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Nanomaterials and the Environment

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A white policy paper:
Nanomaterials and the Environment

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Abstract—This white policy paper will discuss what is known about nanomaterials (manufactured products less than 100 nanometers in size) and what further knowledge is needed to assess the potential impact of nanomaterials on the environment and human health. The synthesis of nanomaterials already found in hundreds of products on the market has seen dramatic growth in the last decade in what has been a highly diverse and rapidly emerging technology. While the novel properties that arise when a material is reduced to the nanoscale make them useful for a wide range of applications, little is known about how these properties will affect human health and the environment. These novel properties also confer unusual mechanisms of toxicity and risks that cannot be predicted by existing knowledge or extrapolation from what is known regarding the materials at the macroscale. The prevalence of these nanomaterials in industry and society guarantee that they will eventually enter the environment. As long as the potential risks of nanomaterials are unclear, measures may be taken to ensure that nanomaterial release into the environment and exposure to the public is not left unchecked.

Keywords— nanomaterials, nanoproducts, nanotechnology, environment

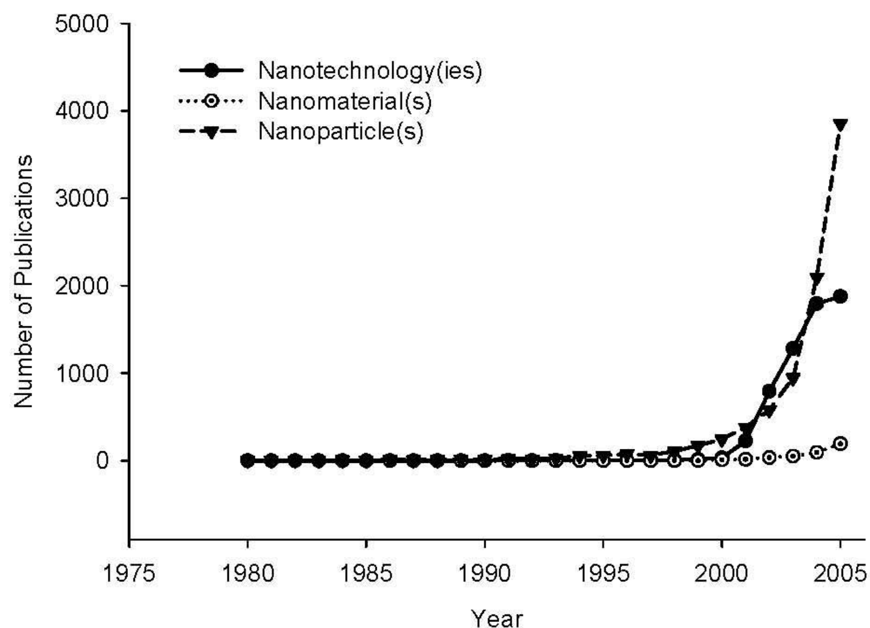

Figure 1. The growth in data found in the literature on manufactured nanoproducts via a search of life science journal articles using the terms “nanotechnology,” “nanomaterial,” and “nanoparticle.”

Examples and Characteristics of Nanoproducts

Table 1

Structure	Size	Base Material	Example
Tubes	Diameter: 1-100 nm	Carbon	Single-walled carbon nanotubes (SWCNTs), multi-walled carbon nanotubes (MWCNTs)
Wires	Diameter: 1-100 nm	Metals, semiconductors, oxides, sulfides, nitrides	Silicon nanowires, Cadmium tellurium nanowires
Crystals, clusters	Radius: 1-10 nm	Semiconductors, metals, metal oxides	Quantum dots, Titanium dioxide, Silicon dioxide
Spheres	Radius: <100 nm	Carbon	Fullerenes (C60, buckyballs)

Adapted from J. Jortner and C. N. R. Rao [3]

INTRODUCTION

The use of nanomaterials, manufactured products less than 100 nanometers in size, has seen dramatic growth in the last decade and promises to continue to grow in the future. Currently, nanomaterials are used in medical devices, pharmaceuticals, environmental remediation, and in scores of consumer products ranging from cosmetics to electronics, with numerous forthcoming applications [1, 2]. Forecasts predict nanotechnology, the science of using nanomaterials and nanodevices, to be a ten billion dollar industry by 2010, growing to one trillion dollars by 2015. Figure 1 demonstrates in graphic form the growth in data found in the literature on manufactured nanoproducts via a search of life science journal articles using the terms “nanotechnology,” “nanomaterial,” and “nanoparticle.”

Nanomaterials can be composed of many different base materials and have different structures. A few examples of nanomaterials are listed in Table 1 [Adapted from 3]. What makes nanomaterials unique lies at the nanoscale, in which these materials undergo changes in quantum mechanical effects and physical properties compared to the identical materials synthesized at the macroscale [4, 5]. For example, gold in its bulk form has been regarded to be chemically inert, especially to reactions with oxygen and hydrogen. However, at the nanoscale, gold has been found to be extremely reactive and is extensively being developed as a catalyst for a large range of chemical reactions [6, Reviewed by 7, 8]. Typical nanomaterials include carbon-based fullerenes (buckminsterfullerene, buckyballs, C60 fullerenes) and nanotubes, which have been used to selectively target and destroy cancer cells [9]; quatum dots, which are nanoscale semiconductor crystals used to track protein transport in biological systems; and metal oxanes, such as titanium oxide, which are used in sunscreens for their UV reflecting capability and for the formulation of membranes and films [10].

Past experience has shown development of innovative products is not always associated with benign consequences in the long-term, as illustrated by methyl tertiary butyl ether (MTBE), dichloro-diphenyl-trichloroethane (DDT) and chlorofluorocarbons (CFCs), compounds which have had significant adverse health and environmental impacts. While the novel properties that arise when a material is reduced to the nanoscale make them useful for a wide range of applications, little is known about how these properties will affect human health and the environment. These novel properties also confer unusual mechanisms of toxicity and risks that cannot be predicted by existing knowledge or extrapolation from what is known regarding the behavior of these materials at the macroscale [5]. The potential risks nanomaterial poses promises to be contentious until the uncertainties regarding toxicity are known. Because nanomaterials have so many applications, with more to come, the prevalence of these materials in industry and society is ensured. The purpose of this review is

to discuss what is known about nanomaterials and what further knowledge is needed to assess the potential impact of nanomaterials. Since fate and transport of nanomaterials under a variety of conditions has not been systematically studied, this paper will attempt to address the potential risks and hazards of nanomaterials in a general way using the few examples that are available.

NANOMATERIALS AND THE ENVIRONMENT

Release of nanomaterials into the environment will most likely arise from several points in the nanomaterial "life-cycle," including release during the manufacturing process, use of the products into which nanomaterials are incorporated, and, inevitably, with the disposal of these products. Yet, little is known about nanomaterial fate and behavior in the environment. Mobility and interaction with biological systems is largely dependent on the specific size, shape, and chemistry of a nanomaterial. Thus, different types of nanomaterials will have different types of impacts on the environment and human health.

One striking example that underscores the unique and unpredictable behavior of nanoparticles, is that of fullerenes. It would be predicted that an all-carbon molecule, such as a fullerene, would be quite hydrophobic and insoluble in water. Interestingly, researchers found the individual hydrophobic fullerene molecules to acquire charge, becoming capable of forming larger aggregate structures (nC60) which suspend in water [11, 12]. Such suspensions would permit greater distribution of fullerenes in the aqueous environment. Additionally, salt-free solutions solubilize [13] while high salt conditions neutralized the nC60 fullerene crystals, causing them to fall out of solution [14, 15], allowing for accumulation in sediments. These studies and others demonstrate that fate of fullerenes can change depending upon the properties of the aquatic ecosystem in which they are found.

Once in the environment, a number of factors may sequester, modify, mobilize or degrade nanomaterials, thereby influencing their bioavailability and potential toxicity. An important factor that will affect the environmental fate of nanomaterials is hydrophilicity, as mentioned above. Water-solubility correlates with the potential for dispersion over vast areas and increases the potential for exposure. It is unknown whether nanomaterials with low water solubility will bind with organic molecules in the aquatic environment to increase their affinity for the aqueous phase and potentially increase exposure to biota. As discussed below, interactions with bacterial communities, mineral surfaces, and pH gradients are also likely to influence the fate and potential risks of water-soluble nanomaterials.

Water solubility of a nanomaterial is so important that unique surface coatings and derivatives are being developed to deliver nanomaterials for in situ ground water remediation and delivery of drugs. For example, nanoiron is coated before being introduced into the environment for ground water remediation [16, 17]. Quantum dots consist of a metal complex core which is coated for biological activity [reviewed by 4]. Hydroxylation of fullerenes, intentionally or inadvertently during the production process, will increase their solubility [18]. Adding charged functional groups or surface coatings generally

improve water solubility and suspension characteristics of nanoparticles, but can also impart selectivity in physical or chemical interactions.

Another factor that will affect the fate of nanomaterials in the environment is the ability to form large colloidal aggregates. Carbon nanotubes and nanoiron particles form aggregates of much larger dimensions than the individual nano-sized particles [reviewed by 19, 20]. The large surface areas of smaller nanoparticles may allow for enhanced bioavailability and consequently, greater potential for exposure and toxic effects. Supporting this, evidence suggests the adverse effects of fullerenes on bacterial populations to be greater for smaller aggregates than for larger ones [21], and the antimicrobial properties of TiO_2 nanoparticles to be inversely related to the particle size [22]. In contrast, the tendency of a nanomaterial to attach to surfaces or form aggregates can prevent its flow through porous media such as soil or reduce its bioavailability and exposure potential. Thus, factors that promote coalescence of nanomaterials in the environment can modify transport and subsequent toxicity. Depending on the specific nanomaterial, aggregation may mitigate both exposure and toxicity in some cases, while in others nanomaterial aggregation may increase risk of toxic effects.

Besides water solubility and aggregation, oxidation-reduction (redox) reactions are believed to be important for the transformation and environmental fate of nanomaterials. Chemical or biological oxidation is able to add, remove, or modify functional groups associated with mineral-based nanomaterials. The high electron affinity and ability to participate in redox reactions [reviewed by 23] make fullerenes capable of producing reactive oxygen species, which can oxidize organic compounds in the environment and which are key players in the induction and propagation of oxidative stress in vivo.

Microorangisms often mediate redox reactions in the environment. It is highly plausible that the interaction of nanomaterials with microorganisms normally present in soil and groundwater may alter their transport, retention, bioavailability and toxicological characteristics. Whether these biotransformations can occur to an appreciable extent in the natural environment and how such transformations could affect nanomaterial toxicity is unclear. The contribution of bacteria and fungi in soil and water to the degredation of manufactured nanomaterials needs further examination. Conversely, the effects of nanomaterials on microbial populations in the natural environment are also important to consideration. Microorganisms are a principle component of many ecosystems, serving as a basis of food webs and as important contributors to soil health. As such, disturbing microbial homeostasis would ultimately affect biota in all parts of the system. The ability of photo-activated TiO_2 nanoparticles to effectively oxidize organic matter and inactivate microbes [24-26] is not only highly useful for treatment of water systems, but also presents a possible risk to natural microbial populations if discharged without restraint into the environment.

As seen with TiO_2 nanoparticles, ultraviolet (UV) radiation can also change the characteristics of nanomaterials [27, 28]. Fullerenes strongly absorb UV light and in a manner similar to TiO_2, photoexcitation can lead to the generation of cytotoxic reactive oxygen species (ROS) [23]. Quantum dots have also been

found to degrade under photolytic and oxidative conditions [29], as occurs in the natural environment. Compromising the bioactive coat of quantum dots can expose the metalloid core, which is potentially toxic and which may participate in undesirable or unanticipated reactions.

In summary, environmental fate is dependent on the chemistry of the specific nanomaterial and can further be influenced by environmental conditions such as physical binding or chemical reactivity with other compounds, water solubility, aggregation, and oxidation-reduction reactions. These modifications will greatly influence the behavior of nanomaterials, including their interaction with fauna and flora, accumulation in biological systems and toxicity.

NANOMATERIALS AND BIOLOGICAL SYSTEMS

Once exposure occurs, the biological fate of nanomaterials depends on the balance of four processes: absorption, distribution, metabolism and excretion. To determine the risk of nanomaterials, information is needed for each of these processes. Some studies have been done, but more are needed. Below is a discussion of the biological fate of nanomaterials – what is known and some areas needed to be further explored.

Exposure and absorption

Currently, we lack a complete understanding of what forms of nanomaterials are bioavailable or whether they will bioaccumulate. However, we do know that exposure to nanomaterials can occur via dermal, gastrointestinal, or inhalation routes. While exposure will depend on a number of factors, such as how well nanomaterials are contained during manufacture, how widespread their use becomes, and if they are biodegradable or recoverable, the extent of absorption into the biological system depends on the chemical and physical properties of the nanomaterial.

Nanomaterials are incorporated into many consumer products that are meant to be applied to the skin. Whether a nanomaterial enters the body through the skin can depend upon whether the skin is injured, to what degree the skin is flexed [30], and to what degree the nanomaterials are lipid soluble. The latter may depend upon the surface coating or carrier of the nanomaterial. For example, studies are currently be done to optimize carriers of nanomaterials for topically applied medicine [30, 31]. Current dermal exposure to nanomaterials occurs via sunscreen and cosmetics, such as by UV absorbing TiO_2 and ZnO. There have been no human clinical reports of toxicity from TiO_2 and ZnO, and these two nanomaterials have only been found toxic at very high doses in cell culture system [32]. However, quantum dots topically applied to intact skin at occupationally relevant doses were found to penetrate and localize within the dermis in a few hours, which is a concern for occupational settings [33]. If nanomaterials contaminate the water, air, or soil, dermal exposure may become widespread for many organisms.

Gastrointestinal tract (GI) exposure may occur from the use of nanomaterial-containing cosmetics or drugs or as a result of the mucociliary escalator clearing nanomaterials from the respiratory tract [34]. Animals may also ingest nanomaterials on their skin when grooming. Once in the GI tract,

nanomaterials can be absorbed, although the extent of absorption depends upon particle size, with smaller particles crossing the GI tract more readily than larger particles [35]. In fact, a challenge with designing nanomaterial drug delivery systems is that nanomaterials tend to aggregate in the gut, which increases their size and lowers their absorption [36]. Chemical property also influences absorption; for example, ingested iridium nanomaterials are not taken up by the GI tract very well [37], but C60 fullerenes are readily absorbed [38] due to their hydrophobic nature. The extent to which nanomaterials can enter the food chain and whether they will bioaccumulate is unknown.

Besides dermal and GI tract exposure, there is the potential for inhalation of nanomaterials. This is a large concern in industrial settings. Widespread inhalation of nanomaterials may also occur if nanomaterials become airborne and enter the atmosphere. Due to their small size, nanomaterials can form light dusts that are easily distributed in the air, inhaled and deposited in the lung. The size (single or aggregate) and shape of a nanomaterial help determine where it deposits within the lung. Because of the difficulty conducting uniform, controlled inhalation experiments, many pulmonary studies of nanomaterials have been done via intratracheal instillation; a fine dust of nanomaterials is placed in the trachea, and the animal breaths the dust down into the rest of the lung. Intratracheal instillation of nanotubes [39, 40], SiO_2 [41], and TiO_2 [42] have resulted in pulmonary inflammation, granulomas, and/or interstial fibrosis. We do not know if breathing nanomaterials would result in acute toxicity in humans or whether toxicity would be latent, such as occurs with asbestos. Even so, studies support the ability of TiO2 to produce pulmonary inflammation in rodents [43, 44].

Distribution

The translocation of nanomaterials from one organ to another is not well understood. However, it does appear that once nanomaterials are absorbed into the biological system, they can distribute throughout the body. Quantum dots injected into the dermis translocate to the lymph nodes [45]. Macrophages and dendritic cells in the lymph nodes may take up these particles [46, 47], leading to perturbation of the immune system. Self protein interactions with particles may change their antigenicity, initiating autoimmune responses. Nanomaterial-protein complexes have also been used to facilitate antigen uptake by dendritic cells leading to enhanced immune response [48].

When rats were gavaged with I^{125}-labelled polystyrene particles (50 nm), a small percentage of the particles were found 8 days later in the liver, spleen, blood and bone marrow [35]. Within the lung, nanomaterials can be taken up by alveolar macrophages [49], enter epithelium [34] or interstium [50], or translocate across the alveolar epithelium [51]. Once through the alveolar epithelium, gold nanoparticles were found in the pulmonary capillaries [51]. Due to the cardiovascular effects of ultrafine particulates, it is probable that nanomaterials can distribute throughout the circulatory system [34]. Silica-overcoated magnetic nanoparticles containing rhodamine B isothiocyanate given intraperitoneally to mice were able to cross the blood-brain barrier and found in the brain [52]. Nanomaterials are known to enter the brains of monkeys, rats, and fish via the olfactory bulb [53-55]. Taken together, these studies demonstrate that

nanomaterials can distribute within the cells and fluids of the body and translocate from organ to organ. Nonetheless, this translocation is highly variable and, again, dependent on particle size, surface characteristics, and chemical composition. The extent to which a nanomaterial enters into and translocates within the body will have significant impact on human health and the environment.

Metabolism

Once nanomaterials distribute and reach a target, results can either be beneficial, as for a drug, or toxic. Metabolism plays a large factor. To date, the primary cause of nanomaterial-induced toxicity is thought to be the generation of reactive oxygen species (ROS) [34, 56]. Quantum dots [57], single walled nanotubes [58],[59], and fullerenes [60] are associated with oxidative stress and/or the production of ROS. For example, lipid peroxidation was found in the brains of large mouth bass exposed to fullerenes [61], and ROS production, lipid peroxidation, oxidative stress, and mitochondrial dysfunction were found after keratinocytes and bronchial epithelial cells were incubated with single walled nanotubes [59]. The shape of nanomaterials (leading to electron instability) as well as the presence of surface metals and/or redox-cycling organic chemicals are thought to be instrumental in producing free radicals [56].

ROS is harmful because it can damage cell membranes (membrane lipid peroxidation), leading to permeability problems; cross-link and fragment proteins; and cause lesions in DNA. Ultimately, this can lead to cell death or, if the system is overwhelmed, death of the individual. For instance, the ability of both fullerenes [11] and TiO_2 [62] to generate ROS confers antimicrobial properties. While bacteria are limited in their ability to take up particles >5 nm, it has been speculated that they die from nanomaterial induced oxidative stress caused by their cell membrane, which houses their electron transport / ATP energy generating system, interacting with nanomaterial-induced ROS [10]. We do know that biological systems have oxidative defense systems that can combat ROS, but these systems can become overwhelmed leading to toxicity. Currently, we do not know if nanomaterials can produce enough protein/DNA damage to cause cancer and at what levels or time of exposure this may occur.

Fullerenes and other nanomaterials are often derivatized for compatibility with biological systems. This means they will interact with cellular membranes and may even be endocytosed. Redox sensitive nanomaterials, such as fullerenes, could participate in oxidation reactions to damage the cell membrane and affect cell permeability and fluidity, leaving cells more susceptible to osmotic stress or hindering nutrient uptake, electron transport, and energy transduction.

Excretion

Only a few studies have reported clearance mechanisms. For example, 98% of ingested C60 fullerenes was reported in feces of rats [38], and alveolar macrophages were found to phagocytize nanomaterials [34]. Surface chemistry and physical properties will influence to what extent nanomaterials are cleared from the body by urine/feces, dermis, hair, breast milk, breath, or whether they will be sequestered in body tissue for many years. Ultimately, excretion

influences the length of time that the body is exposed to nanomaterials and how nanomaterials are released into the environment.

In summary, there is evidence that nanomaterials can be absorbed, distributed, metabolized, and excreted by the biological system. However, much more information is needed to adequately evaluate the biological toxicity of nanomaterials.

CONCLUSIONS AND DIRECTIONS FOR THE FUTURE

Whether or not applications for nanomaterials involve their direct introduction into the environment, as with the use of nanoiron in groundwater remediation and the widespread incorporation of nanomaterials into commercial products, it is clear that nanomaterials will eventually enter the environment. The great diversity of nanomaterials and types of applications, multiple potential points of release into the environment as well as varied routes of exposure to populations makes addressing the potential risks a complex task. Only recently have researchers begun to study the potential ecological risks and impacts of nanomaterial release into the environment [reviewed by 63, 64]. To date, how much exposure to nanomaterials may adversely affect living organisms remains unknown, as do specific mechanisms of toxicity.

If nanomaterials prove harmful after being widely distributed in commerce, then the consequences will not be limited to adverse health and environmental consequences. Expensive remediation efforts may ensue. A negative public perception of nanomaterials, as illustrated by the case of genetically modified organisms, may thwart the many potential benefits nanotechnology can offer.

There is a high level of uncertainty in terms of potential toxicity and latent, unforeseen impacts of nanomaterials in the environment. As long as the hazards of nanomaterials are unknown, it is advisable to take uncertainties into account and use precautionary measures to ensure that nanomaterial release into the environment and exposure to the public is not left unchecked. To appropriately address potential risks, better methods for the detection and quantification of nanomaterials in the workplace and environment (air, water, soil) must be developed. Given that different types of nanomaterials will have different toxicological properties and types of impacts on human health and the environment, there may be a need to establish a standardized set of criteria for assessing the most critical toxicological parameters and potential risks of nanomaterials on an individual basis. A standard of safety and suitable protective measures must be determined for those who are likely to be exposed to nanomaterials, especially in the occupational setting. Educational outreach services and information needs to be made available to industrial hygienists, physicians, healthcare providers, veterinarians, and wildlife managers about possible exposure scenarios and proper precautionary measures to be taken to avoid undue exposure. Potential environmental, health and safety concerns should be accessed early on in the researching and processing of manufactured nanomaterials. A system by which researchers and manufacturers may be encouraged to register, identify likely exposure scenarios, and provide at least a basic toxicological profile for their products should be established. Clearly, it is in

the best interest of the public, regulatory agencies, and industry to integrate safety, toxicology, and environmental concerns into the research and manufacture of nanomaterials. Nanotechnology and its prospects should be promoted in a responsible and safe manner that acknowledges potential risks of nanomaterials being incorporated into widespread commercial production.

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REFERENCES

[1] Akerman ME, Chan WC, Laakkonen P, Bhatia SN, Ruoslahti E. 2002. Nanocrystal targeting in vivo. *Proc Natl Acad Sci U S A* 99:12617-12621.

[2] Harris TJ, von Maltzahn G, Derfus AM, Ruoslahti E, Bhatia SN. 2006. Proteolytic actuation of nanoparticle self-assembly. *Angew Chem Int Ed Engl* 45:3161-3165.

[3] Jortner J, Rao CNR. 2002. Nanostructured advanced materials. Perspectives and directions. *Pure and Applied Chemistry* 74:1491-1506.

[4] Hardman R. 2006. A toxicologic review of quantum dots: toxicity depends on physicochemical and environmental factors. *Environ Health Perspect* 114:165-172.

[5] Yamamoto A, Honma R, Sumita M, Hanawa T. 2004. Cytotoxicity evaluation of ceramic particles of different sizes and shapes. *J Biomed Mater Res A* 68:244-256.

[6] Haruta M. 1997. Gold as a low-temperature oxidation catalyst: factors controlling activity and selectivity. *3Rd World Congress on Oxidation Catalysis* 110:123-134.

[7] Bond GC. 2002. Gold: a relatively new catalyst. *Catalysis Today* 72:5-9.

[8] Hutchings GJ. 2004. New directions in gold catalysis. *Gold Bulletin* 37:3-11.

[9] Kam NW, Dai H. 2005. Carbon nanotubes as intracellular protein transporters: generality and biological functionality. *J Am Chem Soc* 127:6021-6026.

[10] Wiesner MR, Lowry GV, Alvarez P, Dionysiou D, Biswas P. 2006. Assessing the risks of manufactured nanomaterials. *Environ Sci Technol* 40:4336-4345.

[11] Fortner JD, Lyon DY, Sayes CM, Boyd AM, Falkner JC, Hotze EM, Alemany LB, Tao YJ, Guo W, Ausman KD, Colvin VL, Hughes JB. 2005. C60 in water: nanocrystal formation and microbial response. *Environ Sci Technol* 39:4307-4316.

[12] Brant J, Lecoanet H, Hotze M, Wiesner M. 2005. Comparison of electrokinetic properties of colloidal fullerenes (n-C-60) formed using two procedures. *Environmental Science & Technology* 39:6343-6351.

[13] Li H, Jia X, Li Y, Shi X, J H. 2006. A salt-free zero-charged aqueous onion-phase enhances the solubility of fullerene C60 in water. *J Phys Chem B* 110:68-74.

[14] Lyon DY, Fortner JD, Sayes CM, Colvin VL, Hughe JB. 2005. Bacterial cell association and antimicrobial activity of a C60 water suspension. *Environ Toxicol Chem* 24:2757-2762.

[15] Brant J, Lecoanet H, Wiesner MR. 2005. Aggregation and Deposition Characteristics of Fullerene Nanoparticles in Aqueous Systems. *Journal of Nanoparticle Research* 7:545-553.

[16] Chang MC, Shu HY, Hsieh WP, Wang MC. 2005. Using nanoscale zero-valent iron for the remediation of polycyclic aromatic hydrocarbons contaminated soil. *J Air Waste Manag Assoc* 55:1200-1207.

[17] Carter SR, Rimmer S. 2005. Aqueous compatible polymers in bionanotechnology. *IEE Proc Nanobiotechnol* 152:169-176.

[18] Rodriguez-Zavala JG, Guirado-Lopez RA. 2004. Structure and energetics of polyhydroxylated carbon fullerenes. *PHYSICAL REVIEW B* 69:075411.

[19] Schrick B, Hydutsky BW, Blough JL, Mallouk TE. 2004. Delivery Vehicles for Zerovalent Metal Nanoparticles in Soil and Groundwater. *Chem Mater* 16:2187-2193.

[20] Zhang W-x, Elliott DW. 2006. Applications of Iron Nanoparticles for Groundwater Remediation. *Remediation* 16:7-21.

[21] Lyon DY, Adams LK, Falkner JC, Alvarez PJJ. 2006. Antibacterial Activity of Fullerene Water Suspensions: Effects of Preparation Method and Particle Size. *Environ Sci Technol* 40:4360 -4366.
[22] Verran J, Sandoval G, Allen NS, Edge M, Stratton J. 2007. Variables affecting, the antibacterial properties of nano and pigmentary titania particles in suspension. *Dyes and Pigments* 73:298-304.
[23] Guldi DM, Prato M. 2000. Excited-state properties of C(60) fullerene derivatives. *Acc Chem Res* 33:695-703.
[24] Agustina TE, Ang HM, Vareek VK. 2005. A review of synergistic effect of photocatalysis and ozonation on wastewater treatment. *Journal of Photochemistry and Photobiology C-Photochemistry Reviews* 6:264-273.
[25] Sunada K, Kikuchi Y, Hashimoto K, Fujishima A. 1998. Bactericidal and detoxification effects of TiO2 thin film photocatalysts. *Environmental Science & Technology* 32:726-728.
[26] Kashige N, Kakita Y, Nakashima Y, Miake F, Watanabe K. 2001. Mechanism of the photocatalytic inactivation of Lactobacillus casei phage PL-1 by titania thin film. *Current Microbiology* 42:184-189.
[27] Wold A. 1993. Photocatalytic Properties of Tio2. *Chemistry of Materials* 5:280-283.
[28] Maness PC, Smolinski S, Blake DM, Huang Z, Wolfrum EJ, Jacoby WA. 1999. Bactericidal activity of photocatalytic TiO2 reaction: Toward an understanding of its killing mechanism. *Applied and Environmental Microbiology* 65:4094-4098.
[29] Derfus AM, Chan WC, Bhatia SN. 2004. Probing the Cytotoxicity of Semiconductor Quantum Dots. *Nano Letters* 4:11-18.
[30] Tinkle SS, Antonini JM, Rich BA, Roberts JR, Salmen R, DePree K, Adkins EJ. 2003. Skin as a route of exposure and sensitization in chronic beryllium disease. *Environ Health Perspect* 111:1202-1208.
[31] Souto EB, Wissing SA, Barbosa CM, Muller RH. 2004. Comparative study between the viscoelastic behaviors of different lipid nanoparticle formulations. *J Cosmet Sci* 55:463-471.
[32] Sayes CM, Wahi R, Kurian PA, Liu Y, West JL, Ausman KD, Warheit DB, Colvin VL. 2006. Correlating nanoscale titania structure with toxicity: a cytotoxicity and inflammatory response study with human dermal fibroblasts and human lung epithelial cells. *Toxicol Sci* 92:174-185.
[33] Ryman-Rasmussen JP, Riviere JE, Monteiro-Riviere NA. 2006. Penetration of intact skin by quantum dots with diverse physicochemical properties. *Toxicol Sci* 91:159-165.
[34] Oberdorster G, Oberdorster E, Oberdorster J. 2005. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect* 113:823-839.
[35] Jani P, Halbert GW, Langridge J, Florence AT. 1990. Nanoparticle uptake by the rat gastrointestinal mucosa: quantitation and particle size dependency. *J Pharm Pharmacol* 42:821-826.
[36] Florence AT. 2004. Issues in oral nanoparticle drug carrier uptake and targeting. *J Drug Target* 12:65-70.

[37] Kreyling WG, Semmler M, Erbe F, Mayer P, Takenaka S, Schulz H, Oberdorster G, Ziesenis A. 2002. Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. *J Toxicol Environ Health A* 65:1513-1530.
[38] Yamago S, Tokuyama H, Nakamura E, Kikuchi K, Kananishi S, Sueki K, Nakahara H, Enomoto S, Ambe F. 1995. In vivo biological behavior of a water-miscible fullerene: 14C labeling, absorption, distribution, excretion and acute toxicity. *Chem Biol* 2:385-389.
[39] Warheit DB, Laurence BR, Reed KL, Roach DH, Reynolds GA, Webb TR. 2004. Comparative pulmonary toxicity assessment of single-wall carbon nanotubes in rats. *Toxicol Sci* 77:117-125.
[40] Shvedova AA, Kisin ER, Mercer R, Murray AR, Johnson VJ, Potapovich AI, Tyurina YY, Gorelik O, Arepalli S, Schwegler-Berry D, Hubbs AF, Antonini J, Evans DE, Ku BK, Ramsey D, Maynard A, Kagan VE, Castranova V, Baron P. 2005. Unusual inflammatory and fibrogenic pulmonary responses to single-walled carbon nanotubes in mice. *Am J Physiol Lung Cell Mol Physiol* 289:L698-708.
[41] Chen Y, Chen J, Dong J, Jin Y. 2004. Comparing study of the effect of nanosized silicon dioxide and microsized silicon dioxide on fibrogenesis in rats. *Toxicol Ind Health* 20:21-27.
[42] Warheit DB, Webb TR, Sayes CM, Colvin VL, Reed KL. 2006. Pulmonary instillation studies with nanoscale TiO2 rods and dots in rats: toxicity is not dependent upon particle size and surface area. *Toxicol Sci* 91:227-236.
[43] Baggs RB, Ferin J, Oberdorster G. 1997. Regression of pulmonary lesions produced by inhaled titanium dioxide in rats. *Veterinary Pathology* 34:592-597.
[44] Rehn B, Seiler F, Rehn S, Bruch J, Maier M. 2003. Investigations on the inflammatory and genotoxic lung effects of two types of titanium dioxide: untreated and surface treated. *Toxicology and Applied Pharmacology* 189:84-95.
[45] Kim S, Lim YT, Soltesz EG, De Grand AM, Lee J, Nakayama A, Parker JA, Mihaljevic T, Laurence RG, Dor DM, Cohn LH, Bawendi MG, Frangioni JV. 2004. Near-infrared fluorescent type II quantum dots for sentinel lymph node mapping. *Nat Biotechnol* 22:93-97.
[46] Reddy ST, Rehor A, Schmoekel HG, Hubbell JA, Swartz MA. 2006. In vivo targeting of dendritic cells in lymph nodes with poly(propylene sulfide) nanoparticles. *Journal of Controlled Release* 112:26-34.
[47] Lutsiak MEC, Robinson DR, Coester C, Kwon GS, Samuel J. 2002. Analysis of poly(D,L-lactic-co-glycolic acid) nanosphere uptake by human dendritic cells and macrophages in vitro. *Pharmaceutical Research* 19:1480-1487.
[48] Fifis T, Gamvrellis A, Crimeen-Irwin B, Pietersz GA, Li J, Mottram PL, McKenzie IFC, Plebanski M. 2004. Size-dependent immunogenicity: Therapeutic and protective properties of nano-vaccines against tumors. *Journal of Immunology* 173:3148-3154.
[49] Ferin J, Oberdorster G, Soderholm SC, Gelein R. 1991. Pulmonary tissue access of ultrafine particles. *J Aerosol Med* 4:57-68.
[50] Ferin J, Oberdorster G, Penney DP. 1992. Pulmonary retention of ultrafine and fine particles in rats. *Am J Respir Cell Mol Biol* 6:535-542.

[51] Berry JP, Arnoux B, Stanislas G, Galle P, Chretien J. 1977. A microanalytic study of particles transport across the alveoli: role of blood platelets. *Biomedicine* 27:354-357.
[52] Kim JS, Yoon TJ, Yu KN, Kim BG, Park SJ, Kim HW, Lee KH, Park SB, Lee JK, Cho MH. 2006. Toxicity and tissue distribution of magnetic nanoparticles in mice. *Toxicol Sci* 89:338-347.
[53] Oberdorster E. 2004. Manufactured nanomaterials (fullerenes, C60) induce oxidative stress in the brain of juvenile largemouth bass. *Environ Health Perspect* 112:1058-1062.
[54] Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, Carter J, Potter R, Maynard A, Ito Y, Finkelstein J, Oberdorster G. 2006. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. *Environ Health Perspect* 114:1172-1178.
[55] Oberdorster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, Cox C. 2004. Translocation of inhaled ultrafine particles to the brain. *Inhal Toxicol* 16:437-445.
[56] Nel A, Xia T, Madler L, Li N. 2006. Toxic potential of materials at the nanolevel. *Science* 311:622-627.
[57] Tsay JM, Michalet X. 2005. New light on quantum dot cytotoxicity. *Chem Biol* 12:1159-1161.
[58] Manna SK, Sarkar S, Barr J, Wise K, Barrera EV, Jejelowo O, Rice-Ficht AC, Ramesh GT. 2005. Single-walled carbon nanotube induces oxidative stress and activates nuclear transcription factor-kappaB in human keratinocytes. *Nano Lett* 5:1676-1684.
[59] Shvedova AA, Castranova V, Kisin ER, Schwegler-Berry D, Murray AR, Gandelsman VZ, Maynard A, Baron P. 2003. Exposure to carbon nanotube material: assessment of nanotube cytotoxicity using human keratinocyte cells. *J Toxicol Environ Health A* 66:1909-1926.
[60] Yamakoshi Y, Umezawa N, Ryu A, Arakane K, Miyata N, Goda Y, Masumizu T, Nagano T. 2003. Active oxygen species generated from photoexcited fullerene (C60) as potential medicines: O2-* versus 1O2. *J Am Chem Soc* 125:12803-12809.
[61] Oberdorster E. 2004. Manufactured nanomaterials (Fullerenes, C-60) induce oxidative stress in the brain of juvenile largemouth bass. *Environmental Health Perspectives* 112:1058-1062.
[62] Wei C, Lin WY, Zainal Z, Williams NE, Zhu K, Kruzic AP, Smith RL, Rajeshwar K. 1994. Bactericidal Activity of TiO2 Photocatalyst in Aqueous Media: Toward a Solar-Assisted Water Disinfection System. *Environ Sci Technol* 28:934-938.
[63] Colvin VL. 2003. The potential environmental impact of engineered nanomaterials. *Nat Biotechnol* 21:1166-1170.
[64] Liu WT. 2006. Nanoparticles and their biological and environmental applications. *J Biosci Bioeng* 102:1-7.