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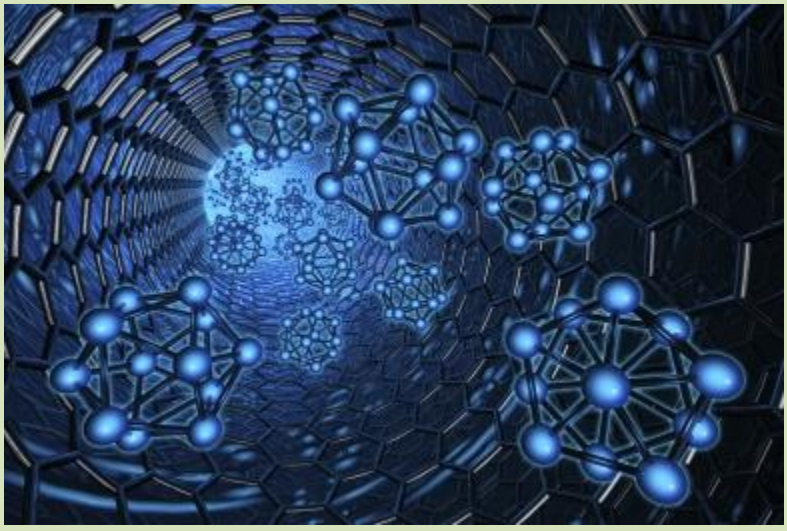
Special Issue on Nonmaterial Toxicity



CSIR- Indian Institute of Toxicology Research
Lucknow, India

IN THIS ISSUE

EDITORIAL

Nanotechnology, relating to the establishment and application of objects ranging between 1 and 100 nanometers, has evolved from an recent technology to one applicable in many environments and products (Colvin, 2003). Today, nano-scale metals oxide (zinc oxides) are consume in various products like sunscreen lotions and scratch-resistant glass while carbon nanotubes(CNT's) are integrated into tennis rackets, and nano-engineered chemical were used for the treatments on fabrics to render them stain-resistant (Bergeson and Auerbach, 2004).

The National Science Foundation has predicted that nanotechnology applications may be valued at more than 1 trillion dollars in the global economy by 2015 (Bergeson and Auerbach, 2004). From other side to consumer products, nanomaterials are also being tested for medical and environmental uses. In 2004, the University of Texas Health Science Center at Houston joined with C Sixty, Inc., a pioneering biopharmaceutical company, to know the use of fullerenes in the delivery of anesthesia and contrast imaging dyes (Mervill, 2003). At present, nanomaterials, super paramagnetic iron oxide particles, are believed to be able to permit for the recognition of cancer earlier than traditional diagnostic tools (Medical and Pharmaceutical Applications for Nanomaterials and Nanoparticles). Furthermore, nanotechnology offers potential in the area of ecological forecasting through computerized sensors the size of dust particles that can relay information on the slightest pollutants.

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Toxicity and Bioaccumulation of Nanomaterial in Aquatic Species

With applications in consumer products, medicine, and the environment, nanotechnology is expected to grow into a one trillion dollar industry. Environmental exposure to nanoparticles, already used in 700 products ranging from stain-free clothing to sunscreens and cosmetics, is steadily increasing. Such a burgeoning technology, however, has many potential negative effects, as little is known about the toxicity and bioaccumulation of nanoparticles, especially in aquatic environments.

A better understanding of these particles can mitigate environmental devastation before this technology fully develops. This project investigated the effects of nano-scale zinc oxide (ZnO) and carbon fullerenes (C60) on Chlamydomonas reinhardtii, green alga, and Daphnia magna, water fleas. Both organisms are model organisms for a toxicology test; more importantly, C. reinhardtii is a natural food of D. magna, making a bioaccumulation study possible. Algae, in general, play an integral role in the ecological system, producing the biomass that forms the basic nourishment for food webs and much of the oxygen humans breathe. Thus large alga population changes due to nanoparticle toxicity will have negative effects on the entire environment.

Three different toxicity tests were conducted: two toxicology tests in which particles were directly introduced in the environments of C. reinhardtii and D. magna and a third test for bioaccumulation of nanoparticles from the alga to the Daphnia. The organisms were treated with nanoparticles, first sonicated to minimize aggregation, at 1, 5, and 10 parts per million (ppm), regular-ZnO or C12, or no particles at all. In the bioaccumulation test some Daphnia were fed nano-treated alga in fresh water while others fed fresh alga with nano-treated water to pinpoint the method of transfer.

The toxicity tests concluded that nano-ZnO and C60 were more toxic to the organisms than regular-sized particles. More alga death occurred at 1ppm of nano-ZnO and C60 as compared to 10 ppm of regular-sized particles; similar results occurred with the Daphnia. The alga data also revealed that zinc oxide was more toxic than carbon, a factor probably due to the higher solubility of the former. The most important result was that the effects of nanoparticles were greatest in the long-term. At 10ppm of nanoparticles, alga populations were never able to recover. Studies so far have only focused on the short-term toxicity of these particles, in accordance with the Environmental Protection Agency's (EPA's) acute toxicity tests. Yet, a long-term study may be more practical in expanding our understanding, as these particles are unlikely to leave the environment after exposure. The data from the bioaccumulation test indicated that a transfer of

nanomaterials from the alga to the Daphnia occurred, primarily through water but also through the alga, but the trend is not conclusive. Modifications in experimental design such as monitoring the Daphnia over a longer period of time may result in a better understanding of the bioaccumulation of nanoparticles and their chronic effects on organisms.

[Journal of the U.S. SJWP (2007)1:01]

Ecotoxicity of selected nano-materials to aquatic organisms.

Present knowledge concerning the ecotoxic effects of nano-materials is very limited and merits to be documented more fully. For this purpose, we appraised the toxicity of nine metallic nano-powders (copper zinc iron oxide, nickel zinc iron oxide, yttrium iron oxide, titanium dioxide, strontium ferrite, indium tin oxide, samarium oxide, erbium oxide, and holmium oxide) and of two organic nano- powders (fullerene-C60 and single-walled carbon nanotube or SWCNT). After a simple process where nano-powders (NPs) were prepared in aqueous solution and filtered, they were then bioassayed across several taxonomic groups including decomposers (bacteria), primary producers (micro-algae), as well as primary and secondary consumers (micro-invertebrates and fish). Toxicity data generated on the 11 NPs reflected a wide spectrum of sensitivity that was biological level-, test-, and endpoint-specific. With all acute and chronic tests confounded for these 11 NPs, toxicity responses spanned over three orders of magnitude: >463 mg/L (24 h LC50 of the invertebrate Thamnoplatyurus platyurus for fullerene-C60) / 0.3 mg/L (96 h EC50 of the invertebrate Hydra attenuata for indium tin oxide), that is a ratio of 1543. On the basis of the MARA (Microbial Array for Risk Assessment) assay toxic fingerprint concept, it is intimated that NPs may have different modes of toxic action. When mixed in a 1:1 ratio with a certified reference material (CRM) sediment, two solid phase assays and an elutriate assay, respectively, showed that five NPs (copper zinc iron oxide, samarium oxide, erbium oxide, holmium oxide, and SWCNT) were able to increase both CRM sediment toxicity and its elutriate toxicity. This initial investigation suggests that chemicals emerging from nanotechnology may pose a risk to aquatic life in water column and sediment compartments and that further studies on their adverse effects are to be encouraged.

[Environ Toxicol. 2008 Oct;23(5):591-8.]

Mapping the Dawn of Nanoecotoxicological Research

Some researchers consider nanotechnology the next industrial revolution, and consumer products and a variety of industries increasingly use synthetic nanoparticles. In this Account, we review the initial accomplishments of

nanoecotoxicology, a discipline that is just a decade old. This new subdiscipline of ecotoxicology faces two important and challenging problems: the analysis of the safety of nanotechnologies in the natural environment and the promotion of sustainable development while mitigating the potential pitfalls of innovative nanotechnologies. In this Account, we provide a snapshot of the publicly available scientific information regarding the ecotoxicity of engineered nanoparticles. We pay special attention to information relevant to aquatic freshwater species commonly used for risk assessment and regulation. Just as the development of ecotoxicology has lagged behind that of toxicology, nanoecotoxicological research has developed much more slowly than nanotoxicology. Although the first nanotoxicolology papers were published in 1990s, the first nanoecotoxicology papers came out in 2006. A meta-analysis of scientific publications covering different environmental impacts of nanomaterials showed that the importance of research into the environmental impact of nanotechnology has gradually increased since 2005. Now the most frequently cited papers in the environmental disciplines are often those that focus on synthetic nanoparticles. The first nanoecotoxicology studies focused on adverse effects of nanoparticles on fish, algae and daphnids, which are ecotoxicological model organisms for classification and labeling of chemicals (these model organisms are also used in the EU chemical safety policy adopted in 2007: Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH)). Based on our experience, we propose a multitrophic battery of nanoecotoxicological testing that includes particle-feeding and a priori particle-"proof" prokaryotic and eukaryotic organisms at different food-chain levels. Using this battery of selected test organisms, we demonstrated that TiO(2) nanoparticles were toxic to algae and that ZnO and CuO nanoparticles were toxic to several aquatic invertebrate test species. Thus, one single biotest cannot predict the ecotoxicological effects of chemicals/nanoparticles, and researchers should use several tests instead. Moreover, produced nanoparticles usually vary in features such as size, shape, and coating; therefore, a single nanoparticle species may actually include many entities with different physicochemical properties. An ecotoxicity analysis of all these variants would require a huge number of laboratory tests. To address these issues, high throughput bioassays and computational (QSAR) models that serve as powerful alternatives to conventional (eco)toxicity testing must be implemented to handle both the diversity of nanomaterials and the complexity of ecosystems.
[Acc Chem Res. 2012 Nov 13]

A study of the mechanism of in vitro cytotoxicity of metal oxide nanoparticles

using catfish primary hepatocytes and human HepG2 cells

Nanoparticles (NPs), including nanometal oxides, are being used in diverse applications such as medicine, clothing, cosmetics and food. In order to promote the safe development of nanotechnology, it is essential to assess the potential adverse health consequences associated with human exposure. The liver is a target site for NP toxicity, due to NP accumulation within it after ingestion, inhalation or absorption. The toxicity of nano-ZnO, TiO(2), CuO and Co(3)O(4) was investigated using a primary culture of channel catfish hepatocytes and human HepG2 cells as in vitro model systems for assessing the impact of metal oxide NPs on human and environmental health. Some mechanisms of nanotoxicity were determined by using phase contrast inverted microscopy, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays, reactive oxygen species (ROS) assays, and flow cytometric assays. Nano-CuO and ZnO showed significant toxicity in both HepG2 cells and catfish primary hepatocytes. The results demonstrate that HepG2 cells are more sensitive than catfish primary hepatocytes to the toxicity of metal oxide NPs. The overall ranking of the toxicity of metal oxides to the test cells is as follows: TiO(2)<Co(3)O(4)<ZnO<CuO. The toxicity is due not only to ROS-induced cell death, but also to damages to cell and mitochondrial membranes.
[Sci Total Environ. 2011 Oct 15;409(22):4753-62]

Copper oxide nanoparticles are highly toxic: a comparison between metal oxide nanoparticles and carbon nanotubes

Since the manufacture and use of nanoparticles are increasing, humans are more likely to be exposed occupationally or via consumer products and the environment. However, so far toxicity data for most manufactured nanoparticles are limited. The aim of this study was to investigate and compare different nanoparticles and nanotubes regarding cytotoxicity and ability to cause DNA damage and oxidative stress. The study was focused on different metal oxide particles (CuO, TiO2, ZnO, CuZnFe2O4, Fe3O4, Fe2O3), and the toxicity was compared to that of carbon nanoparticles and multiwalled carbon nanotubes (MWCNT). The human lung epithelial cell line A549 was exposed to the particles, and cytotoxicity was analyzed using trypan blue staining. DNA damage and oxidative lesions were determined using the comet assay, and intracellular production of reactive oxygen species (ROS) was measured using the oxidation-sensitive fluoroprobe 2',7'-dichlorofluorescin diacetate (DCFH-DA). The results showed that there was a high variation among different nanoparticles concerning their ability to cause toxic effects. CuO nanoparticles were most potent regarding cytotoxicity and DNA damage. The toxicity was

likely not explained by Cu ions released to the cell medium. These particles also caused oxidative lesions and were the only particles that induced an almost significant increase ($p = 0.058$) in intracellular ROS. ZnO showed effects on cell viability as well as DNA damage, whereas the TiO2 particles (a mix of rutile and anatase) only caused DNA damage. For iron oxide particles (Fe3O4, Fe2O3), no or low toxicity was observed, but CuZnFe2O4 particles were rather potent in inducing DNA lesions. Finally, the carbon nanotubes showed cytotoxic effects and caused DNA damage in the lowest dose tested. The effects were not explained by soluble metal impurities. In conclusion, this study highlights the in vitro toxicity of CuO nanoparticles.
[Chem Res Toxicol. 2008 Sep;21(9):1726-32]

DID YOU KNOW?

1) NANOMATERIAL Sare a diverse class of small-scale substances that have structural components smaller than 1 micrometer (1000 nanometers (nm)) in at least one dimension. NMs include nanoparticles (NPs) which are particles with at least two dimensions between approximately 1 and 100 nm in the nanoscale (EPA 2008a; Luoma 2008).

2) NANOMATERIALS can be categorized into three types according to their source: natural, incidental, and engineered.

3) Due to their novel nanoscale size, NANOMATERIALS may possess unique chemical, biological, and physical properties as compared to larger particles of the same material (Keiner 2008).

4) More than 1,000 consumer products that contain NMs are on the market today (WWIC 2011).

How can nanomaterials impact the environment?

1. NMs in solid wastes, wastewater effluents, direct discharges, or accidental spillages may be transported to aquatic systems by wind or rainwater runoff (Klaine et al. 2008).

2. NPs fate and transport in the environment are largely dependent on material properties such as surface chemistry, particle size, and biological and abiotic processes in environmental media. Depending on these properties, NPs may stay in suspension as individual particles, aggregate forming larger sized NMs, dissolve, or react with other materials (Luoma 2008).

3. Because of their small size and slower rate of gravitational settling, some NMs may remain suspended in air and water for longer periods and may be readily transported over much greater distances than larger particles of the same material (EPA 2007; 2009).

4. The mobility of NMs in porous media is influenced by their ability to attach to mineral surfaces to form aggregates. For example, NMs that readily attach to mineral surfaces may be less mobile in ground water aquifers (Wiesner et al. 2006); smaller NMs that can fit into the interlayer spaces between soil

particles may travel longer distances before becoming trapped in the soil matrix (EPA 2007); and soils with high clay content tend to stabilize NMs and allow greater dispersal (EPA 2008a).

5. The surface chemistry and therefore the mobility of NMs in porous media may be affected through the addition of surface coatings. For example, TiO2 can be harmless in soil, but could be problematic in water once a surface coating is added (Lubick 2008).

Some of the genotoxicity studies related to the exposure of carbon nanotubes.

Size	**Form**	**System**	**Summary of findings**	**Reference**
0.7 nm, 0.9–1.7 nm	spheres	Oral administration at doses of 0.064 and 0.64mg/kg of body weight. 8-OHdG analysis	Both NPs were associated with increase in 8-oxoguanine DNA glycosylase in liver and lungs.	Folkmann et al., 2009
SWCNT (D <2 nm x L 4-15μm) and MWCNT (D 10-30 nm x L 1-2 μm)	nanotubes	Oral administration and urinary samples collected for Ames test	No urinary mutagenicity, single-walled and multiwalled CNTs deposited in the lung induced an acute lung and systemic effect, which was more pronounced in the MWCNT exposure	Szendi and Varga, 2008
(D) 0.8–1.2 nm, (L) 0.1–1 μm	nanotubes	Pharyngeal deposition in C57Bl/6 mice lung (40 μg/mouse). Observation 4 hours post exposure	Gene expression in lung and blood: Upregulation of genes involved in inflammation, oxidative stress, coagulation, tissue remodeling. Increased percentage of polymorphonuclear leucocytes (PMN) in	Erdely et al., 2009

			blood and bronchoalveolar lavage (BAL).	
(D) 240 nm, (L) 4.2 μm	nanotubes	(A) Inhalation (4 days) in mice – 5 mg/m 3 Short and mean term responses (1, 7, 28 days), (B) Laryngeal deposition (10 μg/mouse). Short and mean term responses (1, 7, 28 days)	(A) Lung analysis: Inflammation – Granulomas – Fibrosis – Mutation of K-ras. (B) Lung analysis: Inflammation – Granulomas – Fibrosis -No mutation of K-ras. Lower effects compared to inhalation.	Shvedova et al., 2008
(D) 40–60 nm, (L) 0.5–500 μm	nanotubes	Intratracheal deposition in rats. One to 7 mg/kg. Short/mean term responses (1 to 90 days)	Inflammation; dose-dependent thickening of the alveolar lining Particles still present after 3 months	Liu et al., 2008
(D) 1.8 nm, (L)4.4 μm	nanotubes	SWCNTs (1.0 mg/kg) or repeated intratracheal instillation (0.2 mg/kg) once a week for five weeks	Inflammatory response (hemorrhage in the alveolus, infiltration of alveolar macrophages and neutrophiles), but no DNA damage, in the lungs in rats and SWCNTs were not genotoxic in the comet assay following intratracheal instillation in rats.	Naya et al., 2012
(D) 44 nm (D) 70 nm	nanotubes	*in vivo* micronucleus test. 0.3% CMC-Na aqueous solution at 1 mg/mL, ultrasonicated for 5 min, then diluted with the 0.3% CMC-Na solution to reach	The in vivo mammalian erythrocytes micronucleus test revealed the negative outcome for MWCNTs, These findings showed that MWCNTs appear	Ema et al., 2012

		the intended concentrations	not to pose a genotoxic risk to human health	
(D) 8 nm (L) 5 μm	nanotubes	the cytotoxicity, genotoxicity and oxidative effects of particles on primary mouse embryo fibroblast cells	Oxidative stress may be a key route in inducing the cytotoxicity of nanoparticles. Compared with ZnO nanoparticles, carbon nanotubes were moderately cytotoxic but induced more DNA damage determined by the comet assay	Yang et al., 2009
(D) 1.2–1.5 nm (L) 2–5 μm (D) 10–30 nm (L) 0.5–50 μm	nanotubes	The mouse macrophage RAW 264.7 cells treated with CNTs (10 μg/ml) for 24, 48 or 72 h	CNTs increase ROS production.Protracted oxidative stress may cause direct oxidative DNA damage, cytotoxicity and necrosis.ROS participate in cellular signaling, lead to apoptosis and cell cycle arrest.	Di Giorgio et al., 2011
(D) 10–15 nm (L) ~20 μm	nanotubes	Eight-week-old rats were divided into four groups (10 rats in each group), the fresh-air control (0mg/m3), low-concentration group (0.16mg/m3), middle-concentration group (0.34mg/m3), and high-concentration group (0.94mg/m3), and the whole body was exposed to MWCNTs for 5 days	MWCNTs caused a statistically significant increase in lung DNA damage at high concentration (0.94mg/m3) when compared with the negative control group on day 0 and 1 month postexposure	Kim et al., 2012

		(6h/day)		
(D) 400–800 nm, (L) 1–3 μm and (L) 5–30 μm	nanotubes	human bronchial epithelial (BEAS−2B) and lymphoblastoid (MCL-5) cells were treated with SWCNT for 24 or 48 h	Significant increases in micronucleus frequency in a time- and dose-dependent manner in both cell types in the absence of cytotoxicity	Manshian et al., 2012

ON THE LIGHTER SIDE

1) Why do chemists call He, Cm and Ba the medical elements? Because if you can't helium or curium, you barium.

2) Two atoms bump into each other.' I think I lost an electron.' The other asks: 'Are you sure?' The first replies: 'I'm positive.'

3) What did the chemist say when he found two isotopes of Helium? 'HeHe'.

4) Gold walks into a bar, barman shouts Au get out of here!

5) Why did the white bear dissolve in water? Because it was polar.

6) Last night a hypnotist convinced me I was a soft, malleable metal with an atomic number of 82. I'm easily lead.

7) What weapon can you make from the chemicals potassium, nickel and iron? A: KNiFe.

8) Two men walk into a bar, the first orders some H_2O. The 2nd one says 'sounds good, i'll have some H_2O too'. The second man died.

ON THE WEB

1) http://ec.europa.eu/health/scientific_committees/opinions_layman/nanomaterials/en/
2) https://www.sussex.ac.uk/webteam/gateway/file.php?name=sewp180&site=25
3) http://www.epa.gov/
4) http://nano.materials.drexel.edu/

5) http://as.wiley.com/WileyCDA/WileyTitle/productCd-0470746408.html
6) http://english.ihep.cas.cn/rh/KL/nano/
7) http://english.ihep.cas.cn/rh/KL/nano/

CONFERENCES

1) **The 8th Global Conference on Health Promotion (8GCHP)** 10-14 June 2013, Finlandia Hall, Helsinki, FinlandSee also: visiting programme for HiAP-attendees

2) **Work, Wellbeing and Wealth: Active Ageing at Work**
26-28 August 2013, Hotel Crowne Plaza, Helsinki, Finland

3) **International Symposium on Culture of prevention - future approaches** 25-27 September 2013, Helsinki Congress Paasitorni, Finland

4) **European Seminar on Personal Protective Equipment (PPE)** 28-30 January 2014, Rovaniemi, Finland

5) **International Conference on Monitoring and Surveillance of Asbestos-Related Diseases**11–13 February 2014, Hanasaari Cultural Center, Espoo, Finland

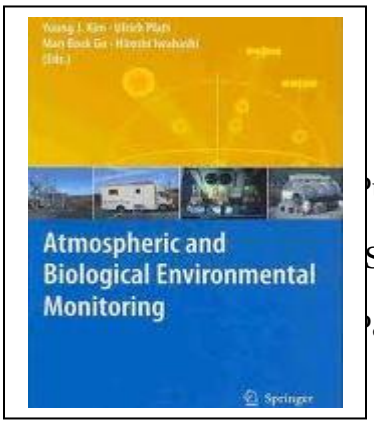
PREVIOUS CONFERENCES

1. EU-US Bridging NanoEHS Research Efforts - A Joint Workshop 2012 25 - 26 October 2012, Finnish Institute of Occupational Health, Helsinki, Finland

2. SENN2012 - International Congress on Safety of Engineered Nanoparticles and Nanotechnologies 28–31 October 2012, Marina Congress Centre, Helsinki, Finland

3. 3rd Barents Occupational Health Workshop 9 - 11 October 2012, Finnish Institute of Occupational Health, Oulu, Finland

BOOK STOP



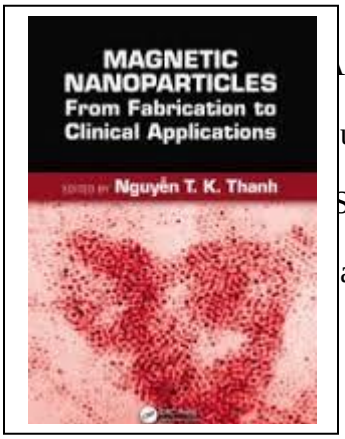
Author(s): Young Joon Kim, Ulrich Platt, Man Bock. Gu

Publisher: Springer Science+Business Media, B.V.

ISBN: 978-1-4020-9673-0

Pages : 311

The harmful impacts of pollution on atmospheric, terrestrial and aquatic environments can cause extreme temperature changes, clean water shortage, and increase toxicity. This book studies environmental pollution impacts, from the mechanism of toxic nanoparticles on the molecular level to the detection of trace gas on the satellite perspective. It presents recent developments in advanced monitoring techniques, efficient process technologies and health impact assessment tools, from environmental scientists of diversified fields. The three sections highlight important aspects of emerging monitoring technologies in Atmospheric Environment, Contaminants Control Process and Environmental Toxicity Assessment.



Author(s): Nguyễn Thi Kim Thanh

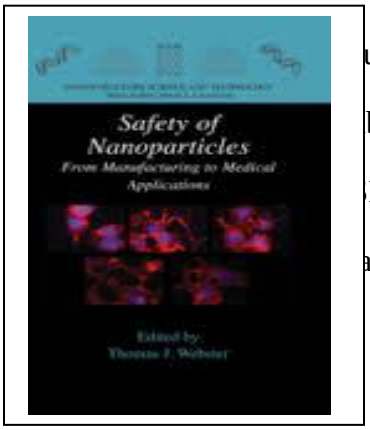
Publisher: CRC Press, Taylor & Francis Group

ISBN: 978-1-4398-6933-8

Pages: 575

Offering the latest information in magnetic nanoparticle (MNP) research, Magnetic Nanoparticles: From Fabrication to Clinical Applications provides a comprehensive review, from synthesis, characterization, and biofunctionalization to clinical applications of MNPs, including

the diagnosis and treatment of cancers.This book, written by some of the most qualified experts in the field, not only fills a hole in the literature, but also bridges the gaps between all the different areas in this field.



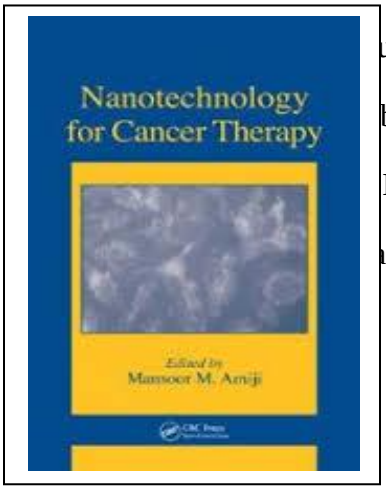
uthor(s): Thomas J. Webster

blisher: Springer Science+Business Media, LLC

BN: 978-0-387-78607-0

ges: 239

In spite of the potential use of nanomaterials as tissue engineering devices, implants, biosensors, and drug delivery devices, there has yet to be a compilation of the risks associated with the in vivo use of nanomaterials. This book intends to provide detailed views of how cells and tissues in the body deal with nanoparticles.



uthor(s): Mansoor M. Amiji

blisher: CRC Press, Taylor & Francis Group

BN: 978-0-8493-7194-3

ges: 840

While simultaneous breakthroughs occurring in molecular biology and nanoscience/technology will ultimately revolutionize all of medicine, it is with our efforts to prevent, diagnose, and treat cancer that many of the most dramatic advances will occur. In support of this potential, the U.S. National Cancer Institute (NCI) established the Alliance for Nanotechnology in Cancer in 2004 and pledged $144.3 million in funding over the next five years.

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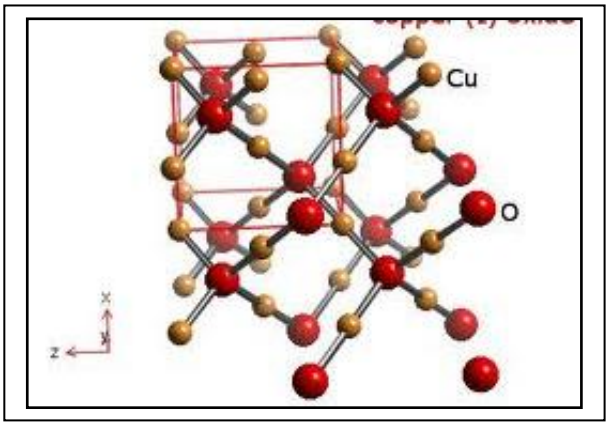
Mini Profile of COPPER OXIDE

NAME OF CHEMICAL: COPPER OXIDE

SYNONYMS: Copper (II) Oxide, Black Copper Oxide, Cupric Oxide



CASRN: 1317-38-0

MOLECULAR FORMULA: CuO

COLOUR/FORM: Black

ODOUR/TASTE: Odorless

PARTICLE SIZE: 200 mesh (98%)

APPEARANCE: Black crystalline powder

PHYSICAL STATE: Solid

M.P.: 1232˚C

SPECIFIC GRAVITY: 6.4 (H2O = 1)

HAZARDS:

Potential Health Effects: Other Health Effects

Persons with hereditary Wilson ’s disease have an abnormally high level of copper in their system. Individuals with this disease exposed to this product may accumulate very high levels of copper may suffer liver pathology, which can be fatal. Episodes of intravascular hemolysis have been observed.

HAZARD RATING:

Health: 2

Fire: 0

Reactivity: 0

TOXICITY DATA:

Acute Toxicity Oral (Rat): Harmful if swallowed – may cause nausea, chills or diarrhea. ORL-RAT LD50: 470 mg/kg

Route	Symptoms	First aid	Target organ
Inh. **&** **Ing.**	Cough, sore throat, shortness of breath, irritation, salivation, nausea, vomiting, gastric pain, diarrhoea and possible hemorrhagic gastritis.	**Ingestion:** Harmful or fatal if swallowed. May cause gastrointestinal irritation with symptoms such as nausea, vomiting, and diarrhea. Copper Oxide is less toxic than more soluble copper salts, such as copper sulfates. Except for occasional acute incidents of copper poisoning, few effects are noted in normal human populations. Effects of single exposure following suicidal or accidental oral exposure have been reported as metallic taste, epigastric pain, headache, nausea, dizziness, vomiting and diarrhea, tachycardia, respiratory difficulty, hemolytic anemia, hematuria, massive gastrointestinal bleeding, liver and kidney failure, and death. In cases of fatal ingestion, death is preceded by gastric hemorrhage, tachycardia, hypotension, hemolytic crisis, convulsions and paralysis. **Inhalation:** May irritate the nose, throat and respiratory tract. Symptoms can include sore throat, coughing and shortness	Respiratory system

		of breath. In severe cases, ulceration and perforation of the nasal septum can occur. If this material is heated, inhalation of fumes may lead to development of metal fume fever. This is a flu-like illness with symptoms of metallic taste, fever and chills, aches, chest tightness and cough. Repeated inhalation exposure can cause shrinking of the lining of the inner nose.	
Cont.	Irritation, redness, itching, pain, conjunctivitis, ulceration or clouding of the cornea.	**Eyes** Exposure to particulates or solution of this product may cause redness and pain. Prolonged contact may cause conjunctivitis, and corneal abnormalities. **Skin** This product can cause irritation of the skin with pain, itching and redness. Prolonged exposure may cause dermatitis, eczema and skin discoloration. Dermal exposure has not been associated with systemic toxicity but copper may induce allergic responses in sensitive individuals.	Skin & Eyes Eye

PERSONAL PROTECTIVE EQUIPMENT: Avoid contact with eyes, skin and clothing. Wear chemical splash goggles, chemical-resistant gloves and chemical-resistant apron.

Use ventilation to keep airborne concentrations below exposure limits. Always wear a NIOSH-approved respirator with proper cartridges or a positive pressure, air-supplied respirator when handling this material in emergency situations (spill or fire).

STORAGE: Keep container tightly closed when not in use. Store containers in a cool, dry location, away from direct sunlight, sources of intense heat, or where freezing is possible. Material should be stored in secondary containers or in a diked area, as appropriate. Store containers away from incompatible chemicals (see Section 10, Stability and Reactivity). Storage areas should be made of fire resistant materials. Post warning and "NO SMOKING" signs in storage and use areas, as appropriate. Use corrosion-resistant structural materials, lighting, and ventilation systems in the storage area. Floors should be sealed to prevent absorption of this material. Have appropriate extinguishing equipment in the storage area (i.e., sprinkler system, portable fire extinguishers). Empty containers may contain residual particulates; therefore, empty containers should be handled with care. Do not cut, grind, weld, or drill near this container. Never store food, feed, or drinking water in containers that held this product. Keep this material away from food, drink and animal feed. Inspect all incoming containers before storage, to ensure containers are properly labeled and not damaged. Do not store this material in open or unlabeled containers. Limit quantity of material stored. Store in suitable containers that are corrosion-resistant.