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RESEARCH ARTICLE

PHYSICOCHEMICAL PROPERTIES OF SILICA NANOPARTICLES AND HEALTH HAZARDS

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Abstract

Large-scale industrial production and global commercialization of Silica Nanoparticles in recent year had resulted in increased risk of human exposures. However, there is a lack of knowledge on the health and environmental effects of such substances and information on their handling and disposal is also frequently incomplete. The current article, review, the physicochemical properties of the different nanosized silica materials that can affect their interaction with biological systems. The article also discuss the biological mechanisms involve in generating toxicity of nanosilica (both crystalline and amorphous), genotoxicity, immunotoxicity, ecotoxicity, workplace exposure, handling practices and alternatives of disposal of silica aerogels nanoparticle.

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Introduction:-

Nanoparticles (NPs) are objects with a diameter less than 100 nm, but no clear size cut-off exists. The most recent proposed definition of the NP is based on surface area rather than size (should have a specific surface area > 60 m^2/cm^3) [1], thus reflecting the critical importance of above parameter in governing the reactivity and toxicity of nanomaterials (NMs). The toxic effects of NMs can be understood by physicochemical properties which include primary particle size, agglomeration/ aggregation state, size distribution, shape, crystal structure, chemical composition, surface chemistry, surface charge and porosity [2-4]. Nowadays, fast growth in nanotechnology has taken place as a consequence of the advantages of using NPs, including Silica Nanoparticles (SiNPs), in many fields. Moreover, the synthesis, handling and use of SiNPs represent an increased risk for human health need to be evaluated [5-8].

The materials composed of silicon dioxide (SiO_2) are commonly known as silica and occur in crystalline and amorphous forms. Crystalline silica (CS) is a common mineral found in the earth's crust. Materials like sand, stone, concrete and mortar contain CS. It is also used to make products such as glass, pottery, ceramics, bricks and artificial stone. Quartz and more specifically α-quartz is a widespread and well-known material. Upon heating, α-quartz is transformed into β-quartz, tridymite and cristobalite. Porosil is the family name for porous crystalline silica. Quartz exists in natural and synthetic forms, whereas all porosils are synthetic. Amorphous silica can be divided into natural specimens (e.g., diatomaceous earth, opal and silica glass) and human-made products. Apart from CS, which is one of the main components in the Earth's crust (in the forms of α- and β-quartz, α-tridymite, α- and β-cristobalite, keatite, coesite and stishovite), engineered or synthetic amorphous silica (SAS) NPs are among the most produced NPs worldwide for construction materials, industrial and consumer products[9].

Depending on the method used for the synthesis – pyrogenic, precipitation, sol-gel- three different SAS nanomaterials are obtained, namely fumed silica, precipitated silica and colloidal silica [10,11]. Moreover, with the

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emergence of the nanomedicine field, mesoporous silica (MS) and organosilica NPs have also been largely synthesized and studied for drug delivery, imaging and biosensor applications due to their good biocompatibility and superior loading properties in comparison with the crystalline and amorphous silica [12]. SAS NPs are of utmost interest when searching for health or environmental effects of silica aerogels.

The application of SAS, especially SiNPs, has received wide attention in many industries. SiNPs are produced as additives to cosmetics, drugs, printer toners, varnishes and food on an industrial scale. In addition, nanosilica is being developed for biomedical and biotechnological applications such as cancer therapy, DNA transfection, drug delivery, and enzyme immobilization [13-18]. Recently, many studies reviewed the impact of nanosilica on basic biology, medicine and agro-nanoproducts as the human exposure to SiNPs is increasing day by day due to growing commercialization of nanotechnology products and many aspects related to the size of these NMs have raised concerns about safety [19-22]. Until now, most research has focused on silica particles 0.5 to 10 μm, mainly in crystalline forms, but nanosilica may have different toxicological properties as compared with larger particles. The unique physicochemical properties of nanosized silica that make them attractive for the industry may bring about potential hazards to human health, including an enhanced ability to penetrate intracellular targets in the lung and systemic circulation.

Biocompatibility is an important issue for the industrial development of NPs [23, 24]. Even though no acute cytotoxicity has been observed or reported, the uptake of the NPs by cells may eventually lead to perturbation of intracellular mechanisms. The ability of silica-coated NMs to penetrate the blood-brain barrier also strongly suggests that extensive studies are required to clarify the potential chronic toxicity of these materials [25].

The distinct physicochemical properties of NPs indeed determine their interaction with the cell/within the cell and even subtle differences in such properties can modulate the toxicity and modes of action. However, most of the studies have used poorly characterized particles in terms of their composition and physicochemical properties. The results of toxicity studies then become difficult to interpret and compare and drawing appropriate conclusions is nearly impossible. Although SiNPs could certainly provide benefits to society, their interaction with biological systems and potential toxic effects must be carefully addressed.

Physicochemical Properties of SiNPs:-

The toxicity of many bulk materials is affected mainly by their composition and in the case of NMs, additional physicochemical properties such as size, surface area, surface chemistry, surface roughness, the dispersion medium and ability to agglomerate play a vital role in determining their toxicity (Figure 1).

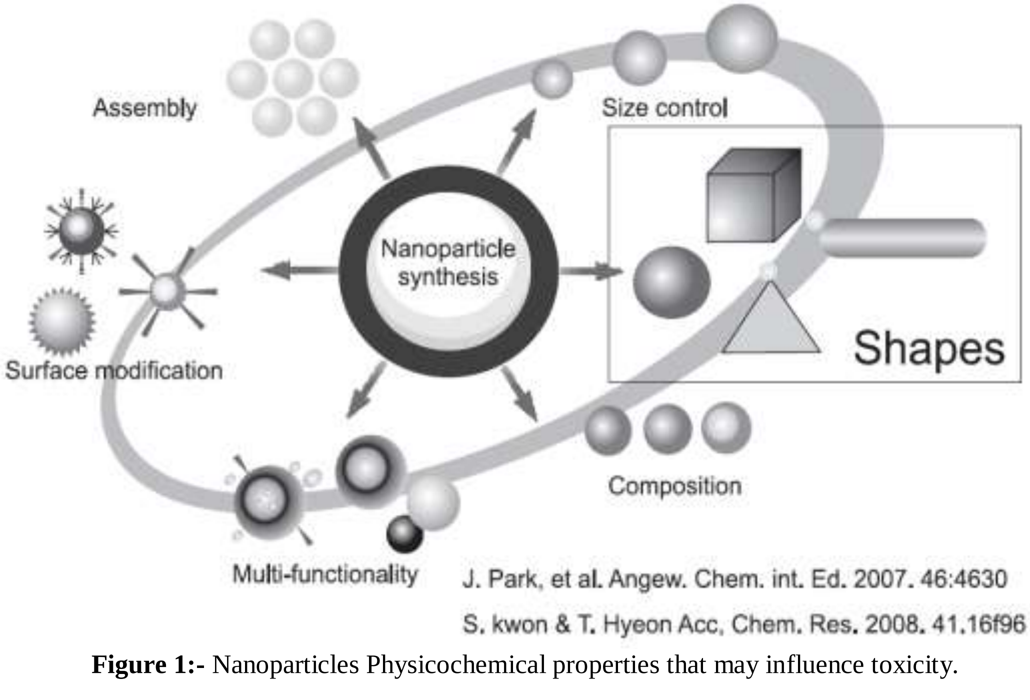

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Figure 1:- Nanoparticles Physicochemical properties that may influence toxicity.

The properties of silica materials which are considered essential for their potential toxicity includes crystallinity, particle size, morphology, porosity, chemical purity, surface chemistry and solubility.

Crystallinity

In crystalline structures such as quartz and porosils, the arrangement of atoms is ordered in all dimensions. The atoms must be arranged periodically in long-range order (at least 10 repeats in all directions) and produce sharp maxima in a diffraction experiment to observe x-ray diffraction crystallinity (XRD) [26]. The threshold for observing crystallinity depends on the unit cell size. For materials with large unit cells, such as porosils, the minimum particle size required is about 10 nanometers to observe a distinct, sharp XRD pattern. Amorphous silica may present some short-range order and lacks long-range order in 3 dimensions and does not exhibit a sharp x-ray diffraction crystallinity pattern.

Particle Size and Morphology

NPs are obtained by direct synthesis of silica sol or by crystallization of nanosized crystals of quartz or porosils [27, 28]. The particle size is determined on the basis of the synthesis parameters. Amorphous silica sol particles tend to adopt the spherical shape so as to reach a minimum of interfacial surface area. Crystalline particles exhibit crystal planes at the surface and the morphology of the crystalline NPs depends on the crystal class such as cubic, hexagonal, tetragonal and orthorhombic. Nearly all NMs, in an aqueous environment, the primary nano-sized silica particles tend to form aggregates.

Porosity

Pores are classified on the basis of their diameter into micropores (< 2 nm), mesopores (2-50 nm), and macropores (> 50 nm). Amorphous sol particles can be microporous or non-porous (dense). The porosity of Stober silica can be either rough particle surfaces with micropores or smooth particle surfaces [29]. Silica gel is a powder with particle size in the micrometer range or larger and is, typically, mesoporous. Zeosils and clathrasils have characteristic pores and cages in the micropore size range, depending on framework topology.

Hydrophilic-hydrophobic Properties

The hydrophilicity of a silica material increases with the number of silanols, or silicon-bonded hydroxyl groups present on the surface and capable of forming hydrogen bonds with physical water molecules. As compared with amorphous silica, the crystalline forms of silica generally contain a lower concentration of surface hydroxyl groups. Colloidal silica, precipitated silica, ordered mesoporous silica and silica gel are hydrophilic because of their high concentration of silanols. Porosils typically are hydrophobic because they lack silanols in the pores of their framework. Silica produced at high temperature, such as pyrogenic and vitreous silica, or calcined at temperatures exceeding 800°C, is almost entirely dehydroxylated and is hydrophobic. Grinding of hydrophobic bulk materials such as quartz and vitreous silica induces silicon and oxygen radicals and surface charges thereby increasing the hydrophilic surface [30].

Solubility

The dissolution and precipitation of silica in water chemically involve hydrolysis and condensation reactions, respectively, catalyzed by hydroxyl ions.The silica solubility depends on the surface curvature of the NPs. SiNPs and nanoporous silica show enhanced equilibrium solubility, of 100-130 ppm [23]. Crystalline silica such as quartz has much lower equilibrium solubility, of 6 ppm [31].

Exposure of SiNPs:-

The rapidly developing field of nanotechnology is likely to become yet another source of human exposure to nanosized particles by different routes: inhalation (respiratory tract), ingestion (gastrointestinal (GI) tract), dermal (skin) and injection (blood circulation) (Figure 2). High production rate of SiNPs and their wide use in a broad variety of applications might lead to significant environmental, occupational and consumer exposure. Solid SiNPs are used as adsorbents, fillers, thickening agents, anti-caking agents, emulsion stabilisers, free-flow agents and carriers in a variety of industrial and consumer products, including pest control, pharmaceuticals, cosmetics and food and feed products. Colloidal silica is widely used in coatings, ink-receptive papers, metal casting, refractory products, catalysts and as a filter aid in food production. Emission to the environment may occur during production and use of SiNPs although the potential amount of anthropogenic SiNPs released into the aquatic environment is estimated to represent only a small fraction of the dissolved silica naturally present in rivers. Analytical data with regard to the possible release of SiO_2 particles from nanocomposites, e.g., by wear and tear, were not available.

Reijnders [32] suggested that SiNPs released from nanocomposites might pose an environmental and health risk. Occupational exposure in SiNPs production is highest during packaging and loading operations, with the highest mean values of up to 3mg/m^3 of inhalable dust and up to 1 mg/m^{3}of respirable dust. The toxicologically relevant, respirable fraction is much lower in the products under normal handling and uses conditions than under experimental conditions. Surface-treated SiNPs may be used in perfumes and hence may be aerosolised during use by consumers. With typical aerosol particle diameters in the 10–100 µm range, most aerosol particles will not be respirable but deposited in the nasopharyngeal region. Oral and dermal SiNPs exposure may arise from the use of personal care products and medicines.Dekkers et al. [33] analysed food products with added silica (E551) which is in the nano size range and estimated the likely oral intake of SiNPs via food.

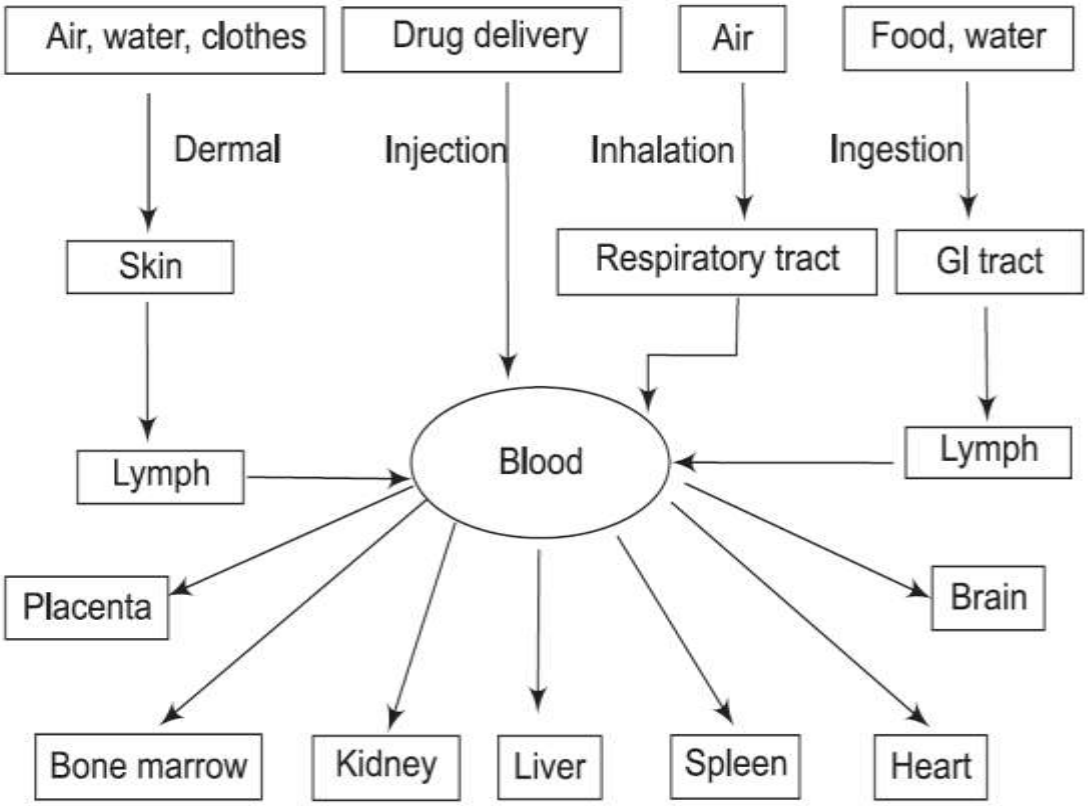

Figure 2:- Nanoparticles routes of exposure [3].

Cellular Uptake of SiNPs:-

Once in the circulation, NMs are taken up into cells by endocytosis (phagocytosis or pinocytosis), membrane penetration, or passive diffusion through trans-membrane channels. The trans-membrane passage of NMs is dependent, on many factors including the physicochemical properties of the particles (chemical composition, size, shape and agglomeration status), cell type (professional phagocytes such as macrophages vs. non-professional phagocytes), serum components and surfactant. After internalization, NMs can travel to several different locations within the cell including the outer-cell membrane, cytoplasm, mitochondria, lipid vesicles, nuclear membrane or become lodged within the nucleus itself. If the concentration is high enough, NMs can damage cellular organelles and DNA which can result in cell death and, at times, disease development (Figure 3).

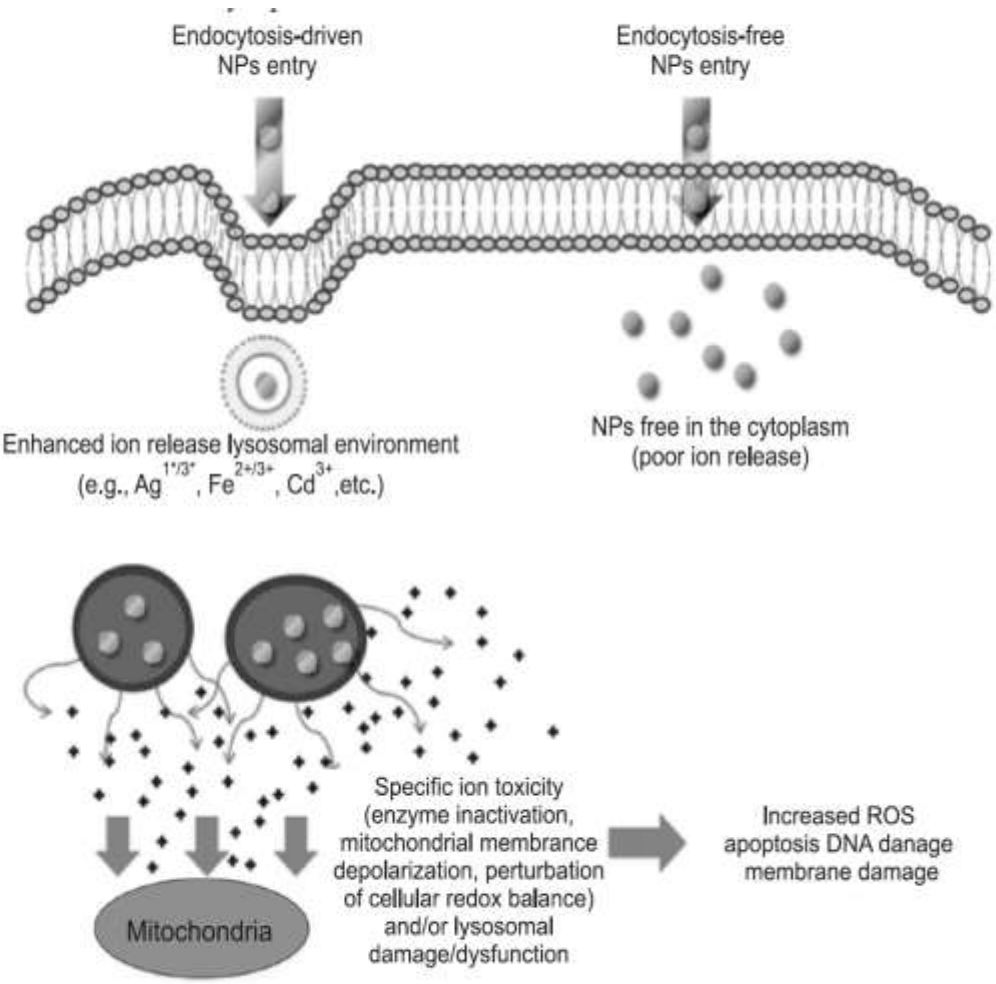

Figure 3:- Interaction of NPs with biological system.

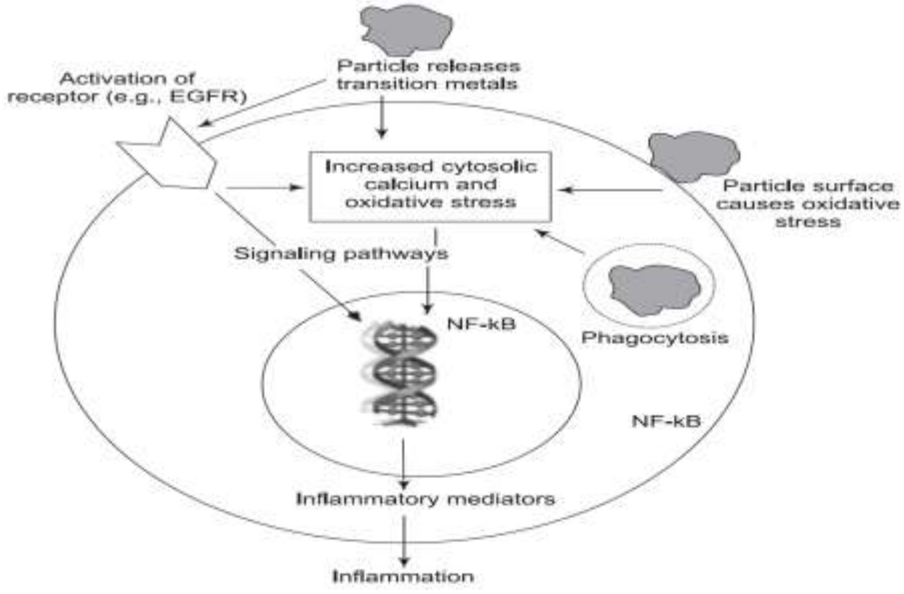

Figure 4:- Hypothetical cellular interaction of NPs (EGFR, epidermal growth factor receptor. Inflammation and oxidative stress can be mediated by several primary pathways. The particle surface causes oxidative stress resulting in increased intracellular calcium and gene activation [34].

SiNPs can enter our body in particulate or dissolved form. Depending on aggregate size and pH, SiNPs dissolve relatively fast in the body to form silicic acid. The tendency to supersaturate increases dissolution and hence distribution and elimination from the body. There are evidences of renal elimination of bioavailable fractions and also of whole particles. After inhalation, oral, intraperitoneal and intravenous exposures, SiNPs are eliminated from the lung tissues and other organs of experimental animals with no indication of accumulation, even after prolonged exposure to high doses or concentrations. Some of the most relevant biological and health effects associated with SiNPs, apart from hemolysis, are neurotoxicity, lung cancer, fibrosis, renal injury, or autoimmunity mediated by the activation of the NFκβ pathway and the release of pro-inflammatory cytokines (Figure 4). For instance, severe chronic lung inflammation has been associated with SiNPs inhalation, particularly to pyrogenic fumed silica, as well as an increased probability of developing autoimmune diseases after silica exposure during occupational settings. However, not all the silica particles are toxic and the differences found between them depend on their physicochemical properties (namely crystallinity, aggregation state and surface chemistry) [35-37]. Exposure to breathable crystalline quartz dust has been largely associated with silicosis, an ancient occupational disease. The silica dust is generated during the grinding, cutting, or abrading of rocks containing quartz crystals and the exposure of workers to the breathable particles during those activities, or the manipulation of the silica powder leads not only to silicosis but also to other respiratory and systemic diseases [38]. Conversely, the exposition of breathable amorphous silica particles is largely accepted as safer because these particles can be cleared more rapidly from the lungs. However, some studies have shown that crystallinity is not a clear factor associated with toxicity, but depends also on surface activity, the origin of the silica (processing pathway and environmental exposure), or the presence of some impurities, such as metal ions or mineral phases, among other factors [39, 40].

SiNPs Induced Genotoxicity:-

Direct interaction with DNA, oxidative DNA damage, depletion of anti-oxidants, cell cycle arrest and abnormal expression of genes have been identified as potential mechanisms of NP-mediated genotoxicity [41]. Assessment of the genotoxic potential is essential for the carcinogenic risk assessment of NPs. Genotoxic effects may be produced either by direct interaction of particles with genetic material or by secondary damage from particle-induced reactive oxygen species (ROS). SiNPs induce chromosomal aberrations, DNA strand breaks and oxidative DNA damage. OH·, one of the highly potent radicals, is known to react with all components of DNA causing DNA single strand breakage. In addition, other weak chromosomal effects were observed, but again without reaching statistical significance. The potential of four differently sized SiNPs particles (nominal sizes: 10, 30, 80 and 400 nm; actual sizes: 11, 34, 34 and 248 nm) to induce chromosomal aberrations and gene mutations was studied using two in vitro genotoxicity assays [42]. Wang et al. [43, 44] reported on a very slight positive effect of SiNPs in a Comet assay, performed on primary mouse embryo fibroblast cells with a material that was described as having a crystal structure with an average size of 20.2 nm. Taken together, the results obtained in mutagenicity and genotoxicity tests give no evidence that SiNPs induce mutations either in vitro or in vivo. Genotoxicity was observed in vitro, usually at dose levels and concentrations that also induced cytotoxicity.

SiNPs Induced Immunotoxicity:-

SiNPs are one of the three most produced NPs and are widely used in dietary supplements, vaccine adjuvants, dental fillers and drug delivery. However, the toxicity of SiNPs to the immune system has received an increasing amount of attention. SiNPs interact with the immune system in many ways. They may have toxic effects on phagocytes, particularly macrophages, dendritic cells (DCs) and T-lymphocytes. The cytotoxicity of SiNPs to the immune system is determined in part by the physicochemical properties of the particles. For example, SiNPs have exhibited dose- and time-dependent toxicity to human lymphocytes in vitro [45, 46]. Epidemiological studies have drawn inconsistent conclusions regarding amorphous silica toxicity. The physicochemical characteristics, such as particle size, shape, composition and crystallinity, affect toxicity towards immune cells and organs.

The immune system and especially the innate immune system, provides the first line of defense against foreign microbes and particulate materials which are basically innate effector cells and humoral factors. NMs can interact with immune competent cells and induce immunotoxicity. Interactions of NPs with the immune system have different outcomes that mostly depend on the characteristics of the NPs [47, 48]. The effector cells that are mainly involved in immune system include monocytes/macrophages, peripheral blood monocytes and polymorphonuclear leukocytes. NPs also interact with dendritic cells (DCs; the key antigen-presenting cells (APCs) of the immune system), lymphocytes, mastocytes and become internalized. The toxicity of NMs to immune cells includes their ability to cause direct cell damage such as apoptosis and necrosis. The function of immune cells changes after interactions with NMs and the immune-specific signalling pathways are influenced. These features are measured by evaluating cell functions, proinflammatory responses, reactive oxygen species (ROS) generation and so on [49, 50]. Evaluating the interaction of NMs and cells is critical for the safety consideration.

Ecotoxicity effects of SiNPs:-

The major uses of SiNPs are in paints, plastics, ceramics and car tires. SiNPs and their agglomerates eventually end up in the environment. Kattan et al. [51] studied the release of amorphous SiNPs from paints using weathering experiments. Silica release from a silica-containing paint was 0.065 mg L^{-1} and the released silica consisted of large particles (32% smaller than 100 nm). When aged, the same paint released 20 mg L^{-1} of silica particles only 10% smaller than 100 nm. Graca and co-authors [52] analysed the existence of NMs in seawater collected from the Southern Baltic Sea. The NMs consisted of nanoparticles and nanofibers, mainly of silica but chrysotile was also found. The concentration of these NMs was also seasonal-dependent and their origin was biogenic and geogenic.

Safety practice handling silica and its disposal:-

Although the amorphous silica is less problematic than CS in terms of safety, the information given in this overview shows that there are studies confirming some degree of toxicity of the former, either to environmental ecosystems or some human cells. On the other hand, some of these materials, such as nanostructured pyrogenic and precipitated SAS and silica gel, have been used for decades without safety concerns in industrial, commercial and consumer applications [53]. Thus, it is of primary importance to wear personal protective equipment and to monitor and ventilate the workplaces where these materials are handled/stored, in order to prevent reaching the exposure safety limits for amorphous NPs. These NPs may cause symptoms like very dry skin and upper respiratory track irritation. Still, it is worth noting that these effects may change according to the size and surface chemistry of the released particles.

Regarding the disposal of silica aerogels, although the deposit in landfills is a common strategy for the end-of-life of silica aerogels, problems arise from that approach, since low molecular weight silica volatile compounds are formed during the anaerobic process. The most interesting approach for end-of-life of aerogels is the depolymerization of the siloxane bonds in order to provide recycled monomers/oligomers for new aerogels production, allowing a circular economy rationale.

Conclusions:-

Interest in using SiNPs is growing worldwide, especially for biomedical and biotechnological applications such as cancer therapy, DNA transfection, drug delivery and enzyme immobilization. Due to favorable properties like colloidal and chemical stability, the possibility for a covalent surface modification and a high specific surface area, the application cases for silica particles and silica-based materials have grown rapidly. The size and surface physicochemical features of SiNPs contribute decisively to the biological effects of SiO_2 NPs; the complexity of protein-SiNP interactions appears to be affected by the size of SiNPs. Still, the development and synthesis of SiNPs with precisely controlled physicochemical properties like shape, particle size distribution and surface charge are critical steps for their toxicological evaluation and also for their use for biomedical application. Besides the relative lack of information on the safety or hazards of SiNPs, issues such as conflicting evidence reported in the literature as a result of a general lack of standard procedures as well as insufficient characterization of NMs in biological systems need to be addressed.

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