

Nanoparticles for materials design: present & future

B.I. Lee*, L. Qi and T. Copeland

School of Materials Science & Engineering, Clemson University, Clemson, SC 29634, U.S.A.

As nanoparticles are at the forefront of the nanotechnology wave, appropriate applications, production techniques, and long term health effects must be considered. The current and potential applications for nanoparticles are growing and cover an extremely broad range of markets. However, there are a number of hurdles to be overcome before the potential of nanoparticles can be fully realized. This paper will review some of the current state-of-the-art with selected examples, and future concerns and considerations for the nanoparticle technology to be successful. The concerns include safety and health effects of nanoparticles, and the public perception of the technology. Some examples demonstrating the unique properties and behavior of nanoparticles will be presented using the data generated in our lab and elsewhere.

Key words: Nanoparticles, Toxicity, Barium titanate, Size Effect, Iron oxide, Quantum dots.

Introduction

As nanoparticles are at the forefront of the nanotechnology wave, we see a rapid increase in the range of available nanoparticles and the number of companies that produce them. The current and potential applications for nanoparticles are growing and cover a broad range of markets which is estimated to be \$900 million in 2005 and \$11 billion in 2010 [1-3]. This spurs a great deal of interest among entrepreneurs, venture capitalists, and even the best-selling author Michael Crichton [4]. Why are all these now? In the early 20th century, the production of carbon black and, fumed silica in the 1940s exemplified nanoparticle technology before much of the current nanotech fervor. This is because the earlier nanotech was pursued empirically – the materials were discovered, not designed. All materials are made of atoms, molecules, and nanoparticles as building blocks. In the advent of new and more powerful materials characterization tools, we can examine the materials structures at the molecular or atomic scales. Materials can be designed and built from the smallest building blocks for desired structure and functions.

What are nanoparticles? What is the size range to be called nanoparticles? In a recent survey obtained from 100 nanotechnology experts and the results, published by 3i in association with the Economist Intelligence Unit and the Institute of Nanotechnology [5], illustrates widely differing views on the definition of nanotech; 45% responding to the survey the nanoparticles as size

< 100 nm and 17% consider < submicrometer levels. Based on the results, we take the definition of nanoparticles to be discrete particles that have a diameter around 250 nm or less. Why are nanoparticles so interesting? Just because these materials can be made into very small sizes does not necessarily lead to novel properties with practical applications. When novel properties are found, the unknown effects in physiological and environmental exposures create public fear [6]. However, it would be an interesting question to ask if there are any novel properties with these materials at this scale. Materials with particle sizes on the nanoscale between 1 nm and 250 nm lie in the domain between the quantum effects of atoms and molecules, and the bulk properties of materials. Particles at the lower side of this size range are also called quantum dots (QDs). Many physical properties of materials are controlled by phenomena that have critical dimensions on the nanoscale. The ability to fabricate and control the structure of nanoparticles allows the scientist and engineer to influence the resulting properties and, ultimately, design materials to give the desired properties [7].

A wide variety of different techniques are used to produce nanoparticles; the wet chemical or solution method, mechanical size reduction, gas phase synthesis, etc. All of these are being used commercially and each has its own merits and drawbacks. There are many examples where simple mechanical reduction of particle size down to the nanoscale improves the performance and hence open up new products. For example, pyrotechnics and explosives, where nanoparticle Al provides a greater energy release rate; lapping and polishing compounds, where track dimensions on Si chips are approaching 150 nm and the polishing media need to be significantly less than this to keep defects small; and

*Corresponding author:
Tel : +1-864-656-5348
Fax: +1-864-656-1453
E-mail: burt.lee@ces.clemson.edu

magnetic recording media, where higher-density storage is driven by finer particles and grain sizes as storage media approach terabyte capacities [8].

Metallic iron nanoparticles have been demonstrated to be effective for cleaning up contaminated soils and ground waters [9]. The effectiveness of Fe nanoparticles for environmental remediation comes from the enhanced surface reactivity of Fe by the increased surface area. The estimated cost for the clean up is ~\$40/kg and ~\$400 for 100 m² of contaminated area. Nanoparticle size effect on catalytic activity of Ni and Pt was tested by Weber et al. [10]. Size specifics were shown and the maximum catalytic activity was obtained at 19 nm by Ni particles for methanation reaction. The size specific is believed to be influenced by the adsorption behavior of the reactant carbon monoxide molecules. Nanoshells, made of a silicate or silver core nanoparticles surrounded by gold coating, have shown unique optical properties [11, 12]. The hope is that chemically modified nanoshells could identify, bind and unlike traditional chemotherapy, selectively destroy cancer cells. The results could not only be a significant reduction of side-effects from chemotherapy but a higher survival rate through early detection of cancerous cells.

The potential impact of nanoparticles - for good or ill - on the environment and human health is enormous. Some concerns about the potential hazards of nanoparticles (including nanotubes) have been raised in the media [13-19]. Yet there is insufficient scientific evidence to support the perception that nanoparticles/nanotubes pose more risk to humans and the environment than airborne automobile exhaust. Nonetheless, there have already been considerable discussions in the media and the U.S. Congress about the potential hazards of nanoparticles. The general public often learns nanoscience through the mass media. Media reporting is such that negative reports are more prominent and sensational, resulting in disproportionate public attention. Moreover, it is an important part of the responsible scientist's mission to educate the public. This can have important repercussions. For example, one notable organization advocating a mandatory moratorium on synthetic nanoparticles is a Canadian based Erosion, Technology, and Concentration (ETC) Group [20]. A recent report by the ETC Group [21] calls on government to adopt a stronger regulations to ensure the safety of workers and consumers. Scientists and engineers who are proponents of nanotech research, therefore, first need to be aware of what information the public is getting via the mass media.

It is true that nanoparticles are more reactive than larger size particles even based on the increased surface area alone, but not many toxicology studies have yet been carried out on these nanoparticle materials. The lack of genuine scientific data on the potential hazards of nanoparticles means that the debate about the risks

of nanotech today may be entirely overrated [22]. In fact, the concerns about the potential hazards of nanoparticles resemble the controversies over genetically modified (GM) crops that perception has quickly overtaken science in the court of public opinion. A close look at the GM food story suggests that public perception, not scientific data, is at the crux of the debacle [23-27]. Unfortunately, the initial negative perceptions of the unknown risks are difficult to overcome by later scientific evidence. Why? Because risk assessments are rooted in human values, common sense, intuition, imagination, memory and past experience. It shows that individual response to risks is likely to be conditioned by feelings like worry, anxiety and fear [28]. The media benefit from the fear factor. Events that are novel, rare, vivid, and that generate tensions and negative feelings are far more newsworthy than ordinary, mundane, and happy events; thus leading to increased newspaper sales and higher advertisement revenues in a kind of positive feedback loop. These types of the controversies between science and politics are well described and documented in a recent book, "Politicizing Science", edited by Gough [29].

Metal Nanoparticles

There are many good examples of size- and shape-dependent properties in metal nanoparticles [30]. The optical properties of metal nanoparticles are particularly convenient in illustrating the nano-size effects. In fact, the optical properties of metal nanoparticles have been admired for a very long time. In the 4th Century AD, metal nanoparticles contained in the glass of the famous Lycurgus Cup [31] exhibiting changing color depending on the viewing light. Analysis of the glass reveals that it contains a small amount of ~70 nm Ag and Au crystals in an approximate molar ratio of 14:1. It was not until 1857, however, that Michael Faraday reported a systematic study of the synthesis and colors of colloidal gold [32]. From the plethora of existing procedures for the synthesis of metal nanoparticles, the most widely used wet-chemical methods are suitable for production of both spherical and anisometric (rod-like or prismatic) nanoparticles [33-36].

Why do the optical properties of metal nanoparticles depend on the particle size and shape? The optical properties of metal nanoparticles are dominated by the collective oscillation of conduction electrons resulting from the interaction with electromagnetic radiation. Hence these properties are mainly observed in Au, Ag, and Cu in which plenty of free conduction electrons are available. The electric field of the incoming radiation induces the formation of a dipole in the nanoparticle. A restoring force in the nanoparticle tries to compensate for this, resulting in a unique resonance wavelength [30] which depends on a number of factors, among which particle size and shape, as well as the nature of

the surrounding medium, are the most important [34]. Bulk Au looks yellowish in reflected light, but thin Au films look blue in transmitted light. This characteristic blue color steadily changes to orange, purple and red, as the particle size is reduced down to ~ 3 nm. These effects are the result of changes in the so-called surface plasmon resonance [31], the frequency at which conduction electrons oscillate in response to the alternating electric field of incident electromagnetic radiation. For nonspherical particles, such as rods, the resonance wavelength depends on the orientation of the electric field. Apart from the linear optical properties, nonlinear optical properties are also of great interest for applications of metal nanoparticles in ultrafast optical switches [37]. In particular, the third-order susceptibility of metal nanoparticles at wavelengths around the plasmon resonance achieves large values with very fast (< 1 ps) response times.

Nanoparticles in Biomedical Applications

In biomedical applications of nanoparticles, magnetic particles have been investigated in targeted drug delivery, ultra-sensitive disease detection, gene therapy, high throughput genetic screening, biochemical sensing, and rapid toxicity cleansing [38]. Early applications focused on ultrafine iron oxide (ferrite) particles, which were found to have zero remanence; applying a magnetic field induces a small dipole moment in the ferrite particles, but this moment disappears once the field is removed. This observation led to the use of iron oxide particulate suspensions (ferrofluids) in mechanical applications, for example, as machine clutches. Over the past decade, a number of biomedical applications have begun to emerge for magnetic micro- and nanoparticles of differing sizes, shapes, and compositions [39].

Bao and Suresh [40] used bead-like 5-10 nm superparamagnetic iron oxide nanoparticles that are sufficiently small to reach intracellular markers of disease or viral infection. The iron oxide probes are coated and then functionalized, e.g., with antibodies, oligonucleotides, or peptide ligands. Once administered to the body, by injection of the nanoparticles into the bloodstream, they should recognize the target molecular markers present inside cells. Any iron oxide nanoparticles clustering as a result of target recognition should then induce a specific signal in magnetic resonance imaging, useful for detecting extremely early signs of disease.

Functionalized magnetic nanoparticles are also being considered as smart treatment agents, as well as diagnostic tools [39, 41-43]. Berry et al. [43] showed derivatized iron oxide magnetic nanoparticles can be effective being placed on the target cells without instigating receptor-mediated endocytosis. The idea here is to bind therapeutic drug molecules onto the

surface of a nanoparticle, then use a magnetic field gradient to draw tagged particles towards the intended treatment site. Present-day drug treatment mechanisms rely on a certain proportion of an injected or orally administered pharmaceutical reaching its intended target. Use of magnetic 'tag and drag' could improve treatment efficacy, while simultaneously reducing administered doses. Targeted drug delivery regimes offer particular advantages for cancer patients. Attaching chemotherapy agents to magnetic nanoparticles and then focusing a magnetic field on the target tumor should pull the drug towards malignant cells minimizing the harmful side effects of the treatment chemical. Tissue and cell specific drug targeting can be achieved by using coated nanoparticles via carrier-drug conjugates that contain a ligand recognized by a receptor on the target cell [42]. This leads to various opportunities such as improving magnetic resonance imaging, hyperthermic treatment for malignant cells, site-specific drug delivery, and the manipulation of cell membranes.

For magnetic bio-sensors magnetoresistive biochips may offer many theoretical advantages. These include the detection of low concentrations of genetic mutations or even single target markers. Portability is one of the chief benefits that magnetic biosensors can offer. The sensors would use DNA microarrays to capture specific toxic agents, such as anthrax. Multisensing chips capable of detecting a range of different agents are also being designed. Magnetic nanoparticles that are produced naturally by bacteria may be genetically programmed to produce the particles when placed in certain chemical environments – and at no other times – they could be used to alert military officials to the presence of toxins, or quickly confirm the release of certain agents [38].

Metal sulfides and selenides are easily made into quantum dots (QDs) which have the potential to act as stable, bright fluorophores for labeling biological specimens. If QDs are to be useful for *in vivo* imaging, they must have an adequate circulation lifetime, show high specific deposition, and retain fluorescence over a long period. Ballou et al. [44] have engineered the surface coating of QDs for long-term fluorescence for *in vivo* imaging in mice. They coated core-shell CdSe-ZnS QDs with amphiphilic polyacrylic acid. After injecting the coated QDs into mice, noninvasive fluorescence imaging showed a circulation lifetime of ~ 12 minutes. To improve this, different polyethylene glycol molecules of increasing lengths were coupled to the initial polymer coat. This increased circulation lifetimes up to ~ 70 minutes. Fluorescence imaging also reveals where the QDs are deposited, including the lymph nodes, bone marrow, liver, and spleen. Fluorescent signals were still observed after eight months, demonstrating the long-term stability of the QDs *in vivo*.

The broad absorption and narrow emission of semiconductor QDs, combined with their brightness and

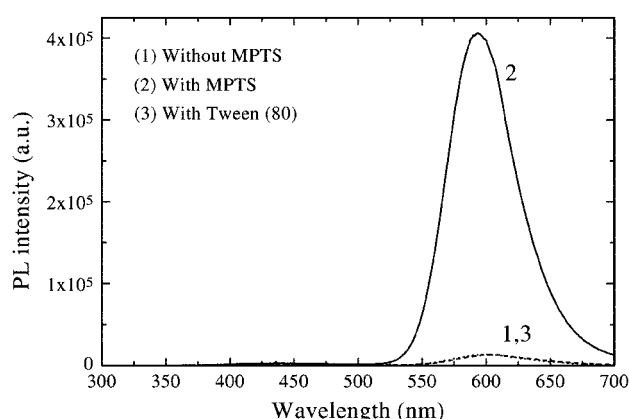


Fig. 1. PL enhancement of ZnS:Mn^{2+} by passivation with 3-methacryloxypropyl trimethoxy silane.

photostability, makes them far better fluorophores for biological labeling than organic dyes. However, the emission from single QD blinks on and off, limiting their use for labeling individual biological molecules. The off-state is thought to occur when a charged dot loses an electron to a surface trap state. If blinking could be suppressed, quantum information processing using single photon sources might also benefit. Blinking in QD emission under the conditions relevant to biological imaging experiments could be suppressed by passivation of QD surfaces with small thiol-containing molecules according to Hohng and Ha [45]. They showed that Streptavidin-coated CdSe/ZnS QDs were immobilized on a biotinylated surface and the emission intensities from hundreds of dots were recorded over time. Hohng and Ha believe that the QD polymer coating has holes that allow only small molecules to pass through to bind onto the ZnS surface. The authors suggest that the thiol moiety, an electron donor, can transfer electrons to the surface traps as Lee et al. described their results in enhanced photoluminescence (PL) of surface passivated ZnS nanophosphors by 3-methacryloxypropyl trimethoxy silane (MPTS) as shown in Fig. 1 [46, 47]. This appears to prevent loss of electrons from the QD to the traps and reduces the blinking frequency.

Luminescent Properties

Visible light emission from phosphors are affected by the particle size as shown by Copeland et al. [48-50]. Within the 100 nm range, the smaller the size, the brighter the photoluminescence as shown in Fig. 2. This is believed to be attributed to the Purcell effect [51-53]. In the case of PL, the surface of the particle has little effect since the bombarding photons are much more energetic than the electrons. However, as the particle size decreases, the Purcell effect [52] may become more significant. The spontaneous emission from the excited state of an atom can be significantly altered by placing it in a cavity with dimensions on the

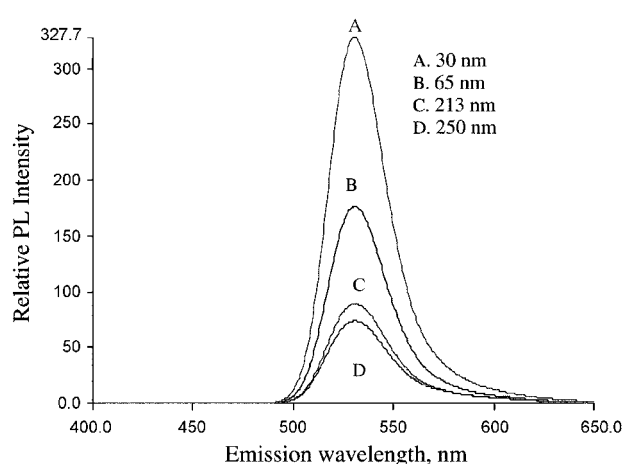


Fig. 2. PL spectra of $\text{Zn}_2\text{SiO}_4/\text{Mn}$ with different particle size; A) 30 nm, B) 65 nm, C) 213 nm, D) 250 nm, after firing in air at 1100°C.

order of its electromagnetic wavelength. The effect has been shown in cavities as large as 180 nm [51]. As the volume of the cavity decreases, the spontaneous emission rate increases [52] by the Purcell factor: $3Q(\lambda/n)^3/(4\pi^2V)$, where V is the cavity volume, λ is wavelength of the incident light, n is the refractive index of the material, and Q is the smaller cavity's inverse line width.

Crystallite Size and Phases

In the case of barium titanate (BaTiO_3 or BT), particles smaller than ~250 nm, determined by x-ray diffractometry (XRD), are shown to exhibit a cubic crystalline phase at room temperature and the size larger than that exhibits tetragonal phase [54]. Schlag and Ericke [55] showed the size-driven phase transition and ferroelectricity in nanocrystalline BT. Lee et al. [56] transformed the XRD cubic phase BT, whose crystallite size is ~50 nm, to tetragonal without increasing the particle or crystallite size as shown in Figs. 3-5. How can this

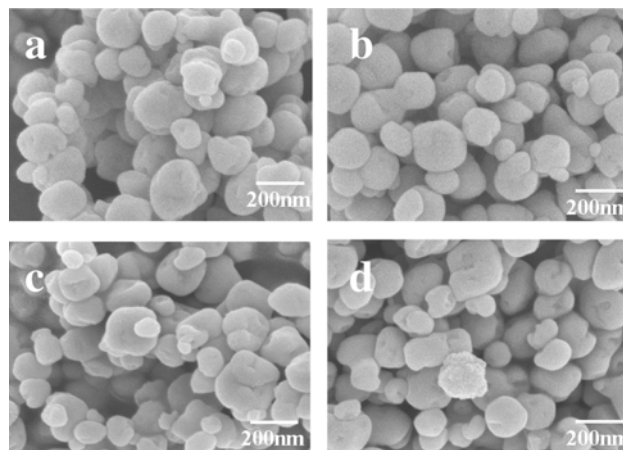


Fig. 3. SEM micrographs of the hydrothermal BaTiO_3 particles after solvothermal treatment with DMF; (a) before treatment, (b) 170 °C for 24 hours, (c) 200 °C for 6 hours, (d) 200 °C for 24 hours.

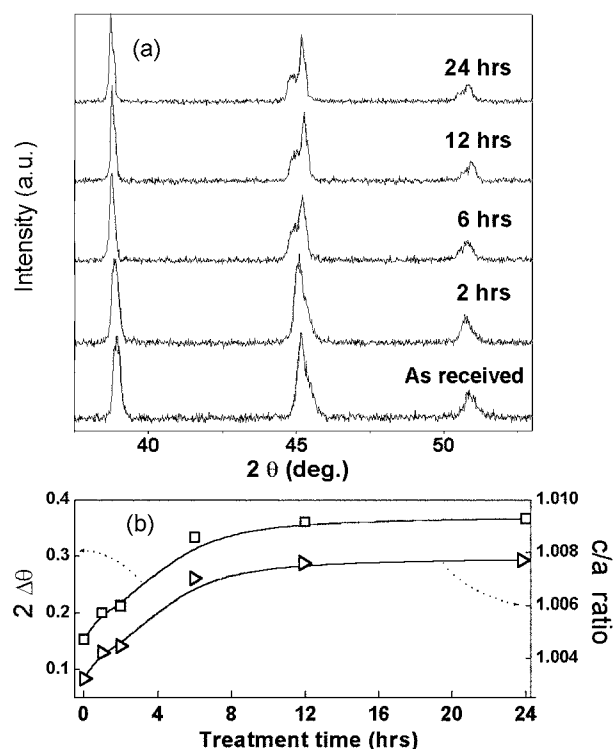


Fig. 4. (a) X-ray diffraction patterns of the hydrothermal BaTiO_3 particles after solvothermal treatment in DMF at 200 °C for different time; (b) peak splitting of the {200} planes and the calculated c/a ratio of samples treated in DMF at 200 °C for different time.

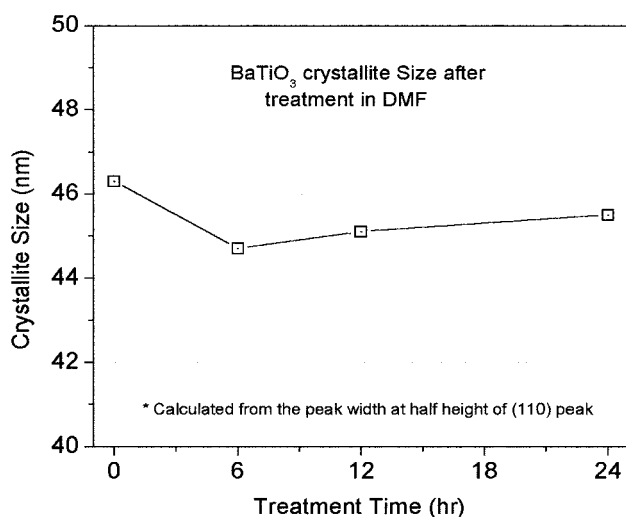


Fig. 5. XRD Crystallite sizes of BT, as a function of DMF treatment time, calculated from the Scherrer's equation.

happen?

The paraelectric (cubic) – ferroelectric (tetragonal) phase transformation in barium titanate is caused by distortion of the oxygen octahedron. The displacement of Ti^{4+} to an off-center position in one direction of the six oxygen ions surrounding it leads to the formation of a polar anisotropic structure upon cooling. This transformation is found to be suppressed in the BaTiO_3

nano-particles (usually $<1\ \mu\text{m}$) [57, 58]. This suppression causes the paraelectric cubic phase to remain stable down to room temperature without transforming to the tetragonal phase at $\sim 130\ ^\circ\text{C}$ as for the bulk crystals [59].

The most often cited causes for this transformation suppression include the size-effect [60–63] and lattice hydroxyl defects [64–66]. The size-effect may be explained by the core (tetragonal)-shell (cubic) model, where the untransformed shell with fixed thickness imposes a clamping constrain on the particle. As the particle size gets smaller, the clamping effect becomes stronger and suppresses the transformation to a greater extent [67, 68].

As some researchers have pointed out [64, 69, 70], the lattice hydroxyl groups play a role in the suppression of the cubic-tetragonal transformation. This is because the charge defects and cation vacancies associated with the hydroxyl groups cause interruption of the long-range cooperative interaction of BaTiO_3 lattice. Hennings and Schreinemacher [64] proved the presence of lattice hydroxyl groups and the relation of their release to the crystallographic recovery in hydrothermal BaTiO_3 . The lattice hydroxyl effect is, nevertheless, often interfered with the size effect because particles will grow or agglomerate when they are heated to remove the hydroxyls. Moderate heating ($<500\ ^\circ\text{C}$) may suppress significant particle growth, but is not enough to fully release the lattice hydroxyls and recover the transformation [71].

In our recent work [56, 59] a significant increase of tetragonality in chemically-treated BT particles was observed after treating the BT in hot dimethylformamide (DMF), which is believed to promote the release of lattice hydroxyls as confirmed by Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), thermogravimetric analysis (TGA), etc. The tetragonality change is monitored by calculating the {200} peak splitting of the XRD pattern. Figure 3 shows the scanning electron micrographs of the samples before and after being treated with DMF under different conditions. It can be seen that the hydrothermal BaTiO_3 particles experienced no apparent morphology changes even after 24 hours treatment at 200 °C.

The XRD patterns of the samples treated with DMF at 200 °C for different lengths of time are shown in Fig. 4a. An apparent splitting of the (200) and (002) planes for tetragonal BT (t-BT) is shown when samples were treated for about 5 hours, and continued to increase as the treatment continued. The tetragonal distortion was also observed in the samples treated at lower temperatures. The peak splitting ($\Delta\theta$) and the c/a ratio for the treated BaTiO_3 samples are shown in Fig. 4b. The c/a ratio for samples treated at 200 °C varies from 1.003 (as-received) to about 1.008 (24 hours). Considering the coexistence of tetragonal and cubic phases and the fully tetragonal distortion ($c/a=1.01$) [60], our treated sample is t-BT, which is also supported by the differ-

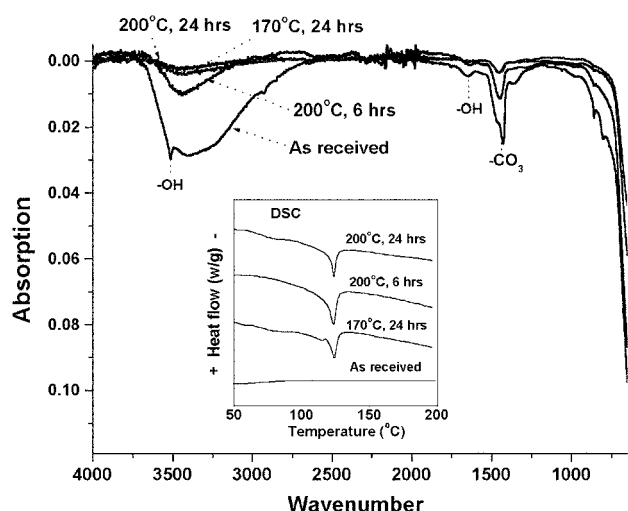


Fig. 6. FTIR spectra of BaTiO_3 samples treated in DMF at 200 °C for different time. Inset is the DSC results of the same samples. The exothermic peaks at 125 °C of treated samples correspond to the tetragonal-cubic ferroelectric transformation.

ential scanning calorimetry (DSC) results shown in the inset of Fig. 6. The endothermic peaks of treated samples at 125 °C represent the tetragonal to cubic transition upon heating, known as the Curie transition point. The BT sample before the treatment is cubic at room temperature as indicated by the XRD and DSC results.

It is believed that this increase of tetragonality results from the release of lattice strain. The presence of hydroxyl groups could be easily detected by FTIR as shown in Fig. 6. High-resolution solid-state proton NMR spectra of the samples treated with DMF at 200 °C for different times are shown in Fig. 7a. Two sharp resonance peaks were distinguished at chemical shift $\delta=5.8$ ppm and 5.0 ppm. According to the reports in the literature [72-74], the peak at 5.8 ppm is attributed to the protons bonded to bridging oxygen ions, i.e., lattice water; the peak at 5.0 ppm is attributed to the protons bonded to the terminal oxygen ions, i.e.,

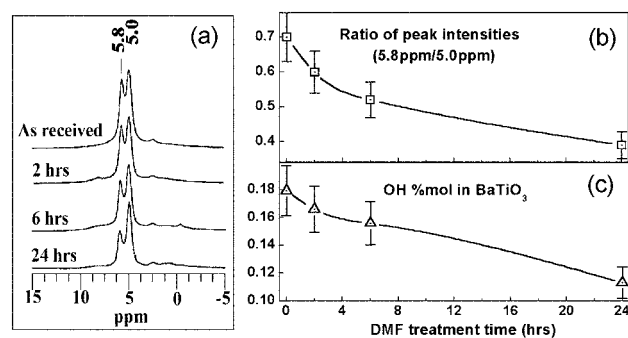


Fig. 7. (a) High resolution solid-state MAS ^1H NMR spectra of BaTiO_3 samples after the DMF treatment at 200 °C; (b) Ratio of ^1H NMR resonance of the lattice hydroxyls to the surface adsorbed hydroxyls (5.8 ppm/5.0 ppm); (c) the molar concentration of the lattice hydroxyls in BaTiO_3 samples after the DMF treatment for different time.

surface water. Deconvoluted information of the NMR spectra is shown in Fig. 7b and 7c. The resonance intensity of the surface water at 5.0 ppm was calculated through the peak area ratio and found to be almost constant. The resonance intensity of the lattice water at 5.8 ppm, which was normalized to the sample weight, decreased with increasing treatment time at 200 °C. The calculated molar concentration of lattice hydroxyls in the BaTiO_3 particles also showed a decreasing trend with longer treatment time.

Issues in Health, Safety, and Public Perception

Although nanotechnology is in its infancy, some researchers and activists are already raising the alarm about the potential dangers of the materials. For instance, the behavior of naturally- occurring nanoparticles is used as an illustration of what could happen with synthetic nanoparticles. Asbestos is a naturally-occurring inert mineral composed of magnesium silicon oxide in a nanoscale fibrous form. It possesses excellent physical/engineering properties for many useful applications, but when inhaled, it can cause lung disease.

Though the risks of nanoparticles may ultimately prove to be minor and avoidable, activists have begun to organize movements against the science, (see, for example, a recent alarming article in the Washington Post [75]). Industry supporters point out that media accounts often confuse facts with popular fiction such as Michael Crichton's best-selling thriller "Prey" [4]. Though media reports are not peer reviewed, we should recognize the power and impact of such articles. How media perceive nanotechnology, right or wrong, needs to be taken seriously by scientists. After all, most of our research support comes from the generosity of the public funding and is based on their perception of the science mainly through mass media.

Nanotechnology is stirring public anxiety and nascent opposition inspired by best-selling thrillers that have demonized the science. What is more, new studies suggesting that not everything in those novels is fantasy – for example, studies have shown that nanoparticles can act as poisons in the environment and accumulate in animal organs [76-78]. Some in California are trying to block construction of a nanotech factory, noting that no government agency has developed safety rules for nano-products. Others want a global moratorium on the field until the risks are better understood [21, 75].

Now, realizing that public perception may be at a turning point, the fledgling industry and government agencies are taking a novel tack, funding sociologists, philosophers and ethicists to study the public's distrust of nano. The struggle for public trust will be challenging, given the frightening tales that have been spun about nano in recent years. In 2000, Bill Joy, co-founder of the computer giant Sun Microsystems, wrote a chilling

and widely read article warning that self-replicating nanomachines could eventually overwhelm the human race and digest the living world into a mass of “gray goo” [79]. In Dan Brown's No. 1 best-selling novel, “Angels & Demons” [80], the Catholic Church denounces nanoscience as evil. These are indeed troubling thoughts, though the physical possibility of the nanomachines acting deadly remains a fictional matter. However, if we do not address these health and safety issues in nanoparticles now, nano-versions of the asbestos, diesel soot and DDT debacles that are the legacy of the last industrial revolution may be the results.

After all the wonderful things nanoparticles can do for us, what are the effects of the nanoparticles on human health? Scientists have known for years that tiny particles such as soot or metal powders can, when inhaled, cause lung disease, cancer and other ailments. The laws of chemistry and physics work differently when particles get down to the nanoscale. As a result, even substances that are normally innocuous can trigger intense chemical reactions. Gold, for example, is a famously inert metal. But nanoparticles of gold are extremely chemically reactive, with the potential to disrupt biological pathways. Titanium dioxide, as another example, is a generally nonreactive ceramic material used in many products, including skin lotions and house paints. Increasingly, however, it is being made in the form of nano-size particles. Tests show that these are highly reactive, generating chemically “hot” free radicals that can literally burn up bacteria. That makes some experts concerned about impacts on soil ecology if the particles are released. Nanoparticles are reported to produce enhanced levels of lung inflammation, fibrosis, and tumor responses when compared with fine-sized particles (size range >100 nm to $3\text{ }\mu\text{m}$) of similar or identical composition [76-78]. It is important to note that the total lung toxicity database for comparing the effects of ultrafine or nanoparticles versus fine-sized particles consists primarily of studies on three particle-types: titanium dioxide (TiO_2), carbon black, and diesel particles on rats [81-83].

Pulmonary toxicity studies in rats demonstrate that lung exposures to ultrafine or nanoparticles produce greater adverse inflammatory responses compared with larger particles of identical composition at equivalent mass concentrations. Surface properties (e.g., surface area) and free radical generation by the interaction of particles with cells appear to play important roles in nanoparticle toxicity [76-78]. Contributing to these effects is the very high size-specific deposition of nanoparticles when inhaled as singlets rather than aggregated particles [84]. Results from the limited toxicological database have fostered the perception that all nanoparticles are toxic [85]. As the results of newly-generated nanoparticulate toxicity studies are reported in the scientific literature, we will find the issue of nanoparticle toxicity is more complicated than previously

thought. Few data exist regarding the health and environmental effects of engineered nanoparticles, yet some organizations and activists are calling for bans or moratoriums on the research, development, and sale of these materials. Foremost among those activists is Mooney [86], who has called for a moratorium on commercial production of nanomaterials until their risks are better elucidated and regulations put in place. He spearheaded much of the opposition to agricultural biotechnology — opposition so successful that it made biotech giant Monsanto Co.'s name synonymous with “PR failure” and resulted in European restrictions on imported crops that continue to cost the United States hundreds of millions of dollars in lost trade every year.

Recent toxicity studies have demonstrated that high-dose, intratracheally-instilled, single walled carbon nanotubes in the lungs of rats may produce unusual foreign-body tissue reactions [85]. Because there is a paucity of health, safety, and environmental data on nanomaterials, hazard studies need to be implemented with a variety of nanoparticle types before any firm conclusions can be derived about their potential risks. Lam of Wyle Laboratories in Houston and his colleagues [87] introduced three kinds of carbon nanotubes, after washing, into the lungs of mice and examined them as much as three months later. All three types caused lung granulomas — abnormalities that interfere with oxygen absorption and can progress to fatal lung disease. Although each mouse got just one exposure, the lesions got worse over time, with some progressing to tissue death. On average the reactions were worse than those in mice given equal amounts of quartz particles, which toxicologists use as their “serious damage” standard. The other study was led by David Warheit at DuPont Co.'s Haskell Laboratory involving similar exposures in rats [84]. Perhaps not surprisingly, 15 percent of the animals getting the highest dose died from lung blockages within 24 hours and all the surviving rats developed granulomas, without the inflammatory responses that usually accompany those lesions [85]. Shvedova et al. [88] reported that unpurified carbon nanotubes interfered with the free radical elimination mechanism in cultured skin cells, allowing the cells to suffer oxidative stress. What happens to nanoparticles months and years after their release is currently unknown. Like all factories, carbon nanotube facilities must submit “material safety data sheets” describing the substances they handle and assuring that appropriate measures are in place. But the data sheets that nanotube factories are filing to regulators are simply for graphite. The U.S. Environmental Protection Agency is considering proposals for what would be its first funded studies on the potential impacts of nanoparticles on the environment. The agency's request for proposals, published last year, begins candidly, “There is a serious lack of information about the human health and environmental implications of manufactured nanomaterials” [75]. Studies of nano-

technology's health and environmental impacts are beginning to appear in peer-reviewed journals and government and industry officials are nervous about the public opinion solidifying long before then. Therefore, the nanoparticle manufacturers should more aggressively pursue research on the potential health and environmental effects of these materials. If the industry delays or fails to carry out the study, it would only prolong the debate and increase the destructive potential which is against the interest of the industry.

Inhaled particles may not always stop at the lung. Experiments by toxicologists Gunter Oberdörster and coworkers [78] at University of Rochester showed that nanoparticles can make their way from a rat's throat into its brains, apparently via the nasal cavities and olfactory bulb. How nanoparticles interact with cells in the brains is not known. Rats exposed to ^{13}C -labeled nanoparticles for six hours show an increase in ^{13}C concentration in parts of the brain. There is a persistent increase in ^{13}C in the olfactory bulb and some inconsistent evidence of increases in the cerebellum and cerebrum. Nanoparticles deposited in the nasal region of rats are translocated along the olfactory nerve to the olfactory bulb. The results pose a number of questions for further study of environmental exposure to nanomaterials. A number of issues are yet to be resolved: the mechanism of neuronal uptake; how physical and chemical properties of the particles affect transport; how far the particles can penetrate the central nervous system beyond the olfactory bulb; and the long-term toxic effects of accumulation in the brain.

As the properties of QDs can be improved or modified for various applications by introducing an adsorbed layer or a particle surface coating, they are likely to play an important role in the toxicity testing and corresponding safety assessments of nanoparticles. Derfus et al. [89] showed QD toxicity of CdSe in hepatocyte cells as a model for the liver. Surface oxidation of CdSe QDs in air and under exposure to UV light led to a dramatic decrease in cell viability. The introduction of surface coatings on CdSe, by ZnS capping layer with organic ligands followed by cross-linking, reduced the oxidation and hence the cytotoxicity of the nanoparticles. Using a pulmonary bioassay toxicity methodology, pigment-grade TiO_2 particles with different surface coatings/treatments, demonstrated that one of the TiO_2 particle surface coatings produced increased pulmonary inflammation compared with the other formulations containing different surface coatings [90]. The presence, absence, or composition of surface coatings may serve to complicate our perceptions regarding the toxicity of nanoparticles. Few data exist regarding the health risks of dermal or oral exposures to nanomaterials. What is needed at this time is a concerted effort to develop methodologies and protocols concomitant with the implementation of hazard/toxicity

studies, as well as workplace exposure assessments, to better ascertain the impact of nanomaterials on human health.

Summary and Conclusions

Nanoparticles and nanomaterials represent an evolving technology that has the potential to have an impact on an incredibly wide number of industries and markets. There are many novel properties and applications of nanoparticles demonstrated; from catalysis, environmental remediation, biomedical to information displays, and electronics. What does the future hold for nanoparticles and their manufacturers? The use of nanoparticles is set to escalate and the market has the potential to increase dramatically over the next ten years as more uses for these materials are developed and commercialized. A major impact will be in the medical and pharmaceutical markets as new treatments relying on nanoparticles obtain licenses for use. However, there are many other applications where the time-to-market is considerably less than for the pharmaceutical and medical sector, particularly for consumer goods. But there are still many challenges facing nanomaterials producers that need to be overcome before this potential can be fully realized, including:

- How to produce materials in volume production at viable prices – many current techniques cannot scale – up sufficiently to produce the cost reductions required to target volume markets.
- Consistency and reliability in volume production – tolerances on size and composition can be achieved reliably for simple compounds such as binary oxides and for more complex materials in small batch production.
- Health, safety, and environment – the profile of nanotechnology has increased in recent months, with a focus on the potential long-term effects of nanoparticles and, more immediately, of nanoparticles on humans and the environment.

We need to assess the risks of nanoparticles on the environment and to occupational exposure, as well as the usefulness of nanoparticles and quantum dots in biomedicine. Some of the concerns expressed in the media, by environmentalist groups, and by some scientists may trigger anxiety leading to anti-nanotechnology. We need to understand the information on the emotional reactions and feelings that nanotechnology risks are as important as – or perhaps more important than – the mere collection of scientific data about the potential hazards of nanomaterials. The failure to understand or acknowledge how the lay public perceive, assess and make decisions about risk may hamper the trajectory of nanotechnology as public policies and business practices are adopted. Perceived risks are real and may very well constitute the tipping point that will decide whether nanotech succeeds.

References

1. M.J. Pitkethly, Nanoparticles as building blocks?, *Nano-today*, Materials Today Supplement, Dec. 2003, pp. 36-42, Elsevier Ltd., Kidlington, UK.
2. The nanotech report 2003, Investment Overview and Market Research for Nanotechnology, Vol. II, Lux Capital, New York (2003).
3. P. Holister and T.E. Harper, The Nanotechnology Opportunity Report, CMP Cientifica, Madrid (2002).
4. M. Crichton, *Prey: a Novel*, HarperCollins; Publisher (November 25, 2002) ISBN: 0066214122.
5. Nanotechnology – size matters: building a successful nanotechnology company, A 3i white paper in association with the Economist Intelligence Unit and the Institute of Nanotechnology, London (2002).
6. M.J. Felton, *Today's Chemist*, March 2004, pp. 19-21, www.tcawonline.org.
7. J.S. Murday, The Coming Revolution: Science and Technology of Nanoscale Structures. The AMPTIAC Newsletter, Spring, 66 (2002) 5-12.
8. N. Kobayashi, Nanotechnology, Hitachi Research Institute Report, Toyo Keizai Shimpou-sha, Tokyo (2001).
9. W. Zhang, *J. Nanoparticle Res.* 5 (2003) 323-332.
10. A.P. Weber, M. Seipenbusch, and G. Kasper, *J. Nanoparticle Res.* 5 (2003) 293-298.
11. J.B. Jackson and N. J. Halas, *J. Phys. Chem. B.* 105 (2001) 2743-2746.
12. S. Lal and S.L. Westcott, *J. Phys. Chem. B.* 106 (2002) 5609-5612.
13. G. Brumfiel, *Nature* 424 (2003) 246-248.
14. R. Dagani, "Nanomaterials: Safe or Unsafe?" *Chemical and Engineering News* 81 (2003) 30-33.
15. B.J. Feder, "Nanotechnology Group to Address Safety Concerns," *New York Times*, July 7, 2003 p. 6.
16. B.J. Feder, "Research Shows Hazards in Tiny Particles," *New York Times*, April 14, 2003, p. 8.
17. Nature's Editorial, "Don't Believe the Hype" *Nature* 424 (17 April 2003) 237.
18. R.F. Service, "Nanomaterials Show Signs of Toxicity," *Science* 300 (2003) 243-245.
19. C. Witchalls, "The Next Asbestos?" *Newsweek* (Atlantic Edition) (2003) 142: 49.
20. www.etcgroup.org.
21. "Size Matters!" ETC Group News Release April 14, 2003.
22. G. Reynolds, "Forward to the future: Nanotechnology and regulatory policy." Nov. 2002, www.pacificresearch.org/pub/sab/techno/forward_to_nanotech.pdf.
23. J.E. Losey and L.S. Rayor, *Nature* 399 (1999) 214-215.
24. R.L. Hellmich, B.D. Siegfried, M.K. Sears, D.E. Stanley-Horn, M.J. Daniels, H.R. Mattila, T. Spencer, K.G. Bidne, and L.C. Lewis, "Monarch Larvae Sensitivity to *Bacillus thuringiensis*-Purified Proteins and Pollen." *Proc. National Academy Sci.* 98 (2001) 11925-11930.
25. K.S. Oberhauser, M.D. Prysby, H.R. Mattila, D.E. Stanley-Horn, M.K. Sears, G. Dively, E. Olson, J.M. Pleasants, Wai-Ki F. Lam, and R.L. Hellmich, "Temporal and Spatial Overlap Between Monarch Larvae and Corn Pollen." *Proc. National Academy Sci.* 98 (2001) 11913-11918.
26. J.M. Pleasants, R.L. Hellmich, G.P. Dively, M.K. Sears, D.E. Stanley-Horn, H.R. Mattila, J.E. Foster, P. Clark, and G.D. Jones, "Corn Pollen Deposition on Milkweeds in and Near Cornfields." *Proc. National Academy Sci.* 98 (2001) 11919-11924.
27. M.K. Sears, R.L. Hellmich, D.E. Stanley-Horn, K.S. Oberhauser, J.M. Pleasants, H.R. Mattila, B.D. Siegfried, and G.P. Dively, "Impact of Bt Corn Pollen on Monarch Butterfly Populations: A Risk Assessment." *Proc. National Academy Sci.* 98 (2001) 11937-11942.
28. G.F. Loewenstein, E.U. Weber, C.K. Hsee, and N. Welch, "Risk as Feelings." *Psychological Bulletin* 127 (2001) 267-286.
29. M. Gough (ed.), *Politicizing Science*, Hoover Inst. Press, Stanford, CA, 2003.
30. L.M. Liz Marzn, "Nanomaterials: formation and colors" *Materials Today*, February 2004 pp. 26-31.
31. U. Kreibitz, and M. Vollmer, *Optical Properties of Metal Clusters*, Springer-Verlag, Berlin (1996).
32. M. Faraday, *Philos. Trans. Royal Soc., London* 147 (1857) 145.
33. A. Henglein, *J. Phys. Chem.* 97 (1993) 5457-5461.
34. P. Mulvaney, *Langmuir* 12 (1996) 788-800.
35. M. Brust, J. Fink, D. Bethell, D.J. Schiffrin, and C.J. Kiely, *J. Chem. Soc., Chem. Comm.* (1995) 1655-1656.
36. I. Pastoriza-Santos and L.M. Liz Marzn, *Langmuir* 18 (2002) 2888.
37. F. Hache, D. Ricard, and C. Flytzanis, *J. Opt. Soc. Am. B* 3 (1986) 1647-1651.
38. P. Gould, "Nanoparticles: probe biosystems" in *Materials Today*, February 2004, pp. 36-43.
39. C.C. Berry and A.S.G. Curtis, *J. Phys. D: Appl. Phys.* 36 (2003) R198-R206.
40. G. Bao and S. Suresh, *Nature* 2 (2003) 715-725.
41. C. Alexiou, R. Jurgons, R.J. Schmid, C. Bergemann, J. Henke, W. Erhardt, E. Huenges, and F. Parak, *J. Drug Target.* 11 (2003) 139-149.
42. A.K. Gupta and A.S.G. Curtis, *Biomaterials* 25 (2004) 3029-3040.
43. C.C. Berry, S. Charles, S. Wells, M.J. Dalby, A.S.G. Curtis, *Intern. J. Pharmaceutics* 269 (2004) 211-225.
44. B. Byron Ballou, C. Lagerholm, L.A. Ernst, M.P. Bruchez, and A.S. Waggoner, *Bioconjugate Chem.* 15 (2004) 79-86.
45. S. Hohng and T. Ha, *J. Am. Chem. Soc.* 126 (2004) 1324-1329.
46. B.I. Lee and S. Lu, *J. Ceram. Proc. Res.* 1 (2000) 20-26.
47. S. Lu, and B.I. Lee Z.L. Wang, and C. Summers, *J. of Lumin.* 92 (2000) 73-78.
48. T.S. Copeland, B.I. Lee, J. Qi, and A.K. Elrod, *J. of Lumin.* 97 (2002) 168-173.
49. T.S. Copeland, B.I. Lee, A.K. Elrod, and J. Qi, "Effect of Particle Size on the Luminescence of Europium Doped Yttrium Oxide Nano-phosphors," *MRS Symp. Proceedings, Nano Particulates*, Vol. 704, Materials Research Soc., Pittsburgh, PA, 2002.
50. B.I. Lee, T.S. Copeland, A.K. Elrod, and J. Qi, "Synthesis of Nano-Sized Europium Doped Yttrium Oxide," *Ceramic Trans*, Vol. 126, Am. Ceramic Soc., Westerville, OH, 2002, pp. 23-29.
51. O. Painter, R.K. Lee, A. Scherer, A. Yariv, J.D. O'Brien, P. D. Dapkus, and I. Kim, *Science* 284 (1999) 1819-1827.
52. J.M. Gerard, and B. Gayral, *Physica E* 9 (2001) 131-139.
53. J.-M. Gerard and B. Gayral, *Journal of Lightwave Technology* 17 (1999) 2089-2095.
54. S. Venigalla, "Hydrothermal BaTiO₃-based dielectric for BME X7R/X5R MLCC Applications," Center for Dielectric Studies, Spring Meeting, Penn State Univ., April 22-23, 2002.
55. S. Schlag and H-F. Eicke, *Solid State Comm.* 91 (1994) 883-887.
56. B.I. Lee, P. Badheka, D.H. Yoon, V. Magadala, and M.

- Wang, J. *Ceram. Porc. Res.* 5[2] (2004) 127-132.
57. F.S. Yen, H.I. Hsiang, and Y.H. Chang, *Jpn. J. Appl. Phys.* 34 (1995) 6149-6154.
 58. T. Yamamoto, H. Niori, and H. Moriwake, *Jpn. J. Appl. Phys.* 39 (2000) 5683-5688.
 59. L. Qi, B.I. Lee, and W.D. Samuels, *Adv. Mater.*, submitted for review.
 60. M.H. Frey, D.A. Payne, *Phys. Rev. B* 54 (1996) 3158-3160.
 61. G. Arlt, D. Hennings, G. De With, *J. Appl. Phys.* 58 (1985) 1619-1623.
 62. K. Uchino, E. Sadanaga, and T. Hirose, *J. Am. Ceram. Soc.* 72 (1989) 1555-1561.
 63. D. McCauley, R.E. Newnham, and C.A. Randall, *J. Am. Ceram. Soc.* 81 (1998) 979-984.
 64. D. Hennings and S. Schreinemacher, *J. Euro. Ceram. Soc.* 9 (1992) 41-46.
 65. S. Wada, T. Suzuki, and T. Noma, *J. Ceram. Soc. Jpn.* 104 (1996) 383-391.
 66. E. Ciftci and M.N. Rahaman, *J. Mater. Sci.* 36 (2001) 4875-4880.
 67. J.C. Niepce, in *Surfaces and Interfaces of Ceramic Materials*, (Eds. L. C. Dufoir et al.), Kluwer Academic, Dordrecht 1989, pp. 521-533.
 68. B.D. Begg, E.R. Vance, and J. Nowotny, *J. Am. Ceram. Soc.* 77 (1994) 3186-3191.
 69. R. Waser, *J. Am. Ceram. Soc.* 71 (1988) 58-61.
 70. Y.M. Baikov and E.K. Shalkova, *J. Solid State Chem.* 97 (1992) 224-229.
 71. H. Jena, K.V.G. Kutty, and T.R.N. Kutty, *Mater. Res. Bull.* 39 (2004) 489-494.
 72. G. Cho, Y. Wu, and J.L. Ackerman, *Science* 300 (2003) 1123-1128.
 73. V.M. Mastikhin, and A.V. Nosov, *React. Kinet. Catal. Lett.* 46 (1992) 123-128.
 74. A. Maijanen, E.G. Derouane, and J.B. Nagy, *Appl. Surf. Sci.* 75 (1994) 204-209.
 75. R. Weiss, "For Science, Nanotech Poses Big Unknowns," *The Washington Post*, Sunday February 1, 2004, page A01, <http://www.washingtonpost.com/wp-dyn/articles/A1487-2004Jan31.html>
 76. K. Donaldson, D. Brown, A. Clouter, R. Duffin, W. MacNee, L. Renwick, L. Tran, and V. Stone, *J. Aerosol Med.* 15 (2002) 213-220.
 77. G. Oberdrster, *Philos. Trans. R. Soc. London, Ser. A* 358 (2000) 2719-2724.
 78. R. Gelin, G. Oberdrster, J.N. Finkelstein, A.C.P. Elder, and C. Cox, *Inhalation Toxicology*, vol. 16, 2004, in press.
 79. B. Joy, Why the future doesn't need us, *Wired Magazine*, April 2000, www.wired.com/wired/archive/8.04/joy.html.
 80. D. Brown, "Angels & Demons," Pocket Star Publisher, June 2001, ISBN 0671027360.
 81. C. Dasenbrock, L. Peters, O. Creutzenberg, and U. Heinrich, *Toxicol. Lett.* 88 (1996) 15-21.
 82. K.E. Driscoll, J.M. Carter, B.W. Howard, D.G. Hassenbein, W. Pepelko, R.B. Baggs, and G. Oberdrster, *Toxicol. Appl. Pharmacol.* 136 (1996) 372-380.
 83. J.L. Mauderly, *Toxicol. Sci.* 62 (2001) 6-11.
 84. D.B. Warheit, B.R. Laurence, K.L. Reed, D.H. Roach, G.A.M. Reynolds, and T.R. Webb, *Toxicol. Sci.* 77 (2004) 117-121.
 85. D.B. Warheit, "Nanoparticles: health impacts?," *Materials Today*, February 2004 pp. 32-35.
 86. P.R. Mooney, "Small is dangerous: the threat of nanotechnology," 30th Anniversary Conf. on Is Small Beautiful? London, UK, Sept. 3, 2003.
 87. C-W. Lam, J.T. James, R. McCluskey, and R.L. Hunter, *Toxicol. Sci.* 77 (2004) 126-134.
 88. A.A. Shvedova, V. Castranova, E.R. Kisin, D. Schwegler-Berry, A.R. Murray, V.Z. Gandelsman, A. Maynard, and P. Baron, *J. Toxicol. Environ. Health, Part A* 66 (2003) 1909-1926.
 89. A.M. Derfus, W.C. Chan, and S.N. Bhatia, *Nano Lett.* 4 (2004) 11-18.
 90. E. Bermudez, J.B. Mangum, B.A. Wong, B. Asgharian, P. M. Hext, D.B. Warheit, and J.I. Everitt, *Toxicologist* 72 (2003) 298A.