

## Degradation Potential and Nano-Toxicity Assessment

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### Description

Nanotechnology encompasses the study and manipulation of particles at the nanoscale (1–100 nm) level, commonly known as nanoparticles. Nanoparticles have unique mechanical and physicochemical properties due to their increased relative surface area and quantum effects, favoring their usage in various applications. In the past decade, the field of nanotechnology has received considerable attention due to its wide variety of applications being extended to the biotechnology, electronics, aerospace and computer industry. More recently, nanotechnology is also applied to the field of nanomedicine, which covers nanotechnology-based diagnosis, treatment and prevention of human diseases such as cancer, improving human health and well-being. Nanoparticles are frequently used as a tool for drug delivery in nanomedicine. They can be categorized into several different groups such as polymers, inorganic nanoparticles and metallic nanoparticles, depending on their physicochemical properties. Polymers such as polysaccharide chitosan nanoparticles (CS-NPs) function in drug delivery due to their ability to facilitate both protein and drug conjugation. The polymer-protein conjugates enhance protein stability but reduce immunogenicity, whereas the polymer-drug conjugates display enhanced permeability and retention effects. More recently, the polymeric nanoparticle poly-(lactic-co-glycolic acid) (PLGA) has also been used as a nanocarrier for drug delivery across the blood-brain barrier due to its biocompatibility and biodegradability, thereby ensuring safe therapy.

Inorganic ceramic nanoparticles such as silica, titania and alumina are also commonly being used for drug administration for cancer therapy due to their porous nature, although their applications are limited due to their non-biodegradable nature. On the other hand, metallic nanoparticles, including superparamagnetic iron oxide nanoparticles, gold shell nanoparticles and titanium dioxide (TiO<sub>2</sub>) nanoparticles, are routinely used for magnetic resonance imaging contrast enhancement and as cancer drug carrier systems, whereas silver nanoparticles (AgNP) are being explored as antibacterial agents for treatment of infectious diseases, due to their ability to stabilize nanoparticles and favorable optical/chemical properties. Notably, carbon nanoparticles, which are comprised of fullerenes and nanotubes, are the most widely used materials for drug delivery purposes due to the fact that fullerenes contain multiple attachment points responsible for tissue binding, and

nanotubes offer high electrical conductivity and strength. Nanoparticles have been used as a tool for the detection of disease biomarkers in both in vivo and ex vivo diagnostic applications, consequently leading to an advancement of proteomics and genomics technologies. For example, streptavidin-coated fluorescent polystyrene nanospheres offer greater sensitivity in the detection of epidermal growth factor receptor (EGFR) in human carcinoma cells, thus providing a more sensitive tool for biomarker discovery. Furthermore, an ultrasensitive nanoparticle-based assay for the detection of prostate-specific antigen (PSA) in the serum was developed, which can provide up to six orders of magnitude higher sensitivity than the conventional assay. Therefore, nanoparticles have also gained popularity in the field of molecular diagnosis and imaging, due to their favourable physicochemical properties of small particle size, flexibility of surface coating and enhanced stability.

### Toxicity of Nanoparticles

Chemical reaction between solid and liquid phase always initiates at the surface molecules of two phases, hence, the surface molecules can directly influence the chemical reactivity. The average specific surface area of the nano-copper (23.5 nm) used in this study is calculated. In accordance with the collision theory in chemistry, huge specific surface area must lead to a high probability of effective collision, which determined the ultrahigh reactivity during molecular interaction. Some chemical reactions are allowed in sense of chemical thermodynamics but could not happen in sense of reaction kinetics. However, when the particle size reduces to nano-scale, the huge specific surface area will sharply speed up chemical reaction and may eventually cause nanotoxicity that micro-scale substance do not have. Nano-copper particles can quickly interact with H<sup>+</sup> in artificial gastric juice, and be converted into ionic states. Micro-copper particles (17m) have much smaller specific surface area which is about 1/940 to the nano-copper. Relative to nanoparticles, the micro-copper appears chemically inert, because of lower specific surface area.

### Mechanisms Underlying Nanotoxicity

Currently, there is a common assumption that the small size of nanostructures allows them to easily enter tissues, cells,

organelles, and functional biomolecular structures (i.e. DNA, ribosomes) since the actual physical size of an engineered nanostructure is similar to many biological molecules (e.g. antibodies, proteins) and structures (e.g. viruses). A corollary is that the entry of the nanostructures into vital biological systems could cause damage, which could subsequently cause harm to human health. However, a number of recent studies have demonstrated that despite the size of the nanostructures they do not freely go into all biological systems but are instead governed by the functional molecules added to their surfaces. For example, citrate-stabilized gold nanostructures entered the mammalian cells but were not able to enter the cytoplasm or nucleus; whereas one can engineer the nanostructure's surface chemistry for access to the nucleus or mitochondria.

A number of in vivo studies have also shown that nanostructures have difficulty entering the brain, which is protected by the blood–brain barrier, unless aided by tailored surface functionalization. Researchers can now engineer nanostructures to direct the intracellular or in vivo biodistribution but the final metabolic fate is still unknown, and strategies for avoiding secondary unintentional behaviors are lacking. Overall the relationship between size, shape, and surface chemistry of nanostructures and their correlation to intracellular and in vivo bio-distribution is unknown. By contrast, pharmaceutical strategies have developed this sort of relationship for a number of drugs and carriers and thus, they have created predictive categorization which will need to be emulated with nanostructures. Systematically, one cannot predict the movements and location of nanostructures after

intracellular or in vivo exposure based on nanostructure properties at this time, and such studies must be done before one can assess the toxicity of nanostructures in a systematic format.

A systematic and thorough quantitative analysis of the pharmacokinetics (absorption, distribution, metabolism, and excretion; PK) of nanostructures can lead to improvements in design of nanostructures for diagnostic and therapeutic applications, a better understanding of nanostructures non-specificity toward tissues and cell types, and assessments of basic distribution and clearance that serve as the basis in determining their toxicity and future investigative directions. PK gives the quantitative in vivo conditions under which the dose achieves or causes any observed toxic effects. Toxicity to specific cell types can be qualified by PK in that the time and concentrations to which they will be exposed can be determined. Residence time and accumulation locations of the dose and metabolites can be the difference between avoiding and experiencing toxic responses. The overall behavior of nanostructures could be summed as follow: (1) nanostructures can enter the body via six principle routes: intra venous, dermal, subcutaneous, inhalation, intraperitoneal, and oral, (2) absorption can occur where the nanostructures first interact with biological components (proteins, cells), (3) afterward they can distribute to various organs in the body and may remain the same structurally, be modified, or metabolized, (4) they enter the cells of the organ and reside in the cells for an unknown amount of time before leaving.