



**NANOPARTICLES**  
*Selected Abstracts*  
**2007**

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**EXTENDED RESEARCH RESULTS:  
NANOTECHNOLOGY & HAZARD ASSESSMENT 2007 PAPERS**

***MEETING REPORT: HAZARD ASSESSMENT FOR NANOPARTICLES--REPORT FROM AN INTERDISCIPLINARY WORKSHOP***

JM Balbus, AD Maynard, VL Colvin, V Castranova, GP Daston, RA Denison, KL Dreher, PL Goering, AM Goldberg, KM Kulinowski, NA Monteiro-Riviere, G Oberdorster, GS Omenn, KE Pinkerton, KS Ramos, KM Rest, JB Sass, EK Silbergeld, and BA Wong

**Environmental Health Perspectives**, November 1, 2007; 115(11): 1654-9.

This report presented the findings from a nanotoxicology workshop held in April 2006 at the Woodrow Wilson International Center for Scholars in Washington, DC. For 2 days, 26 scientists from government, academia, industry, and nonprofit organizations addressed two specific questions: (1) what information is needed to understand the human health impact of engineered nanoparticles; and (2) how is this information best obtained? To assess hazards of nanoparticles, most participants noted the need to use existing in vivo toxicologic tests because of their greater familiarity and interpretability. Most participants agreed that a standard set of nanoparticles should be validated by laboratories worldwide and made available for benchmarking tests of other newly created nanoparticles. The group concluded that a battery of tests should be developed to uncover particularly hazardous properties. Over the long term, research aimed at developing a mechanistic understanding of the numerous characteristics that influence nanoparticle toxicity was deemed essential. Predicting the potential toxicity of emerging nanoparticles will require hypothesis-driven research that elucidates how physicochemical parameters influence toxic effects on biological systems. Finally, the group identified general policy and strategic opportunities to accelerate the development and implementation of testing protocols to ensure that the information generated is translated effectively for all stakeholders.

***WHAT DO WE (NEED TO) KNOW ABOUT THE KINETIC PROPERTIES OF NANOPARTICLES IN THE BODY?***

Werner I. Hagens, Agnes G. Oomen, Wim H. de Jong, Flemming R. Cassee, and Adriënnne J.A.M. Sips.

**Regulatory Toxicology and Pharmacology**, Volume 49, Issue 3, December 2007, Pages 217-229.

The development and applications of nanotechnology occupy major importance in industrial and consumer arenas. However, knowledge about human exposure and possible toxicity of nanotechnology products is limited. To understand the mechanism of toxicity, thorough knowledge of the toxicokinetic properties of nanoparticles is warranted. There is a need for information on the absorption, distribution, metabolism, and excretion (ADME) of nanoparticles and validated detection methods of these man-made nanoparticles. Determination of the ADME properties of nanoparticles requires specialized detection methods in different biological matrices (e.g. blood and organs). In this paper, the current knowledge on the kinetic properties of nanoparticles is reviewed. Also, knowledge gaps from a kinetic point of view (detection, dose, ADME processes) are identified.

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***TOXICOLOGICAL HAZARDS OF INHALED NANOPARTICLES--POTENTIAL IMPLICATIONS FOR DRUG DELIVERY.***

PJ Borm and W Kreyling

**J Nanoscience & Nanotechnology**, May 1, 2004; 4(5): 521-31.

Nanoparticles, defined as particles with a diameter smaller than 100 nm, are increasingly used in different applications, including drug carrier systems and to pass organ barriers such as the blood-brain barrier. However, a large body of know-how is available regarding toxicological effects of nanoparticle after inhalation. A number of effects of inhaled nanoparticles are attributed to: (i) their direct effect on the central nervous system, (ii) their translocation from the lung into the bloodstream, and (iii) their capacity to invoke inflammatory responses in the lung with subsequent systemic effects. This paper briefly reviews the toxicology of inhaled nanoparticles, including general principles and current paradigms to explain their special case in pulmonary toxicology. Because the evidence for health risks of nanoparticles after inhalation has been increasing over the last decade, this paper also extrapolate findings and principles observed in inhalation toxicology into recommendations and methods for testing nanoparticles for nanocarrier purposes. A large gap exists between research on NP in inhalation toxicology and in nanoscaled drug carrying. This paper recommends closer interaction between both disciplines to understand the role of pertinent size and properties and their mechanisms of acute and chronic interaction with biological systems.

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***NANOTECHNOLOGY SAFETY CONCERNS REVISITED***

Stephan T. Stern and Scott E. McNeil

**Toxicological Sciences** 2008 101(1):4-21.

Nanotechnology Characterization Laboratory, Advanced Technology Program, SAIC-Frederick, Inc., NCI-Frederick, Frederick, Maryland.

Received April 12, 2007; Accepted June 14, 2007

Nanotechnology is an emerging science involving manipulation of matter at the nanometer scale. Due to concerns over nanomaterial risks, there has been a dramatic increase in focused safety research. This review summarizes these published findings with regard to: (1) the potential for nanomaterial exposure, (2) the hazard nanomaterials pose to humans and the environment, and (3) the existing deficits in understanding the risk. Recent data highlight the impact of surface characteristics on nanomaterial biocompatibility and point to the inadequacy of the current size-dependent mechanistic paradigms, with nanoscale materials lacking unique or characteristic toxicity profiles. The available data support the ability of the lung, gastrointestinal tract, and skin to act as a significant barrier to the systemic exposure of many nanomaterials. Furthermore, the acute systemic toxicity of many nanomaterials appear to be low. By contrast, the potential pulmonary toxicity of certain nanomaterials, such as carbon nanotubes, is significant, requiring a better understanding of exposure to further evaluate their risk. While these findings arrive at an overall picture of material-specific rather than nanogeneralized risk, any conclusions should clearly be tempered by the fact that nanomaterial safety data are limited. Until such time as the exposures, hazards, and environmental life cycle of nanomaterials have been more clearly defined, cautious development and implementation of nanotechnology is the most prudent course.

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**Toxicological Hazards**

2004

The attributed effects of inhaled nanoparticles.

**Nanotechnology Safety Concerns** 2008

A summary of potential for exposure, hazards posed to humans and deficits in understanding risks.

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**TESTING STRATEGIES TO ESTABLISH THE SAFETY OF NANOMATERIALS: CONCLUSIONS OF AN ECETOC WORKSHOP**

DB Warheit, PJ Borm, C Hennes, and J Lademann  
*Inhal Toxicol*, June 1, 2007; 19(8): 631-43.

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**Testing Strategies To Establish Safety (2007)**

EU Workshop Results demonstrates need for the characterization of nanomaterial, further assessment of airborne and internal exposure scenarios, and the evaluation of hazard potential.

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The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) convened a workshop in Barcelona, Spain (2005) to develop testing strategies to establish the safety of nanomaterials. It brought together nearly 70 scientific and clinical experts from industry, academia, government agencies, research institutes, and nongovernmental organizations. The three major themes of the workshop were: (1) the need for enhanced efforts in nanomaterial characterization; (2) methodologies for assessments of airborne and internal exposures to nanomaterials; and (3) evaluation of the hazard potential, primarily pulmonary or dermal routes of exposures. The summary conclusions of the workshop included: (1) The working definition of nanoparticles was defined as < 100 nm in one dimension or < 1000 nm to include aggregates and agglomerates. (2) Although many physical factors can influence toxicity, including nanoparticle composition, its dissolution, surface area and characteristics, size, size distribution, and shape that largely determine the functional, toxicological, and environmental impact of nanomaterials. (3) With respect to the assessment of external exposures and metrics appropriate for nanoparticles, the general view was that currently it is not possible or desirable to select one form of dose metric as the most appropriate measure source. (4) A clear and immediate need exists to develop instruments that are smaller, more portable, and less expensive than the currently available state of the art instrumentation. With regard to a general testing approach for human health hazard evaluation of nanoparticles, a first step to determine potency may include a prioritization-related in vitro screening strategy to assess the possible reactivity, biomarkers of inflammation and cellular uptake of nanoparticles; however this process must be validated using in vivo techniques. A Tier 1 in vivo testing strategy could include a short-term inhalation or intratracheal instillation of nanoparticles as the route of exposure in the lungs of rats or mice. The endpoints that should be assessed include indices of lung inflammation, cytotoxicity, and cell proliferation, as well as histopathology of the respiratory tract and the major extrapulmonary organs. For Tier 2 in vivo testing for hazard identification, a longer term inhalation study is recommended, and this would include more substantive mechanistic endpoints such as determination of particle deposition, translocation, and disposition within the body. Additional studies could be designed with specific animal models to mimic sensitive populations. With regard to dermal exposures, currently there is little evidence that nanoparticles at a size exceeding 100 nm penetrate through the skin barrier into the living tissue (i.e., dermal compartment). For the evaluation of the health risk of nanoparticles, it must be determined whether they are harmful to living cells and whether, under real conditions; they penetrate through the skin barrier into the living tissue. Emerging topics such as (1) environmental safety testing, (2) applications of nanoparticles for medical purposes, and (3) pathways of inhaled nanoparticles to the central nervous system were also briefly addressed during this workshop. However, these topics should be the subjects of separate workshops and they are not further addressed in this report.



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## ***DNA Damage Induced by Multiwalled Carbon Nanotubes in Mouse Embryonic Stem Cells***

Lin Zhu, Dong Wook Chang, Liming Dai, and Yiling Hong  
Department of Biology, Department of Chemical and Materials Engineering, University of Dayton, Dayton, Ohio.

**Nano Lett.**, 7 (12), 3592 -3597, 2007. Web Release: November 29, 2007. Copyright © 2007 American Chemical Society.

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### **First DNA Assessment of Damage in Mice Suggest Further Scrutiny of Genotoxicity in Nanomaterials (2007)**

Further testing is required.

### **Size Dependent Cytotoxicity of Gold Nanoparticles (2007)**

Gold nanoparticles used in testing.

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Carbon nanotubes (CNTs) have shown promise as an important new class of multifunctional building blocks and innovative tools in a large variety of applications, ranging from nanocomposite materials through nanoelectronics to biomedical devices. Because of their unusual one-dimensional hollow nanostructure and unique physicochemical properties, CNTs are particularly useful as novel drug delivery tools and imaging agents. However, such biomedical applications will not be realized if there is no proper assessment of the potential hazards of CNTs to humans and other biological systems. Although a few reports on the cytotoxicity of CNTs have been published, very little is known about the toxicity at the molecular level. We have for the first time assessed the DNA damage response to multiwalled carbon nanotubes (MWNTs) in mouse embryonic stem (ES) cells. Test results suggest that careful scrutiny of the genotoxicity of nanomaterials is needed even for those materials, like multiwalled carbon nanotubes, that have been previously demonstrated to have limited or no toxicity at the cellular level.

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### ***SIZE-DEPENDENT CYTOTOXICITY OF GOLD NANOPARTICLES***

Yu Pan, Sabine Neuss, Dr., Annika Leifert, Monika Fischler, Dr., Fei Wen, Dr., Ulrich Simon, Prof., Günter Schmid, Prof., Wolfgang Brandau, Prof., Willi Jahnen-Dechent.

**Small**, Volume 3, Issue 11 , pgs 1941 – 1949.  
Received: 29 May 2007; Revised: 27 August 2007  
Copyright © 2007 WILEY-VCH Verlag GmbH & Co. KGaA.

Gold nanoparticles are widely used in biomedical imaging and diagnostic tests. Based on their established use in the laboratory and the chemical stability of Au<sup>0</sup>, gold nanoparticles were expected to be safe. The recent literature, however, contains conflicting data regarding the cytotoxicity of gold nanoparticles. Against this background a systematic study of water-soluble gold nanoparticles stabilized by triphenylphosphine derivatives ranging in size from 0.8 to 15 nm is made. The cytotoxicity of these particles in four cell lines representing major functional cell types with barrier and phagocyte function are tested. Connective tissue fibroblasts, epithelial cells, macrophages, and melanoma cells prove most sensitive to gold particles 1.4 nm in size, which results in IC<sub>50</sub> values ranging from 30 to 56  $\mu$ M depending on the particular 1.4-nm Au compound-cell line combination. In contrast, gold particles 15 nm in size and Tauredon (gold thiomalate) are nontoxic at up to 60-fold and 100-fold higher concentrations, respectively. The cellular response is size dependent, in that 1.4-nm particles cause predominantly rapid cell death by necrosis within 12 h while closely related particles 1.2 nm in diameter effect predominantly programmed cell death by apoptosis.



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## ***DEPOSITION OF ULTRAFINE (NANO) PARTICLES IN THE HUMAN LUNG***

Bahman Asgharian, Owen T. Price

The Hamner Institutes for Health Sciences, North Carolina, USA

**Inhalation Toxicology**, Volume 19, Issue 13\_October 2007 , pgs 1045 – 1054.

Increased production of industrial devices constructed with nanostructured materials raises the possibility of environmental and occupational human exposure with consequent adverse health effects. Ultrafine (nano) particles are suspected of having increased toxicity due to their size characteristics that serve as carrier transports. For this reason, it is critical to refine and improve existing deposition models in the nano-size range. A mathematical model of nanoparticle transport by airflow convection, axial diffusion, and convective mixing (dispersion) was developed in realistic stochastically generated asymmetric human lung geometries. The cross-sectional averaged convective-diffusion equation was solved analytically to find closed-form solutions for particle concentration and losses per lung airway. Airway losses were combined to find lobar, regional, and total lung deposition. Axial transport by diffusion and dispersion was found to have an effect on particle deposition. The primary impact was in the pulmonary region of the lung for particles larger than 10 nm in diameter. The approach used in the proposed model is recommended for more realistic assessment of regional deposition of diffusion-dominated particles in the lung, as it provides a means to more accurately relate exposure and dose to lung injury and other biological responses.

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### **Nanoparticles in the Human Lung (2007)**

Improved approach to assess nanoparticles in the lung as the primary means to state exposure and dose.

### **Nanoparticles As Mechanisms of Pulmonary Toxicity (2007)**

Toxicology of combustion-derived nanoparticles (CDNP) is used to understand health effects following exposure.

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## ***COMBUSTION-DERIVED NANOPARTICLES: MECHANISMS OF PULMONARY TOXICITY***

Kelly BéruBé, Dominique Balharry, Keith Sexton, Lata Koshy, Tim Jones

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**CLINICAL AND EXPERIMENTAL PHARMACOLOGY AND PHYSIOLOGY**

Volume 34 Issue 10 Page 1044-1050, October 2007

The general term ‘nanoparticle’ (NP) is used to define any particle less than 100 nm in at least one dimension and NPs are generally classified as natural, anthropogenic or engineered in origin. Anthropogenic, also referred to as ‘ultrafine’ particles (UFPs), are predominately combustion derived and are characterized by having an equivalent spherical diameter less than 100 nm. These particles, considered to be ‘combustion-derived nanoparticles’ (CDNPs), are of toxicological interest given their nanosized dimensions, with properties not displayed by their macroscopic counterparts. The pulmonary deposition efficiency of inhaled UFPs, along with their large surface areas and bound transition metals, is considered important in driving the emerging health effects linked to respiratory toxicity. The toxicology of CDNPs is currently used to predict the health outcomes in humans following exposure to manufactured NPs. Their similar physicochemistry would suggest similar adverse health effects (i.e. pulmonary (and perhaps cardiac) toxicity). As such, it is essential to fully understand CDNP nanotoxicology in order to minimize occupational and environmental exposure.



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### Effect of Different Class of Nanoparticles on Cell Viability (2007)

Carbon Nanotubes (CNT) were not directly toxic but were able to alter cell behavior.

### Testing Nanoparticles of Unknown Toxicity (2007)

Nanoparticles positioned in cell-free experiments to determine toxicity-related properties and then exposed to cells and rat lungs.

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### ***EFFECT OF DIFFERENT CARBON NANOTUBES ON CELL VIABILITY AND PROLIFERATION***

Milena De Nicola, Daniele Mirabile Gattia, Stefano Bellucci, Giovanni De Bellis, Federico Micciulla<sup>3</sup>, Roberto Pastore, Alessandra Tiberia, Claudia Cerella, Maria D'Alessio, Marco Vittori Antisari, Renzo Marazzi, Enrico Traversa, Andrea Magrini, Antonio Bergamaschi, and Lina Ghibelli

*J. Phys.: CONDENS. MATTER* 19 395013 (7 pgs).

Issue 39 (3 October 2007) Received 22 February 2007; final form 18 May 2007.

Carbon nanotubes (CNTs) are a focus of intense research for their potential applications in multiple diverse applications, including innovative biomedical applications. Due to their recent discovery, little information is available about biocompatibility and toxicity of this new class of nanoparticle. A systematic study on biological interference is not available. We explored the toxicity of three different types of CNTs, differing in preparation, size, contaminants, and morphological type on human leukemic U937 cells. CNTs were found to exert a strong effect on the proliferation of the reporter U937 monocytic cell. However, these CNTs did not significantly affect the cell viability. Results show that CNTs, though not directly exerting a direct cytotoxic effect, are nonetheless able to alter cell behavior deeply, and thus it is recommended to limit health risk due to uncontrolled exposure.

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### ***TESTING NANOMATERIALS OF UNKNOWN TOXICITY: AN EXAMPLE BASED ON PLATINUM NANOPARTICLES OF DIFFERENT SHAPES***

A. Elder, H. Yang, R. Gwiazda, X. Teng, S. Thurston, H. He, G. Oberdörster

**Advanced Materials**, Volume 19, Issue 20, Pages 3124 – 3129.

Special Issue: Special Section on Bionanotechnology. Published Online: 17 Oct 2007.

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Human endothelial and lung epithelial cells were exposed to nanosized Pt shapes following a cellular analysis of their oxidant potential. Despite clear evidence of particle uptake by cells, the Pt nanoparticles were not found to induce cytotoxicity or oxidative stress in either cell type. Results from in vivo respiratory tract exposures suggest that the particles are retained by lung tissue and that minimal-mild lung inflammation results from exposure to the nanosized Pt particles. Platinum nanoparticles were characterized in cell-free experiments for toxicity-related properties and then exposed to cells and rat lungs and the responses examined.



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**Categorization of Nanoparticles To Aid Hazard Identification (2007)**

Nanomaterials must be categorized based on location before their hazards may be properly assessed.

**Toxicity and Risk Assessment of Nanoparticles on Human Health (2007)**

A summary of nanoparticles and human exposure, and their biocompatibility in relation to the potential toxicological effects, risk assessment, and safety evaluation of human health.

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Steffen Foss Hansen, Britt H. Larsen, Stig I. Olsen, Anders Baun  
Institute of Environment & Resources, NanoDTU, Technical University of Denmark, Kgs, Lyngby, Denmark; NanoDTU, Technical University of Denmark, Kgs, Lyngby, Denmark; Department of Manufacturing Engineering and Management, NanoDTU, Technical University of Denmark, Kgs, Lyngby, Denmark

**Nanotoxicology**, Volume 1, Issue 3, September 2007, pgs 243 - 250.

The physical, chemical, and biological properties of nanomaterials differ substantially, as well as the risks they pose. Nanomaterials must be categorized based on their location in the material before their hazards can be assessed. A categorization framework enables scientists to identify the categories of nanomaterials systematically and may be applied to a suggested hazard identification approach aimed at identifying causality between inherent physical and chemical properties and observed adverse effects. Workability of the proposed procedure was tested using nanoparticles as an illustrative case study. A database was generated noting the reported inherent physical and chemical properties of the nanoparticles tested. 428 studies were noted in the database reporting on a total of 965 nanoparticles. Although a limited number of studies have been reported on ecotoxicity, more than 120 and 270 have been reported on mammalian toxicity and cytotoxicity, respectively. Generally, nanoparticles studied have not been characterized, and it was not possible to link specific properties of nanoparticles to the observed effects. Study argues that future research strategies must have a strong focus on characterization of the nanoparticles tested.

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**NANOTECHNOLOGY AND HEALTH SAFETY - TOXICITY AND RISK ASSESSMENTS OF NANOSTRUCTURED MATERIALS ON HUMAN HEALTH**

Singh, Surya and Nalwa, Hari Singh

**Journal of Nanoscience and Nanotechnology**, Volume 7, Number 9, September 2007 pgs 3048-3070(23).

Nanotechnology has recently emerged as the most commercially viable technology of this century because of its wide-ranging applications. Nanostructured materials such as fullerenes, nanoparticles, nanopowders, nanotubes, nanowires, nanorods, nano-fibers, quantum dots, dendrimers, nanoclusters, nanocrystals, and nanocomposites are globally produced in large quantities due to their wide potential applications in skincare and consumer products, healthcare, electronics, photonics, biotechnology, engineering products, pharmaceuticals, drug delivery, and agriculture. Human exposure to nanoparticles is inevitable, as they can enter the body through the lungs or other organs via food, drink, and medicine and affect different organs and tissues such as the brain, liver, kidney, heart, colon, spleen, bone, blood, etc., and may cause cytotoxic effects, deformation and inhibition of cell growth leading to various diseases. Because a very wide variety of nanostructured materials exists, their interactions with biological systems and toxicity largely depend upon their properties, such as size, concentration, solubility, chemical and biological properties, and stability. The toxicity of nanostructured materials could be reduced by chemical approaches such as surface treatment, functionalization, and composite formation. This review summarizes the sources of nanoparticles and their human exposure, biocompatibility in relation to potential toxicological effects, risk assessment, and safety evaluation on human and animal health as well as on the environment.



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***TOO SMALL FOR CONCERN? PUBLIC HEALTH AND NANOTECHNOLOGY***

Bowman, D. M.; Fitzharris, M.

**Australian and New Zealand Journal of Public Health** 2007, 31;4, 382-84.

Although advances in nanotechnology promise to deliver significant benefits to many aspects of health care, increasing concern exists that regulatory regimes do not adequately capture the potential risks associated with this new technology. Concerns have arisen due to preliminary evidence suggesting that some engineered nanoparticles may display undesirable toxicological properties, presenting potential risks to human and environmental health and safety. Within this context, the role of Australia's National Industrial Chemicals and Assessment Scheme and the Therapeutic Goods Administration in regulating nano-based substances is explored. Drawing on earlier regulatory failures, combined with the scientific uncertainty surrounding nanotechnology, this article recommends that Australia adopt a proactive regulatory approach to nanotechnology through amendments to present legislative regimes. The approach articulated in this article strikes a balance between the current approach and that of the European Union's comprehensive new chemicals regime. Immediate regulatory change is called for in order to ensure that the health of the Australian public is adequately protected over the coming years.

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**Public Health and Nanoparticles in Australia (2007)**

Review of Australian industrial chemicals agency in regulating nano-based substances.

**Nanoparticles In Metal Implants (2007)**

Concern about long-term effect on human tissue exposure to nanoparticles, particularly from implants.

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***THE EFFECT OF NANO- AND MICRON-SIZED PARTICLES OF COBALT-CHROMIUM ALLOY ON HUMAN FIBROBLASTS IN VITRO***

I. Papageorgiou, C. Brown, R. Schins, S. Singh, R. Newson, S. Davis, J. Fisher, E. Ingham, and C.P. Case

**Biomaterials**, Volume 28, Issue 19, July 2007, Pages 2946-2958.

Received 22 December 2006; accepted 22 February 2007; available online 1 March 2007.

Wear debris from metal on polyethylene joint replacements causes aseptic loosening as a result of an inflammatory reaction of macrophages to micron-sized particles. Metal on metal implants, which generate nanoparticles, have been reintroduced into surgical practice in order to avoid this problem. There is a current concern about possible long-term effects of exposure to metal particles. In this study, the cytotoxic and genotoxic effects of nanoparticles and micron-sized particles of cobalt chrome alloy have been compared using human fibroblasts in tissue culture. Nanoparticles, which caused more free radicals in an acellular environment, induced more DNA damage than micron-sized particles using the alkaline comet assay. They induced more aneuploidy and more cytotoxicity at equivalent volumetric dose. Nanoparticles appeared to disintegrate within the cells faster than microparticles with the creation of electron dense deposits in the cell, which were enriched in cobalt. The mechanism of cell damage appears to be different after exposure to nanoparticles and microparticles. The concept of nanotoxicology is, therefore, an important consideration in the design of future surgical devices.



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## HEALTH EFFECTS OF NANOMATERIALS

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**Biochem. Soc. Trans.** (2007) 35, (527–531).

Rapid growth in nanotechnology and the future bulk manufacturing of nanomaterials comes the need to determine, understand, and counteract adverse health effects that may occur during manufacture, use, or accidentally. Nanotechnology will affect many aspects of everyday life, and hundreds of products already incorporate nanoparticles. Paradoxically, the unique properties that are being exploited (e.g. high surface reactivity and ability to cross cell membranes) might have negative health impacts. The rapid progress in development and use of nanomaterials is not yet matched by toxicological investigations. Epidemiological studies implicate the ultrafine fraction of particulate air pollution in the exacerbation of cardio-respiratory disease and increased morbidity. Experimental animal studies suggest that the increased concentration of nanoparticles and higher reactive surface area per unit mass, alongside unique chemistry and functionality, is important in the acute inflammatory and chronic response. Some animal models have shown that nanoparticles which are deposited in one organ may access the vasculature and target other organs. The exact relationship between the physicochemistry of a nanoparticle, its cellular reactivity, and its biological and systemic consequences cannot be predicted. It is important to understand such relationships and the hazards they may present.

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### Health Effects of Nanoparticles (2007)

Development and use of nanoparticles must be matched by health hazard assessments.

### Toxic Effects of Nanoparticles (2007)

Perspective from toxicologists about exposure routes, toxic effects, environmental concentrations, and health risk assessments.

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## TOXIC EFFECTS OF NANOPARTICLES AND NANOMATERIALS: IMPLICATIONS FOR PUBLIC HEALTH, RISK ASSESSMENT, AND THE PUBLIC PERCEPTION OF NANOTECHNOLOGY

R. D. Handy; B. J. Shaw

School of Biological Sciences, University of Plymouth, Plymouth, UK

**Health, Risk & Society**, Volume 9, Issue 2, June 2007, pgs 125–144.

Nanomaterials are now being manufactured and used in many products. However, our knowledge of the human health effects and environmental concentrations of engineered nanomaterials or nanoparticles is incomplete. This article gives a toxicologists perspective, outlining possible routes of uptake by humans, environmental concentrations, known or suspected toxic effects, and the practical implication for human health risk assessments and public perception. Humans are already exposed to a range of natural and man-made nanoparticles in the air, and exposure via the food chain, water supply, and medical applications is likely. Toxicology studies on animals, and cells *in vitro*, raise the possibility of adverse effects on the immune system, oxidative stress related disorders, lung disease and inflammation. However, the doses needed to produce these effects are generally high and it remains to be seen if such exposure is possible via the environment or the work place. Data on exposure is also needed for risk calculations. Current legislation does not specifically address nanoparticles or nanomaterials, and there are concerns about nomenclature, defining nanomaterials as new substance under chemicals regulations such as REACH, and the appropriateness of current test methods.



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***NANOTOXICITY OF IRON OXIDE NANOPARTICLE INTERNALIZATION IN GROWING NEURONS***

Pisanic TR, Blackwell JD, Shubayev VI, Fiñones RR, Jin S.  
Department of Bioengineering, University of California, San Diego La Jolla, CA

**Biomaterials**, 2007 Jun;28(16):2572-81. Epub 2007 Feb 11.

Magnetic nanoparticles (MNPs) have shown great promise for use as tools in a wide variety of biomedical applications, some of which require the delivery of large numbers of MNPs onto or into the cells of interest. Here we develop a quantifiable model cell system and show that intracellular delivery of even moderate levels of iron oxide (Fe<sub>2</sub>O<sub>3</sub>) nanoparticles may adversely affect cell function. More specifically, we show that exposure to increasing concentrations of anionic MNPs, from 0.15 to 15 mg of iron, results in a dose-dependent diminishing viability and capacity of PC12 cells to extend neurites in response to their putative biological cue, i.e. nerve growth factor. The cytotoxicity results of biomaterials in our model system imply that more study into the acute and long-term effects of cellular Fe<sub>2</sub>O<sub>3</sub> internalization is both warranted and necessary.

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**Toxicity of Iron Oxide Nanoparticles (2007)**

Moderate levels of iron oxide nanoparticles may adversely affect cell function.

**Removal of Inhaled Nanoparticles From Human Lungs (2007)**

Nanoparticles may be effectively removed from the lung surface and cleared into the larynx.

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***EFFICIENT ELIMINATION OF INHALED NANOPARTICLES FROM THE ALVEOLAR REGION: EVIDENCE FOR INTERSTITIAL UPTAKE AND SUBSEQUENT RE-ENTRAINMENT ONTO AIRWAYS EPITHELIUM***

Manuela Semmler-Behnke, Shinji Takenaka, Steffanie Fertsch, Alexander Wenk, Jürgen Seitz, Paula Mayer, Günter Oberdörster, and Wolfgang G. Kreyling

**Environmental Health Perspectives**, Volume 115, Number 5, May 2007.

Inhaled nanoparticles (NPs, < 100 nm) may translocate from epithelial deposition sites of the lungs to systemic circulation. We studied the disappearance of NPs from the epithelium by sequential lung retention and clearance and bronchoalveolar lavage (BAL) measurements in healthy adult Wistar Kyoto (WKY) rats at various times over 6 months after administration of a single 60- to 100-min intratracheal inhalation of iridium-192 (<sup>192</sup>Ir) –radio labeled NPs. A complete <sup>192</sup>Ir balance of all organs, tissues, excretion, remaining carcass, and BAL was performed at each time point. Directly after inhalation we found free NPs in the BAL ; later, NPs were predominantly associated with alveolar macrophages (AMs) . After 3 weeks, lavageable NP fractions decreased to 0.06 of the actual NP lung burden. This is in stark contrast to the AM-associated fraction of micron-sized particles reported in the literature. These particles remained constant at about 0.8 throughout a 6-month period. There is a strong size-selective difference in particle immobilization. We conclude that NPs are much less phagocytized by AMs than large particles but are effectively removed from the lung surface into the interstitium. Even from these interstitial sites, they undergo AM-mediated long-term NP clearance to the larynx.

