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Drug Delivery Using Nanotechnology: Advantages and Risks On Human Health.

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ABSTRACT

Nanotechnologies have become a significant priority worldwide. Several manufactured nanoparticles with one dimension less than 100 nm are increasingly used in consumer products. Using nanoparticles, it may be possible to achieve improved delivery of poorly water-soluble drugs by delivering drug in small particle size increase the total surface area of the drugs allowing faster dissolution in blood stream. Faster the dissolution translates in to faster absorption by human body targeted delivery of drugs in a cell- or tissue-specific manner. A nanoparticle has emerged as a promising strategy for the efficient delivery of drugs used for the treatment of some diseases by specific targeting. These carriers are designed in such a way that they are independent in the environments and selective at the pharmacological site. For nanoparticles the situation is different as their size opens the potential for crossing the various biological barriers within the body.Although for pharmaceutical use the current requirements seem to be adequate to detect most of the adverse effects of nanoparticle formulations, it cannot be expected that all aspects of nanoparticle toxicology will be detected. So, probably additional more specific testing would be needed.

Keywords: drug delivery, nanoparticles, toxicology, pharmaceuticals

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INTRODUCTION

Every person has been exposed to nanometer sized foreign particles; we inhale them with every breath, and consume them with every drink. In truth, every organism on Earth continuously encounters nanometer-sized entities. The vast majority causes little ill effect, and goes unnoticed, but occasionally an intruder will cause appreciable harm to the organism. The most advanced of the toxic intruders are viruses, composed as they are of nucleic acid-based structures that allows them to not only interfere with biological systems, but also to parasitically exploit cellular processes to replicate themselves. Among the more benign viruses are the ones causing the familiar human symptoms of the common cold or flu, which are the evident manifestations of biochemical battles occurring between these foreign intruders and our immune systems, whose nanometer sized constituents (chemicals, and proteins) usually destroy and remove the viral invaders. A growing number of recent studies show, however, that nano- and micro-organisms may play a role in many chronic diseases where infections pathogens have not been suspected, diseases that were previously attributed only to genetic factors and lifestyle. Among these diseases are: leukemia (caused by viruses from the Retrovirus and Herpes virus families) [1], cervical cancer (Papilloma virus) [2], liver cancer (Hepatitis virus) [3], gastric ulcer (Helicobacter pylori) [4], nasopharyngeal cancer (Epstein-Barr virus) [5], kidney stones (nanobacteria) [6], severe acquired respiratory syndrome SARS (Corona virus) [7], heart disease (Chlamydia pneumonia) [8], juvenile diabetes (Coxsackie virus) [9], Alzheimer's disease (Chlamydia pneumoniae) [10], pediatric obsessive-compulsive disorder (Streptococcal bacteria) [11], psychotic disorders (Borna virus) [12], and prion diseases such as mad cow disease (proteins - prions) [13].

The misapprehension of nanotoxicity may create a general fear that all nanomaterials are toxic. The online [14] and printed media [15] are inadvertently making no distinction between nanostructured fixed structures, which are not likely to cause harm (such as computer processors), and detachable or free nanoparticles, which are likely to cause adverse health effects. While uncontained nanoparticles clearly represent a serious health threat, fixed nanostructured materials, such as thin film coatings, microchip electronics, and many other existing nanoengineered materials, are known to be virtually benign. Many synthetic nanoparticulate materials produce positive health effects, for example functionalized fullerene chemicals that act as antioxidants. The use of nanoparticles in medical diagnostics and treatment is driven by their safety, as well as utility.

In the present paper we briefly discuss nanoparticles classifications and review the natural and anthropogenic nanoparticle sources together with their associated health effects and treatment. We also present current opinions and research results related to the health implications and toxicology of nanoparticles, and we define exposure pathways, and migration or translocation mechanisms within biological systems, adverse health effects, and treatment.

NANOSTUCTURES USED IN DRUG DELIVERY

Figure 1: Nanoscale dimension structures

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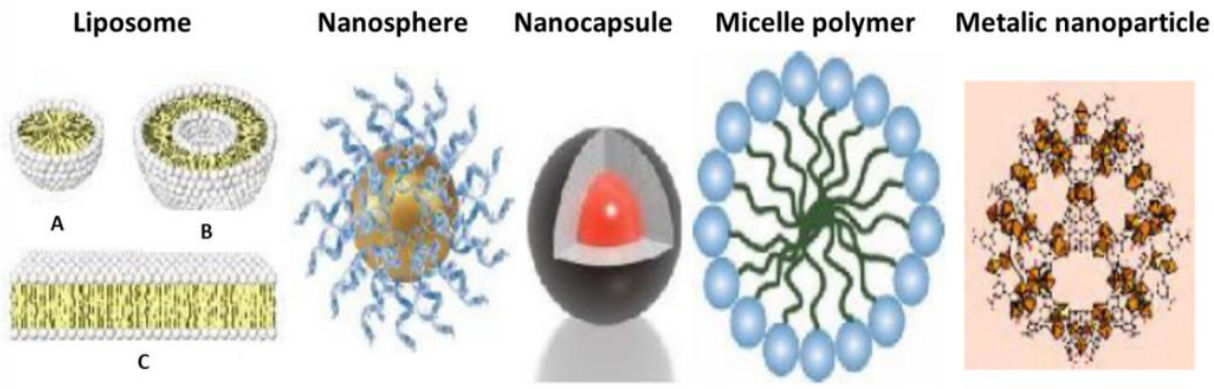

Figure 2: Architecture of nanoparticles. [39]

Interestingly, the products that proudly use the "nano" brand(Fig.1) are only a small percentage of the number of consumer products that actually contain nanotechnologies, for instance in the microelectronics, cosmetics, pharmaceutical and food industries. The field of nanotechnology is vast and interdisciplinary, ranging from medicine and healthcare to construction and consumer electronics. For this reason the definition of "nano" may vary and even among experts no consensus can be found today. The weakest definition of nanotechnology claims the ability to control matter at a level below 100 nm. A more demanding definition requires that new effects or functions have to play a critical role. Structures at the atomic and molecular scale obey rules that strongly differ from those in our macroscopic world, such as quantum effects which give rise to new applications.

Nanomaterials are used as diagnostic and therapeutic agents as well as drug delivery devices. Examples are liposomes, emulsions, polymers etc.(as shown in Fig,2).

Liposomes

Liposomes are the initial nanodrug delivery devices discovered in 1960 with limitation of rapid destruction by hepatic macrophages. They are lipid bilayer membranes having aqueous interior. Liposomes can also be of single lamella of membrane or multilamellar with multiple membranes. The molecules used for their preparations are similar to biological membranes, hence can be used to improve efficacy and safety of different drugs. Active substance if lipid soluble is located in lipid layer while water soluble in aqueous space. Amphotericin and hamycin, the cancer chemotherapeutic agents are delivered by Liposomes. New generation "stealth liposomes" have ability to escape macrophages due to coating and thus have longer half life.[16-20]

Emulsions

These are oil in water type mixtures which are stabilized with surfactant for maintenance shape and size. Active compound is emulsified in water phase. They are used for improving safety and efficacy.[21]

Polymers

These are polymer-drug or protein conjugates which reduce immunogenicity and increases half life. They increases permeability and provide stability to the compound even after endocytosis.[22-23]

Ceramic nanoparticles

These are made of ceramic nanoparticles like silica, titania and aluminia. They are biocompatible and used in cancer chemotherapy but have safety concern as they are nonbiodegradable.[24]

Metallic particles

They are used as active or passive targeting agents. Generally they are supermagnetic in nature, such as iron oxide nanoparticles.[25-26]

Gold shell nanoparticles

These nanomaterials consist of dielectric corewith thin shell of gold or metallic shell. These agents' possess good optical and chemicalproperties useful in biomedical imaging.[25] Nano shells are also useful in cancer chemotherapyand being investigated in diabetes.[27-28]

Carbon nanomaterials

In this group Nanotubes and Fullerenes fall.Nanotubes were discovered in 1991, they are tubular structures like a sheet of graphite rolled into a cylinder capped at one or both ends by a buckyball. They have excellent electrical conductivity and strength. Amphotericin B nanotubes are used in cancer chemotherapy with better efficacy [29-32]. Fullerenes are novel carbon allotrope having numerous points. They are used as diagnostic agents but can stimulate fullerene antibodies. [16,17,33] Carbon 60 (C60), is a three dimensional structure of carbon atoms which is a spherical molecule of about 1 nm in diameter comprising of 60 carbon atoms. The physical properties of fullerene include high hardness, which is harder than steel, and the ability to withstand great pressure. Fullerene finds its uses in lubricants, drug delivery and electronic circuits, solar cells, and sensors.

Quantum dots

They are semiconductor nanomaterials with fluorescent properties. They are used as diagnostic and therapeutic agents [16,34]QDs are nanocrystals made up of semiconductor materials. Nanomaterials do not follow the classical Newtonian principles of physics as does matter in bulk, rather they follow the quantum mechanics where the energy is quantized in packets, because of the confinement of the electronic wave function to the physical dimension of the particle. This phenomenon is referred as quantum confinement. As a result, the optical properties of the particles can be finely tuned depending upon its size. Particles thus can be made to emit or absorb specific wavelength of light by controlling their size. The properties of QDs can be applied in transistors, solar cells, LEDs, laser diodes, medical imaging and diagnostics, quantum computing, etc.

Nanopores

These are high density pores with wafers and allow oxygen, glucose and insulin like materials. But prevents immunoglobulin from passing hence can be used as devices for protection of transplant from host defense system. In diabetic cases, β pancreatic cells can be transplanted by these devices.[35]

Nanobubbles

They are bubbles like nanomaterials in which anticancer drugs can be incorporated. They can selectively target tumor cell under the influence of ultrasound exposure. Rapaport used doxorubicin by this method.[16,36]

Dendrimers

These nonomaterials have regular branching pattern, the number of which can be controlled depending upon the need. It has spherical structures from which branches arise and makes cavities which can be used for transport of drugs in targeted cancer cells.[32] These nanomaterials are nanosized polymers units.[37]There are numerous chain ends which are located on the surface of dendrimers which can be used for various functions such as enhanced chemical reactivity, catalysis, etc. The dendrimers can act as nanoscale carrier molecules for targeted drug delivery. Water filtration is another area where dendrimers can be used for their property of treating metal ions.

Respirocytes

These nanodevices are artificial red blood cells with censors on the surface which can be monitored on computer screen. Have 236 times more oxygen supplying capacity in unit volume and time in comparison to red blood cells.[36]

Microbivores

They are artificial white blood cells having property to circulating microbes in blood stream.[37]

DRUG DELIVERY

In nanotechnology nano particles are used for site specific drug delivery. In this technique the required drug dose is used and side-effects are lowered significantly as the active agent is deposited in the morbid region only. This highly selective approach can reduce costs and pain to the patients. Thus variety of nano particles such as dendrimers, and nano porous materials find application. Micelles obtained from block co-polymers, are used for drug encapsulation(fFig.3) They transport small drug molecules to the desired location. Similarly, nano electromechanical systems are utilized for the active release of drugs. Iron nano particles or gold shells are finding important application in the cancer treatment. A targeted medicine reduces the drug consumption and treatment expenses, making the treatment of patients cost effective. Nano medicines used for drug delivery, are made up of nano scale particles or molecules which can improve drug bioavailability. For maximizing bioavailability both at specific places in the body and over a period of time, molecular targeting is done by nano engineered devices such as nano robots [40]. The molecules are targeted and delivering of drugs is done with cell precision. *In vivo* imaging is another areawhere Nano tools and devises are being developed for *in vivo* imaging.Using nano particle images such as in ultrasound and MRI, nano particles are used as contrast. The nano engineered materials are being developed for effectively treating illnesses and diseases such as cancer. With the advancement of nanotechnology, self-assembled biocompatible nano devices can be created (Fig.4) which will detect the cancerous cells and automatically evaluate the disease, will cure and prepare reports.

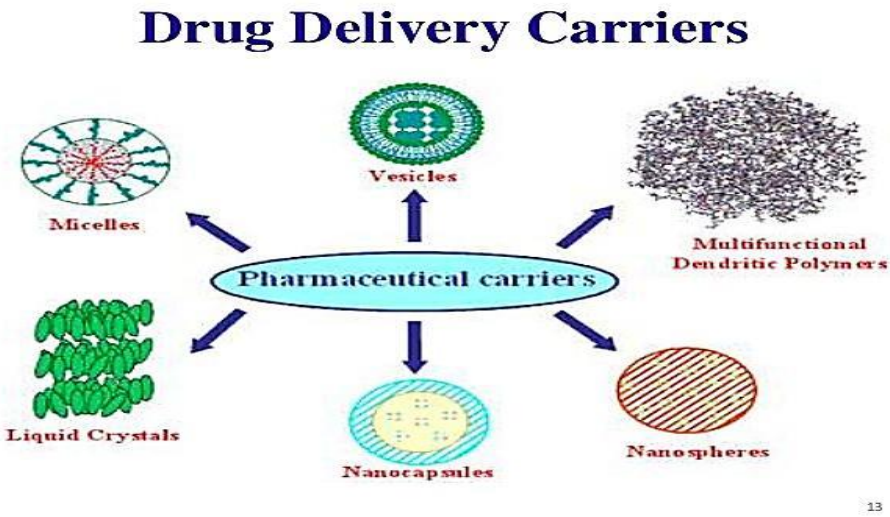

Figure 3: Different Delivery systems with nanostructures.

One is tempted to think that nanoparticles (such as dust, or ash particles), while similar in size to viruses, would be more benign, as these materials lack the viruses' ability to replicate. Nevertheless, while non-replicating bodily intruders do not directly take control of cellular processes, some have been shown to sufficiently interfere with cellular function to influence basic process of cells, such as proliferation, metabolism, and death. Many diseases can be associated with dysfunction of these basic processes, the most notable being cancer (uncontrolled cells proliferation), and neurodegenerative diseases (premature cell

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death). In addition, several diseases with unknown cause, including autoimmune diseases, Crohn's, Alzheimer's, and Parkinson's diseases, appear to be correlated with nanoparticles exposure. Conversely, the toxic properties of some nanoparticles may be beneficial, as they are thereby able to fight disease at a cellular level, and could be used as a medical treatment, by for example targeting and destroying cancerous cells. Very small particles, so-called nanoparticles, have the ability to enter, translocate within, and damage living organisms. This ability results primarily from their small size, which allows them to penetrate physiological barriers, and travel within the circulatory systems of a host.

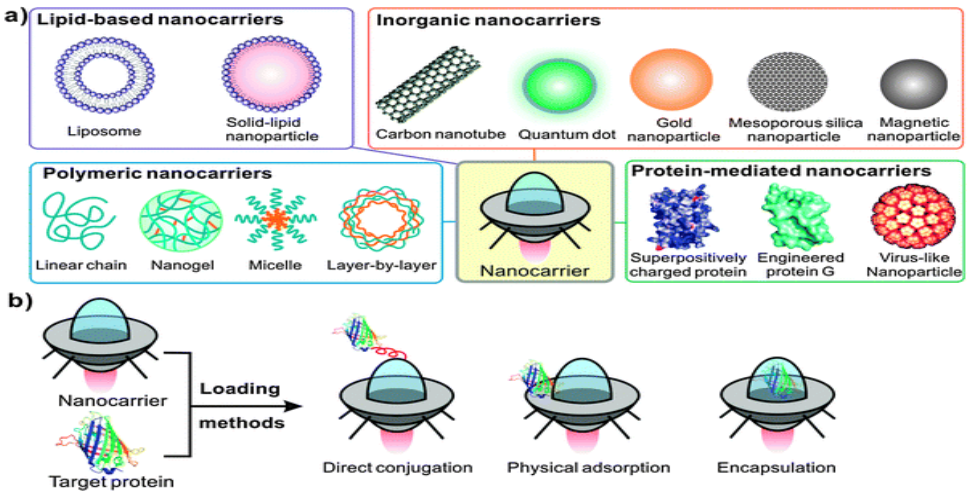

Figure 4: Various Drug carrier systems with nanostructures

While natural processes have produced nanoparticles for eons, modern science has recently learned how to synthesize a bewildering array of artificial materials with structure that is engineered at the atomic scale. The smallest particles contain tens or hundreds of atoms, with dimensions at the scale of nanometers - hence nanoparticles. They are comparable in size to viruses, where the smallest have dimensions of tens of nanometers (for example, a human immunodeficiency virus, or HIV, particle is 100 nm in diameter), and which in the emerging science of nanotechnology might be called 'nano-organisms'. Like viruses, some nanoparticles can penetrate lung or dermal (skin) barriers and enter the circulatory and lymphatic systems of humans and animals, reaching most bodily tissues and organs, and potentially disrupting cellular processes and causing disease.

Table 1: Nanoparticles and Their Applications in Life Sciences [38]

Particle class	Materials	Application
Natural materials or derivatives	Gelatine Liposomes Starch	Drug/Gene delivery
Dendrimers	Branched polymers	Drug delivery
Fullerenes	Carbon based carriers	Photodynamics Drug delivery
Polymer carriers	Polyethyleinemine Block copolymers	Drug/gene delivery
Ferrofluids	SPIONS USPIONS	Imaging (MRI)
Quantum dots	Cd/Zn-selenides	Imaging In vitro diagnostics
Various	Silica-nanoparticles Mixtures of above	Gene delivery

The toxicity of each of these materials depends greatly, however, upon the particular arrangement of its many atoms. Considering all the possible variations in shape and chemistry of even the smallest nanoparticles, with only tens of atoms, yields a huge number of distinct materials with potentially very different physical, and toxicological properties. Asbestos is a good example of a toxic nanomaterial, causing lung cancer and other diseases. Asbestos exists in several forms, with slight variations in shape and chemistry yet significantly varying toxicity. Nanometer sized particles are created in countless physical processes from erosion to combustion, with health risks ranging from lethal to benign. Industrial nanoparticle materials today constitute a tiny but significant pollution source that is, so far, literally buried beneath much larger natural sources and nanoparticle pollution incidental to other human activities, particularly automobile exhaust soot.

The pharmacological and therapeutic properties of drugs can be improved by proper designing of drug delivery systems, by use of lipid and polymer based nano particles [41]. The strength of drug delivery

systems is their ability to alter the pharmacokinetics and biodistribution of the drug. Nano particles are designed to avoid the body's defense mechanisms [42] can be used to improve drug delivery. New, complex drug delivery mechanisms are being developed, which can get drugs through cell membranes and into cell cytoplasm, thereby increasing efficiency. Triggered response is one way for drug molecules to be used more efficiently. Drugs that are placed in the body can activate only on receiving a particular signal. A drug with poor solubility will be replaced by a drug delivery system, having improved solubility due to presence of both hydrophilic and hydrophobic environments [43]. Tissue damage by drug can be prevented with drug delivery, by regulated drug release. With drug delivery systems larger clearance of drug from body can be reduced by altering the pharmacokinetics of the drug. Potential nano drugs will work by very specific and wellunderstood mechanisms; one of the major impacts of nanotechnology and nanoscience will be in leading development of completely new drugs with more useful behavior and less side effects.

Thus nano particles are promising tools for the advancement of drug delivery, as diagnostic sensors and bio imaging. The bio-distribution of these nanoparticles is still imperfect due to the complex host's reactions to nano- and micro sized materials and the difficulty in targeting specific organs in the body. Efforts are made to optimize and better understand the potential and limitations of nano particulate systems.

In the excretory system study of mice dendrimers are encapsulated for drug deliver of positively-charged gold nano particles, which were found to enter the kidneys while negatively-charged gold nanoparticles remained in the important organs like spleen and liver. The positive surface charge of the nanoparticle decreases the rate of opsonization of nanoparticles in the liver, thus affecting the excretory pathway. Due to small size of 5 nm, nano particles can get stored in the peripheral tissues, and therefore can get collected in the body over time. Thus nano particles can be used successfully and efficiently for targeting and distribution, further research can be done on nano toxicity so that its medical uses can be increased and improved [44].

Table 2: Nanosystems and its characteristics.[38]

Chemical composition / Structure	Characteristics	Functions
Functionalized Fullerenes (Buckeyballs) and Carbon Nanotubes	Lack of water solubility	Vehicles for nanodrugs delivery; Contrast agents; Photothermal cancer ablation
Lipossomes	Vesicles composed of a lipid bilayer surrounding a hollow core They can be composed of natural phospholipids or other surfactants	Drugs or other molecules can be loaded for delivery to tumors or other disease sites; Liposomes can carry both hydrophobic and hydrophilic drugs and molecules to a target site
Polymeric Micelles	Made with amphiphilic polymers such as the block copolymers poly(ethyleneglycol)-b-poly(e-caprolactone)(PEG-b-PCL),22 poly(styrene) or PLGA	Commonly used for targeted drug delivery; Deliver poorly water soluble drugs such as paclitaxel and amphotericin B
Polymeric Nanospheres	Uniform spherical structures less than a micron in size made from nonbiodegradable or biodegradable polymers	Effective agents for transdermal drug delivery Diagnose human epidermal growth factor receptor 2 (HER2)-positive and integrin-positive cancer cells *in vitro*
Dendrimers	Large, complex molecules with a well-defined branched chemical structure; Monodisperse, highly symmetric, highly branched, and generally spherical	Allow carriage of drugs or molecules for imaging; Dendrimer-based conventional nanocomposites are been studied as possible antimicrobial agents against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*
Polymer-Coated Nanocrystals	Prevents aggregation and helps in establishing a stable nanosupension	Macrophage-based delivery to sites of HIV infection and sequestration
Nanoshells	Spherical particles consisting of a dielectric core surrounded by a thin metallic shell, most commonly gold	Biomedical imaging and cancer treatment
SPIO Nanoparticles	A core of magnetite or maghemite with a coating of polysaccharides, polymers, or monomers	Iron oxide particles in the range of 1–100 nm possess superparamagnetic properties that make them attractive for biomedical imaging, diagnosis, and therapeutics
Quantum Dots	Semiconductors with spatially confined excitons that afford them unique optical and electrical properties	Their distinct fluorescence spectra make them valuable tools for biomedical imaging

THE APPLICATIONS OF NANO PARTICLES IN DRUG DELIVERY

Abraxane, is albumin bound paclitaxel, a nano particle used for treatment of breast cancer and non-small- cell lung cancer (NSCLC). Nano particles are used to deliver the drug with enhanced effectiveness for treatment for head and neck cancer, in mice model study ,which was carried out at from Rice University and University of Texas MD Anderson Cancer Center. The reported treatment uses Cremophor EL which allows the hydrophobic paclitaxel to be delivered intravenously. When the toxic Cremophor is replaced with carbonnano particles its side effects diminished and drug targeting was much improved and needs a lower dose of the toxic paclitaxel. Nano particle chain was used to deliver the drug doxorubicin to breast cancer cells in a mice study at Case Western Reserve University. The scientists prepared a 100 nm long nano particle chain by chemically linking three magnetic, iron-oxide nano spheres, to one doxorubicinloaded liposome. After penetration of the nano chains inside the tumor magnetic nanoparticles were made to vibrate by generating, radiofrequency field which resulted in the rupture of the liposome, thereby dispersing the drug in its free form throughout the tumor. Tumor growth was halted more effectively by nanotechnology than the standard treatment with doxorubicin and is less harmful to healthy cells as very less doses of doxorubicin were used. Polyethylene glycol (PEG) nano particles carrying payload of antibiotics at its core were used to target bacterial infection more precisely inside the body, as reported by scientists of MIT. The nano delivery of particles, containing a sub-layer of pH sensitive chains of the amino acid histidine, is used to destroy bacteria that have developed resistance to antibiotics because of the targeted high dose and prolonged release of the drug. Nanotechnology can be efficiently used to treat various infectious diseases [45].

Researchers in the Harvard University Wyss Institute have used the biomimetic strategy in a mouse model. Drug coated nano particles were used to dissolve blood clots by selectively binding to the narrowed regions in the blood vessels as the platelets do. Biodegradable nano particle aggregates were coated with tissue plasminogen activator, tPA, were injected intravenously which bind and degrade the blood clots. Due to shear stresses in the vessel narrowing region dissociation of the aggregates occurs and releases the tPA-coated nano particles. The nano therapeutics can be applied greatly to reduce the bleeding, commonly found in standard thrombosis treatment. The researchers in the University of Kentucky have created X-shaped RNA nano particles, which can carry four functional modules. These chemically and thermodynamically stable RNA molecules are able of remaining intact in the mouse body for more than 8 hours and to resist degradation by RNAs in the blood stream. These X-shaped RNA can be effectively performing therapeutic and diagnostic functions. They regulate gene expression and cellular function, and are capable of binding to cancer cells with precision, due to its design [46]. 'Minicell' nano particle are used in early phase clinical trial for drug delivery for treatment of patients with advanced and untreatable cancer. The minicells are built from the membranes of mutant bacteria and were loaded with paclitaxel and coated with cetuximab, antibodies and used for treatment of a variety of cancers. The tumor cells engulf the minicells. Once inside the tumor, the anti-cancer drug destroys the tumor cells. The larger size of minicells plays a better profile in sideeffects. The minicell drug delivery system uses lower dose of drug and has less side-effects can be used to treat a number of different cancers with different anti-cancer drugs. Nano sponges are important tools [47] in drug delivery, due to their small size and porous nature they can bind poorly-soluble drugs within their matrix and improve their bioavailability. They can be made to carry drugs to specific sites, thus help to prevent drug and protein degradation and can prolong drug release in a controlled manner.

5. NANOFOODS AND NANO AGROCHEMICALS POSE NEW HEALTH RISKS

The incorporation of manufactured nanomaterials into foods and beverages, nutritional supplements, food packaging and edible food coatings, fertilisers, pesticides and seed treatments creates a host of new exposure pathways and a whole new array of risks for the public, workers in the food industry and farmers[48]. However, since there is no register of which nanomaterials are used and in what quantity or what food products and food contact materials they are used in[49]. The evidence of potential harm associated with certain nanomaterials has become stronger.

Why nanomaterials pose new risks

•Nanomaterials are generally more chemically reactive than larger particles of the same chemicals
•Nanoparticles have greater access to our bodies than larger particles

- Greater bioavailability and greater bioactivity may introduce new toxicity risks;
- Nanomaterials can compromise our immune system response;
- Nanomaterials may have long term pathological effects.

Absorption through the digestive tract Numerous in vivo experiments using rats and mice have demonstrated gastrointestinal uptake of nanoparticles[50-54] and small microparticles[55-57]. Pathological examination of human tissues suggests(as Shown in Fig.5) ingestion and translocation of microparticles[58-59]. The absorption rate of substances via the gastrointestinal tract appears to depend on their properties such as size and surface structure. In one study looking at rats, the smaller the nanoparticles the higher the uptake via the digestive tract[60]. In another study mice were fed 4 nm gold particles. These were later detected in the liver, kidney, spleen, lung and brain. Larger 58 nm particles remained in the gastrointestinal tract[61]. Studies have shown that nanomaterials may affect the human intestine. When human colon cells were treated with nano-sized polystyrene, which is commonly used in food packaging, these became more permeable to iron[62]. It has been observed that the daily exposure of people in the Western world to submicrometre-sized mineral particles has resulted in 'pigmented cells' loaded with these particles in parts of the intestinal tract. The particles have been observed to be composed of aluminosilicates, titanium dioxide and a small percentage of non-aluminium-containing silicates such as silica (SiO2) and magnesium trisilicate(talc)[53].

Preliminary evidence suggests that existing levels of nanoparticles up to a few hundred nanometres in size in processed food may be associated with rising levels of immune system dysfunction and inflammation of the gastro-intestinal tract, including Crohn's disease[64-67]. Individuals with Crohn's disease or colon cancer have been found with nanomaterials in their intestinal tissue[68]. Nanomaterials in the human body Our bodies' defensive mechanisms are not as effective at removing nanoparticles from our lungs, gastrointestinal tract and organs as they are with larger particles[69]. Nanoparticles are also more adhesive than larger particles to surfaces within our bodies[70]. As a result of these factors and their very small size, nanoparticles are much more likely to be taken up into our cells and tissues than are larger particles. A growing body of evidence demonstrates that some nanomaterials are more toxic per unit of mass than larger particles of the same chemical composition[71-75]. Nanomaterials have been detected in the heart, liver, spleen, lung, kidney, brain and bone marrow. Insoluble nanomaterials may accumulate and remain in the body for extended periods[76]. In one study, particles of 200-300 nm reached the foetus via the placenta. It is not known whether this causes harm to the placenta or the unborn child[77-78]. Currently there is no data on whether it is possible for nanomaterials to pass into breast milk[79]. The cell membrane is no obstacle to nanomaterials penetrating into cells, unlike larger particles. Studiesshow that 30 nm nanoparticles can even penetrate into the nucleus[80]. Non-degradable nanoparticles may lead to long-term health damage, even in the absence of acute toxicity.

A small number of clinical studies suggest that nondegradable nanoparticles and small microparticles which do not provoke an acute toxic response can accumulate in our bodies and over time result in the development of 'nanopathologies', such as granulomas, lesions (areas of damaged cells or tissue), cancer or blood clots[81-82]. The Federal Institute for Risk Assessment and the Federal Environment Agency in Germany believe there is clear evidence that some nanomaterials have greater carcinogenic potential then microscale particles of the same material[83]. Health concerns with nanomaterials in food and food contact materials

NanoSilica

Uses: Used as a 'trickle and flow' aid in powdered food products, as a clearing agent in beer and wine, as a food additive and a food coating.
Health concerns:

- Several recent studies have shown liver toxicity when animals were injected with nanosilica[84]. Animal studies suggest that nanosilica can be absorbed from the gastrointestinal tract as nanoparticles, become systemically available, and accumulate in tissues Some studies suggest that nanosilica can cross the blood-brain barrier and possibly the placenta [85];
- A recent study where rats were fed synthetic amorphous silica (SAS) - a form of nanostructured and that the nanostructured silica accumulated in the spleen[86].

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- Recently a consumer intake of silica from food was estimated at 9.4mg/kg of body weight per day of which 1.8mg/kg body weight per day was estimated to be in the nano size range[87].

Nano-silver

Uses: In the Woodrow Wilson inventory of nano products, silver is the most common nanomaterial mentioned in product descriptions[88]. A recent court case in the US found that the use of nano-silver was 'ubiquitous' and that there was no way for consumers to avoid exposure[89]. Food and food contact products food containers, packaging, cutting boards, salad and collapsible coolers. In agriculture, it is used in poultry production and agricultural and aquacultural disinfectants[90].

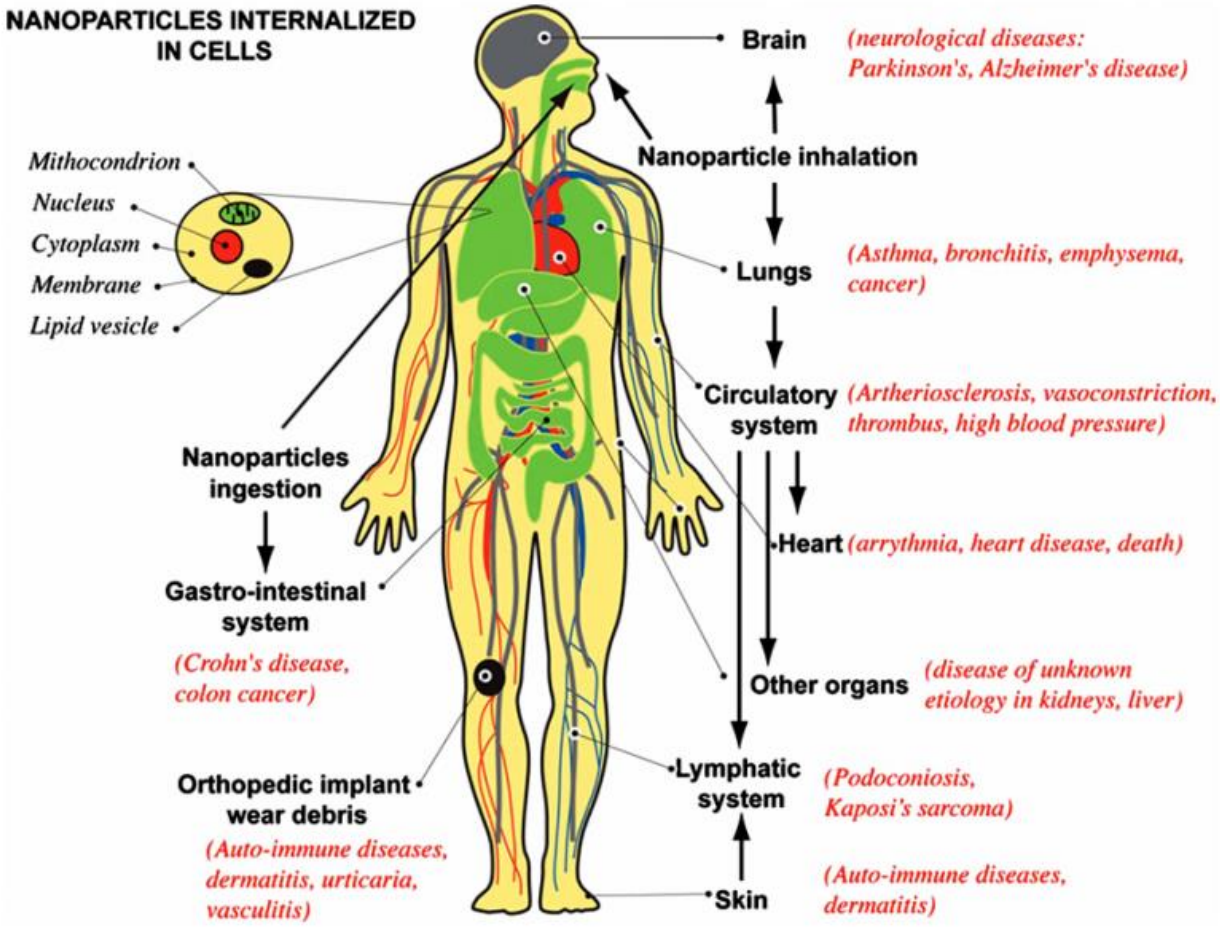

Figure 5: Pathways of exposure with affected organs and associated diseases (reprinted from Buzea et al. 2007) Buzea, C., Pacheco, I. I., and Robbie, K. (2007). "Nanomaterials and nanoparticles: Sources and toxicity." Biointerphases, 2(4), MR17–MR71.

Health concerns:

• There is mounting evidence that nano-silver may have greater toxic effects when compared with bulk silver. Nano-silver can better penetrate biological barriers and attach itself to the outside of cells[91]. Nanoscale silver can also enter the bloodstream and reach all organs of the body including the brain, heart, liver, kidneys, spleen, bone marrow and nervous tissue;

• Animal studies have shown placental transfer and foetal uptake of nano-silver[92]. is disturbing when one considers a recent study which found that exposure to nanosilver widely used as a model organism for the study of embryological development in other vertebrates including humans[93];

• Health experts have also raised concerns that the widespread use of nano-silver in consumer

products will further increase the problem of superbugs[94].

Nano Titanium dioxide

Uses: A whitener and brightener in a range of food products Health concerns:

• ECHA is currently reviewing the safety of titanium dioxide (including the nano form) because of concerns it may be harmful to the environment and human health[95];
• In contrast to bulk particles of titanium dioxide, nanoscale titanium dioxide is biologically very active. Studies show that titanium dioxide can damage DNA[96], disrupt the function of cells, interfere with the defense activities of immune cells and, by adsorbing fragments of bacteria and 'smuggling' them across the gastro-intestinal tract, can provoke inflammation[97-102]. A single high oral dose of titanium dioxide nanoparticles kidneys and livers of female mice;
• In a 2010 study the German Federal Institute for Risk Assessment (BfR) and the German Federal Environment Agency (UBA) concluded that nanoscale titanium dioxide is a possible carcinogen if inhaled[103];
• Nano titanium dioxide is highly mobile in the body and has been detected in both humans and animals in the blood, liver and spleen[104]. A study using pregnant mice found that they transfer nanoparticles of titanium dioxide to their offspring. This resulted in brain damage, nerve system damage and reduced sperm production in male offspring[105];
• A human exposure analysis of titanium dioxide age range as having the highest exposure because the titanium dioxide content of sweets is higher than any other food products. It also calculated that a typical exposure for a US adult may be of the order of 1 mg of titanium per kilogram of body weight per day[105].

Nano Zinc oxide

Uses: Surface coatings

Health Concerns:

• Nanoscale zinc oxide (ZnO) is toxic when ingested and has been found to cause lesions in the liver, pancreas, heart and stomach. A recent review of the safety of nano zinc oxide by the European Safety stated that "clear positive toxic responses in some of these tests clearly indicate a potential for risk to humans."[106] Inhalation exposure of nano zinc oxide induces lung inflammation, leading the SCCS to conclude that "the use of ZnO nanoparticles in spray products cannot be considered safe."[106]

Nano Copper

Uses: dietary supplements[107]

Health Concerns:

• The German Federal Institute for Risk Assessment compared the acute toxicity of micro- and nanoscale copper. No adverse effects were observed with microscale copper – however, nanoscale copper showed adverse effects on the kidney, spleen and liver of mice[108].

Carbon nanotubes

Uses:

food and food contact products containing carbon nanotubes, food packaging and food sensors containing carbon nanotubes have been developed[109-110]. The use of carbon nanotubes in fertilizers is also being researched but does not yet appear to have been commercialized[111].

Health Concerns:

• The Australian National Industrial Chemical and Safe Work Australia, which reviewed the safety of carbon nanotubes, found that multi-walled carbon nanotubes "have been shown to induce mesothelioma in rodents"[112].

Nano supplements

The head of the nanotechnology research group at the United Kingdom's Central Science Laboratory warns of unpredictable effects of nanoparticles and nano encapsulated additives: "They can be absorbed faster than desired or affect the absorption of other nutrients. We still know very little, if anything at all"[113]. In 2009, based on the growing number of commercially available nano supplements, the Woodrow Wilson International Center for Scholars' project on emerging nanotechnologies found that the United States Food and Drug Administration had neither the regulatory supplements were safe[114].

CONCLUSIONS

The use of Nanotechnology in medicine and more specifically drug delivery is set to spread rapidly. For decades pharmaceutical sciences have been using nanoparticles to reduce toxicity and side effects of drugs. Up to recently it was not realized that these carrier systems themselves may impose risks to the patient. The type of hazards that are introduced by using nanoparticles for drug delivery are beyond that posed by conventional hazards imposed by chemicals in delivery matrices. However, so far, the scientific paradigm for the possible (adverse) reactivity of nanoparticles is lacking and we have little understanding of the basics of the interaction of nanoparticles with living cells, organs and organisms. A conceptual understanding of biological responses to nanomaterials is needed to develop and apply safe nanomaterials in drug delivery in the future. Furthermore a close collaboration between those working in drug delivery and particle toxicology is necessary for the exchange of concepts, methods and know-how to move this issue ahead.

Nanoparticles have potential applications in the field of medical sciences including new diagnostic tools, imaging agents & methods, targeted drug delivery, pharmaceuticals, bio implants and tissue engineering. Drugs with high toxic potential like cancer chemotherapeutic drugs can be given with better safety profile with the utility of nanotechnology. A single molecule of drug can be assisted to reach the desired site in order to reduce the side effects of the dose and its quantity. Quantum dots with MRI can produce excellent pictures of a tumor. Gold nanoshells can be used to detect, find, accumulate, and potentially destroy the tumor by heating the Nanoparticles. In the future, we can visualize a world with medical nanodevices, implanted or even injected into the body. A global perspective and collaboration might be needed in the field of research &development to give such benefits to mankind.

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