety of biological barriers therefore reaching the most sensitized organs [62]. Researchers have suggested that NPs which are not more than 11 nm can behave like a gas [63] and possess the ability to move through tissues as well as organs straightforwardly, interrupting the cell's normal biochemical milieu [64].

While almost anything can be harmful at an elevated dose, the more relevant question is - Nanomaterials have ability to agglomerate into bulk particles, which has potential to amend their properties [65] and have an impact on the behavior in the internal and external environments along with their potential exposure and ingress into the living system. These accumulate in the respiratory tract [66] and display toxic profile on account of their high surface area [67], greater surface activity [68], minute radii [69], unusual morphology or ability of degradation into minute particles post to accumulation [70].

Particles which are generated from the erosion of nanomaterials also serve as a source of potential risk when these display nano-size dependent biological performance [70]. These particles possess great accumulation efficiency in the respiratory system of healthy human beings with asthma or other chronic pulmonary disorders. If inhaled, these nano-size entities accumulate dispersedly on the alveolar of alveolus, resulting into a speckled chemo- attractant signal and leading to drop in recognition potential and action of response by macrophages [71].

Toxicity of Metallic Nanoparticles

Metallic nanoparticles, commonly abbreviated as MNPs, are among the most extensively utilized category of engineered nanomaterials. High level exposure of silver over long period time accounts for condition known as argyria, a blue gray discoloration of the body. Lower exposure to silver is also known to cause silver to deposit in skin and other parts of the body [72].

In topical groundwork, a number of critiques have demonstrated the masked potential of silver-based nanomaterials to display unique optical, electronic, as well as chemical characteristics [73-74]. Researchers are exploring the prospect of relationship that may exist between physicochemical characteristics of silver-based nanostructures with the derived magnitude of toxicity of these AgNPs [75]. Shape-orientations of these AgNPs viz- beads [76], rods [77], mats [74], sheets [78] and nanosized prisms are being embellished and studied for their bactericidal outcomes. Recent research studies formulated that size and coatings of surfaces constituting this silver based nano entities (AgNPs) play a drastic function in bactericidal properties, with smaller ones observed to endow a high level of toxic outcomes.

Novel methods for synthesis and fabrication of Ag based metal nanomaterials are under critique to discover green proxy to conventional methods of fusion, synthesis, amalgamation and to scout the characteristics evinced by composite as well as hybrid silver doped nanomaterials. The impact that these novel nanomolecules exhibit on biological entities and their milieu must be comprehended to curtail possible calamitous outcomes of these nanostructures in any application. Recent research has scrutinized the consequences of cytotoxicity posed by these AgNPs on the physiology of human body, with specific emphasis on the respiratory or circulatory systems [79], osteoclasts and osteoblasts [80], deformities in embryo development [81].

Investigations reveal physicochemical effects of silver ions by critiquing the sequestering of these ions by AgNPs of varying nanosized as 10nm, 40nm, 50nm, and 70 nm and capping agents against pneumocytes and other shaped lung cells of homo sapiens [82]. Although the capping agent was not found to be involved in triggering poisonous effects, sequestering of Ag^+ into the cellular environment was found endowed to have direct proportionality to the surface area of these particles, its shape and thus mass (size). Additionally, examinations of the uptake of Ag^+ by the cell portrayed a greater cellular content that rarely has correlation with mainly toxic dimension of these structures [83].

Among much popular research, the data incurred from TEM shows that Au nanomaterials are capable of penetrating via HaCaT cells and gets amass in the cell nucleus [84]. Concerning Au nanostructures, gold nanoclusters (AuNCs) endow distinctive electronic nanomolecular entities with pleasing optical as well as chemical characteristics. These glittering metal-based nanoclusters are a novel category of fluorescent compounds displaying promising efficiency of biocompatibility as well as photostability [85]. Toxic outcomes posed by goldmetal-basednanomaterials by ROS generation leads to drop in amount of cell viability. Disturbances in the cytoskeletal network also suffice for a function in the cytotoxicity endowed by AuNPs [86]. The toxicity posed by gold-based nanoparticles on the ecological system, including noxious outcomes on plants as well as on animals, is presently under exploration. In-vivo experiments on mice were carried out to assess the toxicity. Mice were administrated injection of few mg/kg of AuNPs (size range: 3nm- 99nm) in a week. Although nontoxic nanoparticles (with null toxicity) were administered to the mice for which the outcomes illustrated the injecting shot to possess lethal outcomes on the major number of the models tested. The resulting findings are alarming because they show that even seemingly harmless AuNPs may have lethal effects on mammals [87].

A critical study concerning maize also illuminates the possibility of nanotoxicity posed by toxic gold nanomaterials that might bestow on feed as well as food crops. As per the study, elevated concentrations of Gold Nanorods, AuNRs (ie from 300 to 20 mg/L) were set as esplanade for the roots of (Zea maize) maize plants. The AuNRs were verified to deposits in the roots as well as leaves of the maize plants and to impedes with uptake pathways. The outcome also uncovers a reticence in growth of plants as well as in their nutritional absorption. Curtailing doses of AuNRs (minimum:$4.5\times10^{-3}$and maximum: 2.25 mg/L), for the duration of ten days exposure, though, illustrates biocompatibility. The researchers concluded that the fetched correlation that exists between the concentrations of gold nanomaterials with the extent of toxicity

is an interesting parameter that may be exploited to enhance benchmark over the consequential nanotoxicity of AuNRs[88]. Cytotoxicity associated outcomes of these Gold-based nanostructures against tumor cells are accounted to be dependent on the anatomy and morphology or more elaborately surface properties of these nanoparticles [89]. Copper has also been a significant element in research owing to its essentiality in various pathways of complex living organisms. A deficiency of copper leads to anemia and inappropriate embryo development during pregnancy. On a narrow scale, it has a significant part in the O_2 transport during the oxidative phosphorylation (ETC) mechanism and Fe homeostasis [90].

Copper nanoparticles (CuNPs) are magnificent bactericidal agents owing to the chemical stability and heat resistance of the element. This is accredited to a higher value of surface area volume ratio, which permits CuNPs to permeate overpowering membranous hindrance in microbial cells. CuNPs are synthesized and fabricated through several techniques (eg- sol–gel processing, laser ablation etc,) resulting in formation of CuNPs that exhibit varying bactericidal properties [91]. Investigations on interactions between CuNPs and CuONPs against bacterial strain put forward the fact that CuNPs impedes bacterial growth more fruitfully. Feasible reasons comprise a straighter interaction existing for the CuNPs with the bacterial strain, consequently resulting in more level of penetration and cracking of the bacterial membrane. Disruption of cellular membrane led to enzyme's structural malfunction in the cell and ultimately leading to its death [92].

Many Researchers came across an observation of a decline in bacterial inhibition with a surge increment in concentration of copper oxide nanocrystal. There are ample factors accounting for the cell damage like oxidative stress induced by the sequestering of Cu^{2+} ions and speedy anaerobiosis. The assembly of ROS species from the copper oxide nanocrystals may start with the lessening of O_2 and synthesis of $O_2^{\bullet-}$(superoxide anion). These ROS approach the plasma membrane, producing free oxide radicals that enter the cell and cause disorder of the cell's internal content. Eventually, such disruptions by reactive species causes seepage to the bacterial cell [93].

Toxicity of Metal oxide Nanoparticles

Metal Oxide nanoparticles (MONPs) are significant industrial materials broadly, utilized as additives in cosmetics, food colorants and pharmaceuticals [94]. Skin's epidermal layer is usually encountered heavily to these solid nanoballs via the contact to lotions and creams comprising nano-TiO, and nano- ZnO in the form of sunscreen component or fibrous material capped with nanoscale substances to enhance repellant properties against water and stain [95]. It was reported in an inhalation exposure study with the aid of about 2-6 nm TiO, nanoparticles that these nanoparticles get agglomerated forming aerosols particles in the contact chamber with 120-130nm as a geometric mean value of mobility diameter [30]. Toxicologists worked on the cytotoxicity associated with Titanium dioxide nanoparticles by induction of ROS (Reactive Oxygen Species) in already cultured BEAS-2B cells. These cells have conveyed that nanoparticle crept into the cell membrane and translocated to the peri-area of nucleoplasm, thus indicating that these nanostructures have direct interaction with cellular entities to cause unpleasant biological responses in cells. These have been broadly utilized in domestic household products (cosmetics, sunscreen, toothpaste, plastics, paints, self-cleaning devices, pharmaceutical compounds and nutraceutical compounds) medical and industrial applications on account of their tremendous catalytic activity. According to the International Agency for Research on Cancer, titanium-based metal oxide nanoparticles (TiO_2 NPs) are cataloged as a normal carcinogen to humans [96-99].

The phototoxicity of titanium dioxide nanoparticles with sizes varying from 25nm to 325nm and two crystal forms (anatase and rutile) toward human skin keratinocytes under ultraviolet radiation was evaluated. As per the results encountered, ROS are produced by the UV radiation of all titanium dioxide nanoparticles. Furthermore, it was concluded that larger titanium dioxide nanoparticles resulted in less phototoxicity than smaller particles [100]. Aluminum oxide nanoparticles uncover a vast array of applications in many spheres on account of its extra hardness and high physical strength [101]. There are some verified facts that contact with thesenanosize aluminum oxide molecules (Al_2O_3NPs) results into reduced viability in cells, enhanced oxidative stress and mitochondrial dysfunction and thus, amends the expression of proteins of blood–brain barrier [101-102]. Moreover, some investigations revealed that Al_2O_3NPs generate cytotoxicity along with destruction of membrane in Chinook salmon cells that is interceded through anatomical aberrations, oxidative stress and peroxidation of lipids [103]. Iron oxide nanoparticles (Fe_2O_3NPs) have been widely used for biological as well as biomedical applications due to their super-paramagnetic properties. [104]. Cell death in in SKOV-3 cells due to different type of ion oxide nanoparticles are shown in figure 4. In addition, higher specific surface area and greater reactivity of nanoscale zero-valent iron (nZVI) particles lead to the use of these particles in environmental

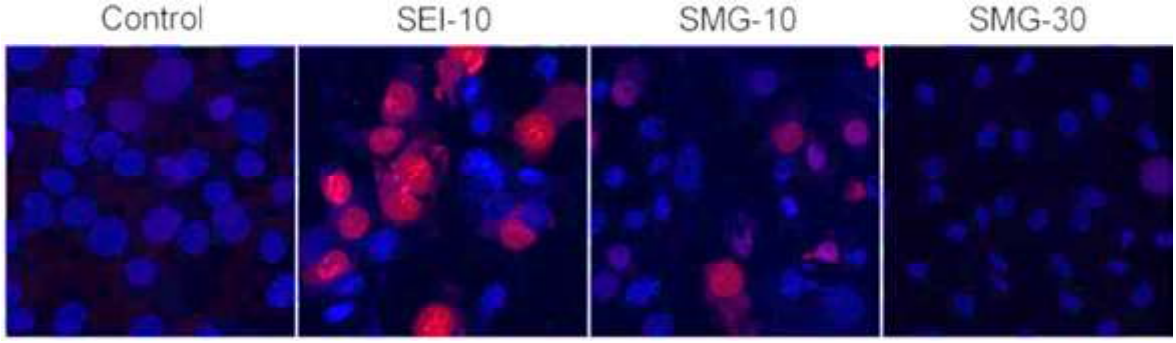

Figure 4: Cell death induced by iron oxide nanoparticles in SKOV-3 cells shown by fluorescent microscopic images. The cell death was confirmed by Hoechst 33342 and PI staining. Hoechst 33342 stains (blue) showing living cells while PI (pink) is showing dead cells [104]

remediation [105]. The study conducted to elucidate the cytotoxicity induced by ROS and the DNA damaging potential of Fe_2O_3 NPs stated that enhanced oxidative stress results into activation of apoptotic pathways consequently leading to reduction in cell viability [106].

Inhalation of Fe_2O_3 NPs was revealed to be the root cause of oxidative stress by accumulating in the liver, spleen, lungs and brain with high ROS, which accounts for inflammation, cell lysis, low cell viability and interruptions in the blood coagulation system [107]. Since zinc oxide NP's diverse application in daily used products, both its exposure as well as nanotoxicity to living systems have increased [108]. More evaluations throw light on the physical properties along with the toxicological outcomes of zinc oxide NPs and showed a significant decrease in cell viability, remarkable morphological changes, apoptosis induction via ROS production [109]. With the help of freshwater algae, comparison research was formulated to determine the nanotoxicity of ZnO nanoparticles, bulk ZnO, and $ZnCl_2$ on freshwater microalgae [110]. Different nanoparticles (CuO, TiO, , ZnO, $CuZnFe_2O_4$, Fe_2O_3, Fe_3O_4) were investigated and the resulting toxicity outcomes were compared to toxicity posed by Carbon based nanoparticles, and MWCNT [111].

Toxicity of Carbon-based Nanoparticles

Carbon based nanomaterials are a novel category of nanomaterials that are extensively used for biomedical applications. It was established that ultrafine carbon-based particles show higher chances of lung penetration than bigger particles and have the ability to cross the blood-brain barrier and effect on the central nervous system. The outcomes portrayed that toxic consequences appear quickly post to exposure and suggested that Carbon nanoparticles translocate from lungs to the blood stream rather than release clotting agents from the lungs. Since, inhalation of asbestos tempt to provoke asbestosis, malignant mesothelioma of the pleura, and lung cancer, there would seem to be a high probability that CNT are also likely to possess noteworthy toxic effects on human well-being due to be their resemblance in structure to asbestos [30]. After CNTs gains entry in the body via dermal or inhalation or oral routes, the prime mechanisms of CNT-induced toxicity are evinced as oxidative stress, DNA damage and mutation (genotoxicity), inflammatory responses, malignant transformation, development of granuloma, and interstitial fibrosis [112].

Genotoxicity is the most detrimental root of cytotoxicity. These nanosized cylinders not only penetrated via the plasma membrane but also get localized inside the boundaries of the nucleoplasm[113].and prompted cell mortality on activation of the tumor suppressor gene that codes for protein called p53, escalating the expression of enzyme, OGG1 and also the protein for double-strand break repair ie- Rad 51, the phosphorylation of H2AX histone at serine residue 139 position of amino acid, and the SUMOylation of XRCC4[114]. CNT-induced oxidative stress has currently been regarded as the most justifiable mechanism. Increased level of intracellular ROS can react with macromolecules that reside in the cell such as DNA, lipids, proteins and harass the homeostasis of the milieu of intracellular environment. Ample studies have shown evidence that transition metals released from CNTs have the potential to cause the conversion of cellular oxygen metabolic products such as H_2O_2 and superoxide anions to hydroxyl radicals. However, highly purified multi-walled carbo nanotubes (MWCNTs) also lead to generation of ROS in the cell, which was sponsored by the large surface area [112].

However, the issue of CNT carcinogenicity has not received enough attention. Single Walled Carbon Nanotubes (SWCNTs) have been

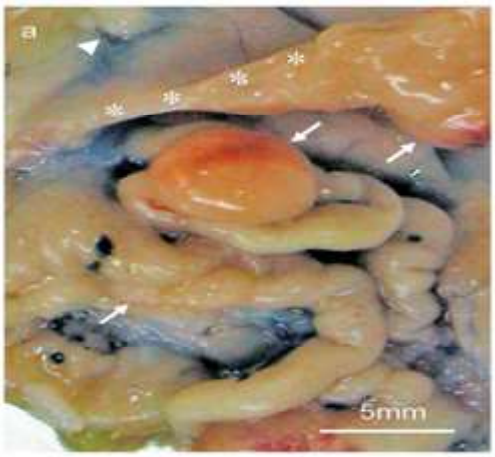

Figure 5: Abdominal viscera of multiwalled carbon nanotube (MWCNT) treated mouse. Fibrous adhesion and multiple peritoneal tumor formation are shown by arrows. The ventral cut end of diaphragm shown by asterisk and black spots are aggregation of MWCNT (reproduced with permission from ref. 117)

linked to tumorigenesis in mice and the malevolent transformation of human pericardial epithelium [115]. Furthermore, recent research confirmed the fact that mesothelial cells were susceptible to be attacked by toxicity posed by CNTs [116] and that mesothelioma was brought on in mice exposed to MWCNTs six months after intraperitoneal injection. These results are striking, and further investigation should concentrate on the questions – if acute inflammatory reactions would endure and develop into mesothelioma following contact to CNTs in humans as well as if inspired CNTs would be able to spread to other tissues and have an impact on the mesothelium [117]. The effect of MWCNT on abdominal viscera of mouse is shown in figure 5. Additionally, all tissues haveshown to have a significant concentration of non-functionalized fullerenes, which indicates a long-lasting accumulation [118].

Several researchers examined the nanotoxicity of fullerene NP in an in vitro as well as an in vivo study. According to an in vitro

Figure 6: The fluorescence emitted by the Carbon Quantum Dots

Table 3: Findings in nanotoxicology in recent researches

Nanomaterials	Size tested	Findings	References
Gold Nanoparticles (AuNP)	14nm	Exhibit only mild toxicity at unit nanomolar concentration	[129]
	20nm	Enhanced viability (decreased nanotoxicity) at 5nM concentration Significant oxidative DNA damage No increase in cell death Downregulation of DNA repair genes (cyclinC, Hus1)	[130]
		Significant reduction in viability of human colorectal adenocarcinoma cells (HT29 cells).	[131]
		In case of HepG2 cells, the concentration of inflammatory marker, so not display variation when compared to control.	[132]
		Elevated expression of lipid peroxidase enzyme as well as DNA damage & cytotoxicity.	[133]
Silver Nanoparticles (AgNP)	10nm	Production of free radical species and induction of oxidative stress that leads to altering in ultrastructure of focal hepatocytes, apoptosis and necrosis.	[134]
	13nm	Altered expression pattern of genes involved in apoptosis and inflammation.	[135]
	20-70nm	Inhibition of Dopamine efflux in both mature and developing neuronal cells.	[136]
	50nm	Targeted nanotoxicity outcomes on mucosal epithelial cells inducing lamellar fusion, hyperplasia and reduction in length of villi.	[137]
Titanium dioxide Nanoparticles (TiO_2 NPs)	40-70nm	Dose dependent increase in DNA damage with TiO_2 NPs Photogenotoxic response displayed by Lymphocytes	[138]
	21nm	Cell viability decreases in time-dependent and dose-dependent manner	[96]
		Gestational exposure significantly impairs the growth and development of placenta in mice. Dysregulation of vascularization and apoptosis.	[139]
Carbon nanostructures	SWCNT	Local effects via induction of oxidative stress and inflammation. An astonishing capability for formation of granuloma and fibrogenesis. These also exhibit the ability to allocate from portico of entry to other cells and tissues and impedes secondary damage.	[140]
	MWCNT	Cellular apoptosis and activation of p53 within 2 hours of exposure Increase in mutation frequency	[141]
	C_{60} Fullerene derivative	Anti-mutagenic effect	[142]
Cadmium Tellurium Quantum Dots (CdTe QD)	2-10nm	Oxidative stress induced in particular range of concentration. Reduction in DNA damage as compared to control	[143]
Cadmium Selenide Quantum Dots (CdSe QD)	3-8nm	Surface oxidations release reduced form of cadmium that cause cell death. The core of this QDs leads to apoptosis. Major toxicity events include ocular edema, pericardial edema and spinal curvature	[124]
Carbon quantum Dots (CQDs)	2-8nm	Specific trophic level toxicity Oxidative stress and pH alterations served as potential mechanism of nanotoxicity of Quantum Dots.	[144]
Cobalt Nanoparticles (CoNP)	100-500nm (256nm)	Dose dependent increase in DNA strand breakage and micronucleus frequency at sub cytotoxic doses.	[145]
CNT, CuO, TiO_2, ZnO, Fe_3O_4		Increase in DNA damage (Dose-dependent) induced by these NPs in the order – CuO>ZnO>CNT Oxidative lesions caused by CuO, ZnO and Fe_3O_4	[111]

investigation, contact to C70 fullerene for a day (i.e., 24 hours) at a concentration of 25.2 g/mL caused human keratinocyte and lung cancer cells to produce more intracellular ROS [119]. Additionally, it was noted that fullerene aggregates at concentrations lesser than

unit mg/L have no harmful effects. However, fullerene aggregates cause cytotoxicity as their concentration rises by depleting mitochondrial membrane potential and raising intracellular ROS levels, which in turn causes macrophage apoptosis by activating the mitochondrial pathway [120].

Toxicity of Quantum dots

Quantum dots (abbreviated as QDs), as a prime tool in advancing nanotechnology products, are extensively utilized in biomedical applications for theragnostic purposes on account of their unique characteristics. Therefore, it becomes essential for scientists to illuminate the undesirable consequences of QDs on living systems [121]. These are nanocrystals, comprising 1000 - 100,000 atoms displaying unusual "quantum effects" such as extensive fluorescence as shown in Figure 6. QDs are at present, supplied in biomedical imaging, and electronic industries [122].

Most scrutinizing works on QDs have shown that post to their entry into the body via various pathways and routes, these cross physiological barriers and were primarily allocated among the mesh endometrial system, and manifested various immune responses and tissue scratch. Inflammation is one of the major responses brought about by QDs. Inflammatory response is a cascade of reactions brought about by various stimuli and is the main process by which the body constructs and repairs damaged tissues and defends it from foreign entities and pathogens. It is an effective defense tool for the immune system to eradicate foreign matters and repair damaged tissues [123].

The toxicity associated with these QDs is accounted for by parameters such as the size of these QDs, the dosage composition, the method of synthesis, administration route and the capping agent used. The most used QDs is CdSe QDs (Cadmium Selenide Quantum Dots). As cadmium accumulates in the skin and is non-degradable tends to have more toxicity. Reports suggested that Cadmium based QDs leads to local neutrophils inflammation in the respiratory system. The oxidation of these cadmium based QDs results in the formation of reduced form of cadmium which is fatal to cells. One more reason for death by the cytotoxicity of these QDs is the oxidation of lipids and proteins of the cell [124-125]. It was also found that CdTe QDs when encrusted with mercaptopropionic acid and cysteamine were cytotoxic to PC12 cells of rat in culture at nearly 11ìg/ml concentration. Uncrusted QDs were found to be cytotoxic at concentration of 1 ìg/ml [126].Research reveals that diffusion of QD565 and QD655 in rat skin is primarily restricted to the primary stratum corneum strata of epidermis[127]. To investigate cytotoxicity, experiments were conducted on cell viability assay for determining the difference in the level of cell damage corresponding to the sizes and chroma of mercapto-undecanoic acid (MUA) QDs as well as the cell types. The outcomes revealed that the cell viability gets reduced with increasing concentration of MUA-QDs. However, in the case of Vero cell with reddish fluorescence QD (QD640), the cell damage was found less compared to the others. Moreover, via the flow cytometry analysis it was discovered that this cell damage posed by the toxicity of MUA-QD, leads to cell death after 4-6-hr incubation [128].

Conclusion

This review is based on the prospective and toxicity profile of different nanomaterials and their associated health hazards. A summary about nanomaterials and their classification with diverse application in various fields are covered. As the properties of materials attain a dynamic change when size shifts to the nanoscopic range. The changed properties find applications in many fields. However, the toxicity posed by these nano-sized structures (nanotoxicity) is a matter of concern. Nanotoxicology involves various assays for determination of the nanotoxicity either qualitative or quantitative and various approaches to reduce it. Therefore, it provides a basis for engineering the safe and less toxic nanomaterials that can be enthralled for various applications. This makes nanotoxicology an esplanade to explore after nanotechnology research. The subsequent attempts ought to be executed to mitigate toxicity with enhanced characteristics and with safer kinetics and toxicodynamic as biological toxicity is a major concern with any nanomaterial. There are several ways to lessen the toxicity of nanomaterials, yet this topic is still a matter of interest and needs to be investigated. Furthermore, the fabrication of nanoparticles to nanocomposites is a novel way to reduce the toxicity level. Information for the complete mechanism of genotoxicity is not that clear. Therefore, Nanotoxicology has a great future in industrial and pharmaceutical fields.

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