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NANOTOXICOLOGY: A STUDY OF TOXIC PROPERTIES OF NANOMATERIALS

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ABSTRACT

Nanotechnology is being widely used in various fields such as medicine, cosmetics, and lifestyle. Some daily-use products in which we can find nanomaterials include pharmaceuticals, fabrics, rubber-based products, plastics, and cosmetics. Hence it is evident that the usage of nanomaterials is increasing day by day. Therefore, this is causing an increase in exposure to nanomaterials. The effect of this exposure is being explored through numerous studies over the decades. The studies have revealed some effects such as DNA damage, oxidative stress, lipid peroxidation, and mitochondrial damage. Based on the data gathered and further interpretation several laws and regulations have been laid to protect the interest of all the involved parties, be it the consumer, the manufacturer, or the nature. Formulation of these laws requires a lot of criteria to be considered, hence specialized regulatory bodies have been established to promote nanotechnology as well as create the rules and regulations. With the emergence of bioinformatics, the ill effects of nanomaterials can now be predicted in-silico providing an alternative to in vivo studies. This paper will explore all such recent developments and discoveries in the field of nanotoxicology.

Keywords: nanomaterial, nanotechnology, DNA damage, oxidative stress, nanotoxicology, and engineered nanoparticles

INTRODUCTION

As per International Organization for Standardization, nanotechnology is defined as the 'Application of scientific knowledge to manipulate and control matter predominantly in the nanoscale to make use of size and structure-dependent properties and phenomena distinct from those associated with individual atoms -or molecules.' The flame for this revolutionary science was kindled by physicist Richard Feynman's address at an American Physical Society meeting titled "There's Plenty of Space at the Bottom." (California Institute of Technology (CalTech) on December 29, 1959). Through the talk, Feynmann elucidated the possibility of manipulating and controlling individual atoms and molecules. Professor Norio Taniguchi coined the term nanotechnology. One phenomenon that makes nanotechnology so desirable is that the specific properties of certain materials change at the nano level. This provides an opportunity for scientists to exploit the unique physical, chemical, mechanical, and optical properties of materials that naturally occur at that scale **[1]**.

Real-time estrogen hormone release and real-time inoculation techniques have been started using specialized skin nanotubes. Applications of nanotechnology in animal research also include the creation of animal vaccinations, the production of medications and nutritional release systems, improving the speed at which disease symptoms are identified and facilitating quick treatment, and the development of nucleic acid release systems. Since they are powerful antibacterial and antimicrobial agents, silver nanoparticles are being used to enhance the hygiene of livestock and poultry breeding sites **[2]**.

In agriculture, nanotechnology can be used to develop slow-release nanofertilizers for plant fertilizer use; nanoparticle-encapsulated pesticides for controlled and on-demand release; site-specific drug and nutrient delivery in fisheries and livestock; nanoparticles, nanobrushes, and nanomembranes for water and soil treatment; cleaning and maintenance of fishponds; and nanosensors for assessing plant health and soil quality **[3]**.

Nanoinformatics methods such as quantitative structure-activity/property relationship (QSAR/QSPR) models use nanomaterial descriptors for the optimization of engineered nanoparticles. These modifications ensure improvement in functionality and minimization of any unforeseen hazards **[4]**.

With recent input from research studies, it has been indicated that the smaller the particles are the more reactive and toxic are their effects. It is because any intrinsic properties of particles will likely be emphasized with the increase in surface area per unit mass. It has been demonstrated that the surface chemistry (coating) and in vivo surface changes of nanoparticles play a major role in the potential for enhanced endocytosis, which may also have inflammatory and prooxidant activities. When such particles interact with cells free radicals are generated. Free radicals produce oxidative stress that leads to cell death. Due to the nanoparticles' small size, they may work as haptens to affect protein structures, either by changing how they function or by making them antigenic, which would increase the possibility of autoimmune consequences **[5-6].**

Since this technology is so new the pros and cons have not been explored at an intensive level. Various possible risks and dangers to human life have been hypothesized. Exposure to such synthetic material may result in the development of significant immune and inflammatory responses. Moreover, the environment may be affected by this novel technology. The rate of degradation and shelf life in a natural environment must be investigated before its full-fledged launch into society. This review paper epitomizes a few potential threats nanotechnology can pose. The primary effects explored are on human health and quality of life.

REVIEW OF LITERATURE

Nanotechnology is the manipulation of matter at the molecular or atomic level in order to create innovative materials and devices with new remarkable qualities, and it is closely related to nanoscience. One nanometer is a billionth of a meter, which is incomprehensibly small. Nanotechnology is the combining of knowledge from numerous scientific areas, including biology, physics, chemistry, medicine, and engineering, to customize materials with dimensions ranging from 1-100 nm. The inventive and revolutionary aspect of nanotechnology is related to quantum mechanics concepts **[7-8]**.

Biological effects

Due to the influence of the size of the particles on tissue distribution the toxicity of intravenously injected nanoparticles must be evaluated. Some of the areas that can be explored in regard to nanotoxicity are the difference between the fates of these particles to that of synthetic carries, the possibility of developing unexpected and harmful immunological and pharmacological effects, the possibility of interferences with regular cellular machinery, evaluation of the extent of effects in in-vitro and in-vivo studies, etc. The mechanisms by which metal oxide nanoparticles induce in vitro and in vivo toxicity, such as DNA damage, oxidative stress, lipid peroxidation, and mitochondrial damage, have been summarized by several researchers. Nanomaterials changed protein conformation through the adsorption of proteins.

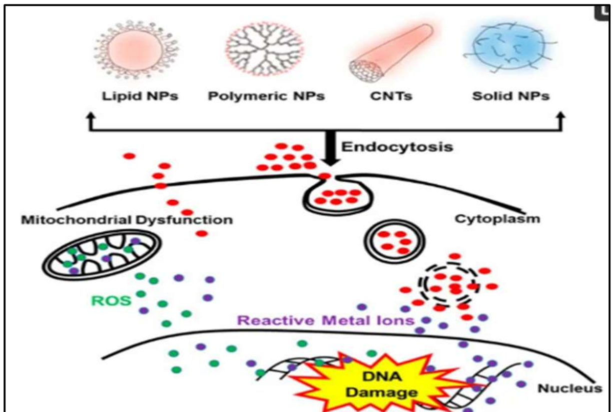

Figure 1: Interactions between cells and nanoparticles, as well as the mechanism of nanoparticle toxicity. Upon cellular uptake, NPs pass through lysosomal pathways, triggering the generation of reactive oxygen species and/or reactive metal ions, resulting in mitochondrial dysfunction and DNA damage. [9]

One of the other potential effects is the development of non-IgE-mediated signs of hypersensitivity. These developments are categorized as idiosyncratic and secondary to complement activation. Infusion of stealth systems, like poly (ethylene glycol)-grafted liposomes exhibit the potential of inducing idiosyncratic reactions. Ways to combat this possible biological effect is through refined surface engineering, which includes better polymer design, linkage modification, controlling the conformation and packaging of grafted polymers, and introducing complement regulatory proteins or inhibitors onto the surface of the nanoparticle **[10]**.

Single-wall carbon nanotubes (CNTs) and fullerenes, C_{60}

Several studies confirmed the cytotoxic effect of CNTs (Carbon Nanotubes) on the lungs of mammals. When the lungs of mice were exposed to CNTs through inhalation formation of granulomas. Further studies led to the revelation of various factors that affect the degree of toxicity and nanoscale activity of CNTs in the physiological environment, such as the presence of metal catalysts, processing methods, degrees of functionalization, and CNT agglomeration.

When CNT and graphene are released from scaffolds and implants and become disseminated in the physiological environment, they can become hazardous. Released CNT and graphene have the potential to modify cellular physiological environments, harming cellular membranes and possibly accumulating in unfavorable places. Since CNT and graphene's nanotoxicological potential effects on human macrophage cells and phagocytes may cause inflammatory reactions on the surfaces of implants and scaffolds, leading to their loosening and the release of metal ions into surrounding tissues, toxicity-related issues of CNT and graphene must be addressed for applications of bone tissue engineering **[11]**.

Studies conducted both in vitro and in vivo demonstrate that CNPs (Carbon Nanoparticles) such as graphene, MWCNTs (Multiple-walled carbon nanotubes), SWCNT (Single-walled carbon nanotbubes), QD (Quantum Dots), nanodiamonds, and fullerenes have a hazardous potential. By causing the creation of reactive oxygen species and DNA damage, they can affect spermatogenesis, sperm morphology and functions, hormonal balance, damaged ovarian tissue, and testicular tissue. However, in vivo research also produced findings that refute the notion that CNPs are hazardous to reproduction. The kind of CNPs, exposure dose, and exposure duration all affect the harmful effect. Studies have produced evidence that CNPs may harm the development of larvae or fetuses. Both invertebrates and vertebrate progeny, such as fish and mammals, are harmed by CNPs. They can harm tissues like the neurological system and the heart, slow down development, induce different abnormalities, and lower survival chances **[12]**.

Titanium dioxide (TiO_2) nanoparticles

Numerous investigations conducted over the years have led to the conclusion that, regardless of concentration, extended exposure to TiO_2NPs has a deleterious impact on zebrafish fertility and embryo survival. Additional findings included abnormalities in the maturation and operation of the ovaries of fish exposed to TiO_2NPs, as well as a delay in ovarian follicle maturation. As a result, titanium dioxide nanoparticles significantly influence this species' reproductive system **[13]**.

Multiple investigations over the years have revealed that aquatic invertebrates and fish species were only moderately harmful to nano-TiO_2. Numerous years have been invested in researching the toxicity of nano-TiO_2. Nano-TiO_2, for instance, may adhere to the surfaces of algal cells and result in the peroxidation of membrane lipids. Ionic strength and pH are only a couple of the numerous variables that can determine how poisonous nano-TiO_2 is. According to certain research, NPs can boost the uptake of co-existing contaminants in organisms as well as adsorb and concentrate various types of pollutants **[14]**.

Several toxicological studies on rats and mice have revealed that exposure to nanoparticles of titanium dioxide can cause physiological responses. These responses include spleen damage, liver fibrosis, apoptosis, oxidative stress, and chronic gastritis. Cardiovascular responses exhibited included heart arrhythmia due to reduced activity of LDH (Lactate dehydrogenase), HBDH (Hydroxybutyrate Dehydrogenase), and CK (Creatine Kinase) increased heart rate, and increased diastolic pressure. The nervous system exhibited the following responses on exposure to titanium dioxide nanoparticles: mitochondrial brain lesion, membrane damage in the brain cells, apoptosis of hippocampal neurons, apoptosis of glial cells, neurogenic diseases, and increased cytotoxicity to PC12 cells by inducing microglial activation **[15]**.

When human hepatocarcinoma cell lines were incubated with various concentrations of TiO_2 nanotubes for 48 hours, the following was observed: inhibition of cell growth, increased apoptosis and cellular ROS levels, and arrested cell cycle at the G1 stage. TiO_2 therapy reduced tumour volume while boosting PERK, Bax, and ATF6 expression in tumour tissues in vivo. This study led to the conclusion that exposure to titanium dioxide nanoparticles caused ROS-induced endoplasmic reticulum stress **[16]**.

A study was conducted to evaluate the in vivo toxicity of industrially prepared TiO_2 nanoparticles on the zebrafish embryo model. The focus of the study was developmental and cytological effects. Further, to determine the mechanism of toxicity both experimentally and computationally, studies of ROS generation, apoptosis evaluation, and effects on neutral lipid accumulation changes were done. Size and concentration-dependent effects on head, trunk, and tail developmental deformities in the embryos of the zebrafish were observed. TiO_2 nanoparticles were also discovered to improve ROS scavenging and apoptotic induction, as well as neutral lipid change, depending on their size and concentration variation via distinct chemical interactions **[17]**.

Nanoparticles of oxides of gold

Due to their unique characteristics, metal nanoparticles, particularly AuNPs, have attracted enormous interest from a variety of scientific fields. These characteristics include a high X-ray absorption coefficient, ease of synthetic manipulation, the ability to precisely control the physicochemical properties of the three particles, a strong binding affinity to thiols, disulfides, and amines, as well as distinctive optical and electronic properties. The synthesis and functionalization of AuNPs have seen significant advancement, leading to more sophisticated diagnostic and therapeutic methods. By virtue of their optical, electrical, physicochemical, and surface plasmon resonance (SPR) capabilities, spheres, and nanorods have been given a distinct place. AuNPs have proven a good option for the technique of localized surface plasmon resonance **[18-19]**.

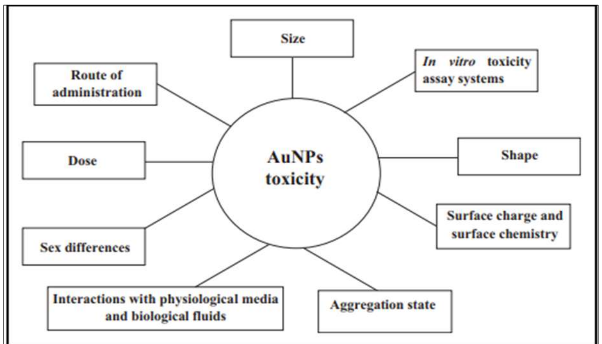

Figure 2: Factors influencing the toxicity of gold nanoparticles [20]

When the toxicity of gold nanoparticles was tested on embryos of zebrafish a delay in the development of eyes and pigmentation was observed. Several tests on mice and rats over the years have led to the following observations: Lungs, kidney hemorrhage, lymphocytic infiltration, and inflammatory response; apoptosis and inflammation of liver tissue; Large particles of spherical AuNPs were observed in blood, spleen, and liver while smaller particles were seen in the spleen, blood, thymus, lungs, liver, kidney, testis, heart, and brain; ROS-induced cytotoxicity that is size-dependent; Induced reduction in RBC, spleen index and body weight **[21]**.

Environmental effects

Man-made nanoparticles may leak into the environment through shipment and handling or because of manufacturing waste. Nanoparticles are also present in personal care items like sunscreen and cosmetics. These particles may seep into the environment when found in electronics, tires, fuel cells, and other consumable goods. They may also enter the environment through landfills and other disposal processes because they are utilized in disposable items like filters and electronics.

Engineered nanoparticles (NPs) have become the MVP of every major field of daily life including agriculture, environment, medicine, and other science and technological areas. An estimate of 260,000 and 309,000 metric tons has been presented for the predicted global annual production of nanomaterials (NMs). The likelihood of accidental/or incidental release of nano-size particles into the environment at each stage of the life cycle of NPs-containing products, i.e., production process, usage phase, and end-of-life stage, is high since the quantities for manufacture and application of NMs are so large. The entry of nanoparticles into aquatic and terrestrial environments produces unknown consequences on ecosystem structure and functioning due to their size-dependent toxic effects. Interaction with living organisms also majorly influences the particular toxic effects **[23]**.

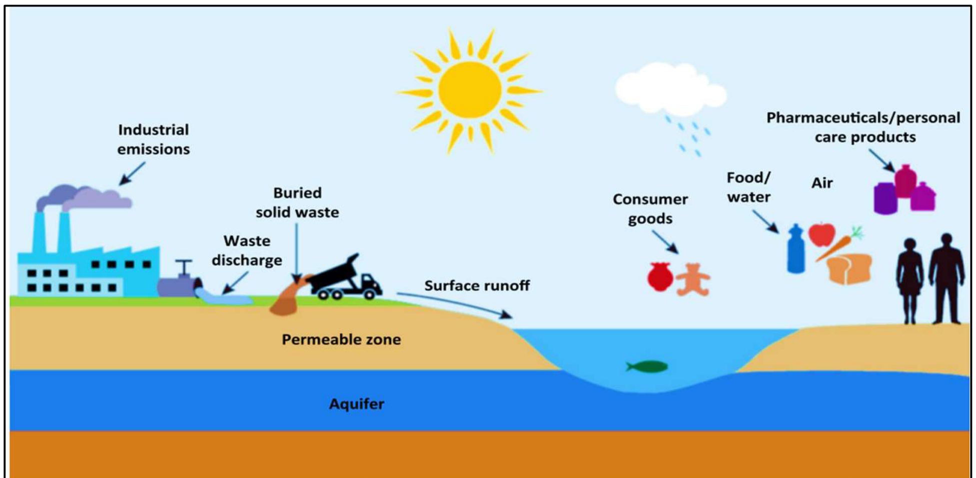

Figure 3: Occurrence, transport, routes, and exposure pathways of nanomaterials in various environmental matrices [23].

Wheat And Engineered Cerium Oxide Nanoparticles

CeO_2NPs have been found to be the top 10 produced nanomaterials in the world. As per reports prepared by European Union (EU) and US Geological Survey (USGS) reports, the estimated. production volume of nano-CeO_2 is 7500–10,000 tons/year, of which more than 80% originates from China. Nano-CeO_2 finds its place in common household items such as sunscreens as a UV blocker, fuel cells, polishing agent, and catalytic converter. In many countries in Europe, Asia Pacific, North America, and South America, CeO_2NPs are also used as a fuel additive as it reduces particulate matter emissions as well as improve engine performance. As a consequence, huge amounts of CeO_2NPs are released into the natural ecosystem. This possesses a potential thread for biota including plants.

The fate of these particles in the environment is dependent on several physical factors as well as matrix conditions. Some of the determinants are particle size, shape, surface charge and coating, degree of aggregation, pH, and ionic strengths. As these factors along with disposal amount promote the accumulation of CeO_2 in intact nano-form, bioaccumulation of these particular particles is possible in humans through the food chain.

A study was conducted on wheat to evaluate the effect of cerium oxide nanoparticles on various physiological factors of the crop wheat. Wheat is a major source of carbohydrates for a significant proportion of the world's population. This dependency makes it of utmost importance for proper studies to be conducted on this commercially important crop.

The physiological factors studied are growth, photosynthesis, and gas-exchange-related physiological parameters. It was observed that a concentration of 500 mg L^{-1} promoted plant growth by promoting photosynthesis, transpiration, and stomatal conductance. However, a concentration greater than 2000 mg had a negative effect on plant growth and photosynthesis-related processes. The varying concentration of nanoparticles had a notable effect on the plant height, biomass, pigment production, and primary macronutrient status **[24]**.

Silver Nanoparticles in Agriculture

The desirable characteristics of silver nanoparticles, such as their plasmonic and optoelectrical properties and anti-bacterial and anti-fungal activities, make them one of the most intensively used nanoparticles in many products in the form of nano-emulsions. Based on several conducted toxicological studies, the effect of AgNPs on plants can either be positive or negative depending on the species, stage of growth, size of nanoparticles, and concentration and exposure conditions. The phytotoxicity of AgNPs is complex due to the simultaneous dissolution and release of toxic silver cations as well as the physical interactions of nanoparticles.

In *Allium cepa* L. AgNPs have been noted to reduce biomass contents, promote DNA damage, and induce oxidative stress through the production of reactive oxygen species (ROS). For *Arabidopsis thaliana,* a model plant for ecotoxicity studies, exposure to silver nanoparticles has been noted to delay flowering and an overall reduction in plant growth and yield. This observation has been attributed to decreased transcription levels of flowering genes. Yang and coworkers (2018) worked on the phytotoxic effects of nano-Ag on *Triticum aestivum* L. The following observations were made: decreased plant biomass, height, grain weight, total protein, and amino acid contents as well as alteration of grains' nutritional value. When the aquatic ecosystem model plant *Spirodela polyrhiza* was exposed to certain concentrations of nanoparticles of silver, the photosynthesis activity and CO_2 assimilation rate slowed down upon interaction with AgNPs.

Rice (*Oryza sativa* L.) is an exceptionally important food crop, irreplaceable to human nutrition as it provides about one-fifth of the calories required by humans worldwide. The interaction of AgNPs with rice was studied. The yield expressed the following characteristics: negative effects on growth, yield, and other physiological as well as other biochemical parameters**.** When plants were exposed to silver nanoparticles there was a reduction in root and shoot length, biomass production, chlorophyll contents, photosynthesis-related physiological parameters as well as macro-and micronutrients in a dose-dependent manner. Also, the exposure level of AgNPs decreased the bioaccumulation of Ag in rice root and shoot tissues, thus alleviating the phytotoxic effects of NPs on plant growth **[25]**.

Nanoinformatic methods for minimizing potential hazards

The measurement of a substance's hazardous impact on the environment or human health is known as a toxicological endpoint. It determines the harmfulness of a substance. The process required for evaluation can either be carried out in vivo or in vitro or in silico studies. In vitro assays are usually preferred for pilot testing due to their time and cost-effectiveness. Additionally, it's important to compare and confirm in vivo observations with in vitro results. The systematic methodology aimed to address the issue of organization, validation, storage, sharing, analyzing, and application of the data related to nanotechnology and nanotoxicology **[26]**.

Machine learning (ML) techniques and algorithms provide an alternative toxicity assessment method. This allows for making an assay without testing organisms or cell lines. Through these techniques prediction of toxic endpoints can be made. A variety of information sources containing the physiochemical properties of nanoparticles is combined with the results of in vitro and in vivo toxicity tests. Classification is one of the most widely used ML techniques. Different types of classifiers, including rules, trees, lazy, functions, bayes, and meta classifiers, are created using ML methods. The most popular classifiers for predicting the toxicity of NPs are neural networks, random forest, Nano-QSAR, Bayesian networks, k-nearest neighbor, linear regression, and support vector machines. Meta-classifiers, like Voting, ensemble support vector machines, and ensemble random forest combine with base classifiers to improve their learning capability **[27]**.

A set of biological instruments known as the "omics approach" can be used to track changes in living things at the level of their genes, gene transcripts, proteins, tiny biomolecules, and biological networks (bioinformatics). Transcriptomics is currently the most advanced omics method employed in nanotoxicology. The most promising benefit that transcriptomics provides is risk assessment through the identification of their mode of action. Early identification of subtle biological effects induced by exposure to NMs at low doses is facilitated by transcriptomics. However, the challenges that require troubleshooting include the lack of standard protocols, analysis algorithms, guidelines, and data management strategies in nanobioinformatics **[28]**.

Molecular descriptors are of utmost importance in traditional (Q)SAR analysis. These descriptors are used to characterize and quantify the physicochemical properties of chemicals. Theoretical descriptors provide a wide variety of physicochemical information and valuable insight into the understanding of the potential relationships between molecular characteristics and biological activity. They can be derived from different theories/semiempirical methods, which may be implemented in commercial software packages. The main problem in the construction of such descriptors for engineered nanomaterials (ENMs) is their complexity and non-uniformity. Instead, crucial factors can be assessed using a variety of experimental methodologies and used as descriptors to create (Q)SAR models, including size, shape, and surface charge **[29]**. It has also been observed that two nanoparticles of the same source, chemical composition, and size may exert very different effects. Hence other factors excluding size and surface area influence the toxic nature. For example, surface coatings. Therefore, nanoinformatics and modeling approaches of machine learning can help in identifying which properties exhibit toxic nature and how exactly they affect an organism. Further information, such as accessible physicochemical properties, solubility, partition coefficients between different solvents, technological conditions, and parameters chosen for manufacturing distinct nanomaterials, can be used to build QSPR models. The development of models can be done through the Online CHEmical Modeling environment (OCHEM) database.

Because OCHEM provides for the seamless integration of classical descriptors and nanoparticle properties, as well as the online publication of data and models, it is ideal for the development and public sharing of data and models for the prediction of nanomaterial toxicity. OCHEM is a platform whose main purpose is to serve as a database for experimentally measured properties and activities of chemical compounds and the development of QSAR/QSPR models. The database module stores data in the original units track users and any modifications they perform to the data and allows the introduction of new units and properties. The database automatically checks for duplicates and allows the editing of single or several records simultaneously. The experimental data uploaded to the database can be simply edited to generate data sets suitable for building predictive QSAR models with a number of machine-learning approaches **[30]**.

One of the key issues that hinder the attempts of computational toxicity approaches to nanotoxicology is the scarcity of consistent and high-quality experimental data. This lack of availability hinders the development of robust and predictive nano (Q)SAR models. The scarcity of such data is mainly caused by a lack of standardized nanotoxicity testing procedures and characterization conditions for physicochemical properties, reflecting that the scientific community is still learning to test ENMs. The establishment of standard protocols is essential for enabling accurate measurement of the physicochemical and biological properties of ENMs. The choice of realistic characterization media/conditions and appropriate toxicity endpoints for ENMs makes accurate measurement of physicochemical and biological properties possible.

The main issues in nanotoxicology continue to be the further application of current testing protocols to NPs, the creation of new ones, validation, storage, systematization, and sharing of the results of numerous studies and projects. The development of reliable and detailed databases of NPs toxicity and ecotoxicity required a combination of many scientific disciplines, such as chemistry, physics, biology, mathematics, statistics, informatics, and other disciplines **[31]**.

CONCLUSION

Biotechnologists are quickly adopting nanotechnology, which is composed of nanoparticles with precisely controllable features, as a key new weapon in their toolbox. Nanostructures will undoubtedly result in new and improved assays and sensing techniques, optically controlled functional materials, highly specific color-coded cellular function probes, and optically based medicinal approaches.

As elucidated by this paper various biologically and physiologically important nanoparticles already exist in the present world. And their usefulness and versatility will ensure an increase in their application in the future world. These nano-sized particles might even occupy a mega-size importance in the coming days. Hence, designing toxicity profiling of nanomaterials is high in demand all over the world. Harmless natural nanomaterials have been existing alongside humans for centuries. But the toxic effects of man-made nanoparticles cannot be ignored. Previously established studies along with upcoming ones elucidate the biological and environmental toxic effects of engineered nanoparticles and nanoparticles produced due to anthropogenic activities.

Every new technology has its own pros and cons. Correct and on-time evaluation of these cons would minimize and assist in anticipating any and every con of this far-reaching nanotechnology.

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