

October 28, 2011

Via: Certified Mail

Jeffrey Wong, Ph.D.
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101 "I" Street
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Career and
Protective Services

Environmental
Health and Safety

Re: DTSC Chemical Information Call-In – Nanometals, Nanometal Oxides, and
Quantum Dots

Dear Dr. Wong,

In response to the January 4, 2011 call-in letter from the Department of Toxic Substance Control (DTSC), the University of Southern California submits the following chemical information and analytical test methods regarding the specified nanomaterials: Nano Silver, Nano Zero Valent Iron, Nano Cerium Oxide, Nano Titanium dioxide, Nano Zinc Oxide, and Quantum dots {California Health and Safety Code §57018-57020}.

The University of Southern California (USC), a leading academic research institution with affiliated hospitals, encompasses over one thousand research laboratories. To obtain the requested information from USC researchers and faculty advisors who may produce, use or oversee the study of nanoparticles, several approaches were employed. Users self-identified in response to a memo distributed to the USC research community; additionally, research protocols submitted to institutional safety committees and annual safety audit reports were reviewed. Information was verified by interview using the DTSC questionnaire as a guide.

Following is the compilation of chemical information and analytical test methods used at USC for the specified nanomaterials.

Nanomaterials at USC; their Chemical and Physical Properties

USC both produces, and purchases from commercial sources (e.g., Invitrogen and e-Biosciences), Nano Silver, Nano Titanium Dioxide, Nano Zinc Oxide and Quantum Dots (but not Nano Zero Valent Iron or Nano Cerium Oxide,) for research and development purposes within USC facilities. The USC materials are not employed for commercial applications.

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Maximum annual quantities produced in USC labs or procured from commercial vendors range from two micrograms to 80 grams, stored in volumes from five micro-milliliters to 100 milliliters. Quantities used in any one laboratory procedure are very minute.

Physical shapes of these materials are most commonly spherical, but also include rod and tripod configurations. Known densities range from one to seven grams per cubic centimeter; surface areas vary from 10 to 300 square nanometers. Nanoparticles are created or purchased only in liquid or solid form. All nanoparticle manipulations are conducted in liquid phase, submerged in a liquid or contained within a controlled atmosphere, minimizing the possibility of airborne emission.

Particle surfaces are modified and subsequently functionalized with amines, carboxylates, polyethylene glycol, mercaptopropionic acid, or dodecanethiol. The materials handled at USC pose little risk of flammability, oxidation or explosion due to the minimal quantities and low concentrations used. While high solvent use present a flammability hazard that may be exacerbated by the reactivity of nanoparticles, no current protocols use a high volume of solvent matrices, and USC Environmental Health and Safety closely monitors the chemical inventory. Currently used forms of the nanoparticles and nano-solutions are considered stable for the laboratory processes employed and for storage in existing glass containers.

All waste involving nanoparticles and nano-contaminated materials is treated as toxic chemical waste, and incinerated through an approved waste treatment facility.

Analytical Test Methods

Paragraphs 1) through 7) below describe current USC applications of the specified nanoparticles, and the associated quantitative and qualitative test methods in use. Referenced publications, included with this memo, provide additional detail regarding analytical test methods.

- 1) Nano silver and quantum dots are used for in-vitro and in-vivo cancer treatment studies to evaluate biodistribution and molecular behavior. These nanomaterials are purchased from Invitrogen in micromolar liquid concentrations in water, buffer or solvent matrices. Nano silver, and quantum dots created from cadmium selenide or zinc sulfide, are functionalized with a peptide coating. Pre- and post-processing nanomaterial concentration is determined using UV/Vis optical absorption measurements. At peak absorbance wavelengths, the cross-sectional absorption of the nanomaterial in various matrices is compared to a blank sample to infer concentration using Beer-Lambert law, reported in moles/liter. Cross-section absorption values for different nanomaterials are available in scientific literature (Attachment A, "Experimental Determination of the Extinction Coefficient of CdTe, CdSe, and CdS Nanocrystals").

Other nanomaterial detection methods in liquid matrices include size exclusion chromatography analysis and dynamic light scattering. Nanomaterial presence in a non-liquid matrix (e.g., in cells or tissue) is primarily evaluated using transmission electron microscopy (TEM). These characterization methods are used for qualitative assessment, and no concentrations are inferred.

- 2) A comparative study of two analytical techniques uses nano silver clusters. The first technique produces particles in a cryogenic helium superfluid matrix (nanodroplets). Clusters are deposited on a TEM grid using a continuous beam of helium droplets for the assembly and surface

deposition of nano silver; the surface is imaged for study and quantification. Images of clusters on the amorphous carbon substrates are obtained at short deposition times to determine the size distribution of the metal clusters.

The second helium droplet technique, under development, is an in-Situ nano silver structure determination employing laser scattering of clusters in helium. Supporting journal articles are included with this memo (Attachment B, "Surface Deposition and Imaging of Large Ag Clusters Formed in HE Droplets" and C, "Photoabsorption of Ag_N ($N \sim 6-6000$) Nanoclusters Formed in Helium Droplets: Transition from Compact to Multicenter Aggregation").

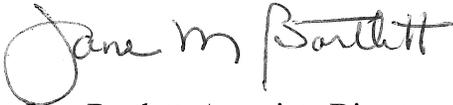
- 3) Nano titanium dioxide is viewed under TEM in a study of particle sizes and shapes.
- 4) Zinc oxide nanoparticles are involved in a study of translocation mechanisms in biological cells, tissues and organs. Primary cultured rat alveolar epithelial cell monolayers (RAECMs) are exposed to ZnO nanoparticles at several $\mu\text{g/ml}$ concentrations. Cellular effects of interest, measured as functions of concentration and time, include morphologic changes, lactate dehydrogenase release, cell membrane integrity, intracellular reactive oxygen species, and mitochondrial activity. A Millicell-ERS quantifies transepithelial electrical resistance, and potential difference in the presence or absence of varying ZnO concentrations in apical fluid, as a function of exposure time. ZnO nanoparticle suspensions in water are sonicated, vortexed, then evaluated by Zetasizer to determine the zeta potential on the surface charge of ZnO nanoparticles. The ICP-MS method is also utilized for ZnO nanoparticle quantitation (Attachment D, "Alveolar Epithelial Cell Injury Due to Zinc Oxide Nanoparticle Exposure").
- 5) Quantum dots used in a kidney filtration study involves amine functionalization on a modified nanoparticle surface (neutral charge; surface area: 20 nm). 100 microliters of a micro-molar nanocrystal solution in a DMSO matrix are conjugated with a fluorescent dye, and injected into small animals. Quantum dot concentration in the animals' circulatory system is determined by fluorescent intensity during in-vivo animal imaging. Upon completion of the imaging, the animals are sacrificed, their circulatory system flushed with saline, and the perfusate collected as a chemical waste. Nanoparticle waste materials are shipped to a waste treatment site for incineration.
- 6) An optical behavior study uses lead sulfide quantum dots produced in liquid form through chemical synthesis (3 gram per year). These spherical nanoparticles (size: 6 nm; surface area: 12-300 nm^2 ; density: 7.6 gr/cm^3) are functionalized with carboxylate coating. The particles are oxidized by thermal exposure and are soluble in organic solvent. Estimates of both particle size and size distribution are obtained using TEM. Visible light absorption optical spectroscopy is used to estimate quantum dot concentration in toluene. The amount of light absorbed by quantum dots at a given wavelength is determined by the material's properties and concentrations, from which quantity can be rendered.
- 7) An analytical study produces approximately 80 grams per year of cadmium selenide quantum dots dissolved in solvent, e.g., 150 mg/ml toluene, functionalized with fatty acids or a fatty amine coating. Solid crystals are obtained by drying a measured volume of solution, weighing the residue, and performing Thermo Gravimetric Analysis (TGA). The high temperature TGA mass represents the pure inorganic, and its concentration in a given solvent can be calculated.

This innovative analytical test method is soon to be published in scientific journals, and will be provided to DTSC upon request.

Additional References

USC Nano Researchers have been extremely cooperative in responding to the DTSC's appeal for information, and expressed their willingness to furnish additional information upon request.

Respectfully submitted,

A handwritten signature in cursive script that reads "Jane M. Bartlett". The signature is written in black ink and is positioned above the typed name and address.

Jane Bartlett, Associate Director of Laboratory Safety and Industrial Hygiene
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Experimental Determination of the Extinction Coefficient of CdTe, CdSe, and CdS Nanocrystals

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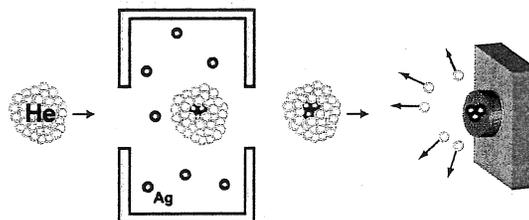
The extinction coefficient per mole of nanocrystals at the first excitonic absorption peak, ϵ , for high-quality CdTe, CdSe, and CdS nanocrystals was found to be strongly dependent on the size of the nanocrystals, between a square and a cubic dependence. The measurements were carried out using either nanocrystals purified with monitored purification procedures or nanocrystals prepared through controlled etching methods. The nature of the surface ligands, the refractive index of the solvents, the PL quantum yield of the nanocrystals, the methods used for the synthesis of the nanocrystals, and the temperature for the measurements all did not show detectable influence on the extinction coefficient for a given sized nanocrystal within experimental error.

Surface Deposition and Imaging of Large Ag Clusters Formed in He Droplets

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ABSTRACT: The utility of a continuous beam of He droplets for the assembly and surface deposition of Ag_N clusters, $\langle N \rangle \sim 300\text{--}6000$, is studied with transmission electron microscopy. Images of the clusters on amorphous carbon substrates obtained at short deposition times have provided for a measure of the size distribution of the metal clusters. The average sizes of the deposited clusters are in good agreement with an energy balance based estimate of Ag_N cluster growth in He droplets. Measurements of the deposition rate indicate that upon impact with the surface the He-embedded cluster is attached with high probability. The stability of the deposited clusters on the substrate is discussed.



Photoabsorption of Ag_N ($N \sim 6\text{--}6000$) Nanoclusters Formed in Helium Droplets: Transition from Compact to Multicenter Aggregation

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Ag_N clusters with up to thousands of atoms were grown in large He droplets and studied by optical spectroscopy. For $N \lesssim 10^3$ the spectra are dominated by a surface plasmon resonance near 3.8 eV and a broad feature in the UV, consistent with absorption by individual metallic particles. Larger clusters reveal unexpectedly strong broad absorption at low frequencies, extending down to ≈ 0.5 eV. This suggests a transition from single-center to multicenter formation, in agreement with estimates of cluster growth kinetics in He droplets. Moreover, the spectra of large clusters develop a characteristic dispersion profile at 3.5–4.5 eV, indicative of the coexistence of localized and delocalized electronic excitations in composite clusters, as predicted theoretically.

DOI: 10.1103/PhysRevLett.106.233401

PACS numbers: 36.40.Mr, 36.40.Vz, 61.46.Bc, 78.67.Sc

Attachment D

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Am J Respir Crit Care Med. 2010 Dec 1;182(11):1398-409. Epub 2010 Jul 16.

Alveolar epithelial cell injury due to zinc oxide nanoparticle exposure.

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Abstract

RATIONALE: Although inhalation of zinc oxide (ZnO) nanoparticles (NPs) is known to cause systemic disease (i.e. metal fume fever), little is known about mechanisms underlying injury to alveolar epithelium.

OBJECTIVES: Investigate ZnO NP-induced injury to alveolar epithelium by exposing primary cultured rat alveolar epithelial cell monolayers (RAECMs) to ZnO NPs.

METHODS: RAECMs were exposed apically to ZnO NPs or, in some experiments, to culture fluid containing ZnO free Zn released from ZnO NPs. Transepithelial electrical resistance (R(T)) and equivalent short-circuit current (I) were assessed as functions of concentration and time. Morphologic changes, lactate dehydrogenase release, cell membrane integrity, intracellular reactive oxygen species (ROS), and mitochondrial activity were measured.

MEASUREMENTS AND MAIN RESULTS: Apical exposure to 176 µg/ml ZnO NPs decreased R(T) and I(EQ) of RAECMs by 100% over 24 hours, whereas exposure to 11 µg/ml ZnO NPs had little effect. Changes in R(T) and I caused by 176 µg/ml ZnO NPs were irreversible. ZnO NP effects on R(T) yielded half-maximal concentrations of approximately 20 µg/ml. Apical exposure for 24 hours to 176 µg/ml ZnO NPs induced decreases in mitochondrial activity and increases in lactate dehydrogenase release, permeability to fluorescein sulfonic acid, increased intracellular ROS, and translocation of ZnO NPs from apical to basolateral fluid (most likely across injured cells and/or damaged paracellular pathways).

CONCLUSIONS: ZnO NPs cause severe injury to RAECMs in a dose- and time-dependent manner, mediated, at least in part, by free Zn released from ZnO NPs, mitochondrial dysfunction, and increased intracellular ROS.

PMID:20639441[PubMed - indexed for MEDLINE] PMID: PMC3029930[Available on 2011/12/1]

Publication Types, MeSH Terms, Substances, Grant Support

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