Ian M. Kennedy*

Nanotechnology and toxicology

Abstract: The Pacific Basin Consortium session on Nanotechnology and toxicology brought together experts from biology and the physical sciences and engineering to discuss the environmental and health impacts of nanotechnology and nanomaterials in particular. The discussion included new findings in the area of inhalation toxicology as well as aquatic toxicology. Opportunities for engineering new forms of particles for toxicology studies were also presented.

Keywords: aquatic life; inhalation; nanotechnology; toxicology; water treatment.

***Corresponding author: Ian M. Kennedy,** Department of Mechanical and Aerospace Engineering, University of California Davis, Davis, CA 95616, USA, E-mail: kennedyim@me.com

The session on Nanotechnology and Toxicology at the Pacific Basin Consortium meeting brought together researchers who are involved in investigating the potential health effects of the new materials that are being produced by nanotechnology. A report was also delivered by a representative of the National Institute of Environmental Health Sciences to give a perspective on the US Government's current approach towards these potential health implications and the response of the government in funding both intramural and extramural research. Some real-world applications and effects of nano materials were discussed in relation to water treatment and aquatic life.

The production of nanoscale materials is increasing throughout the world. Governments around the world have put significant research funding into this area in the hope that new materials will offer functionalities that were previously unattainable. The novel properties of nano materials arise from physical and chemical phenomena that act at scales intermediate between the atomic and macroscopic. Early examples of these sorts of materials include quantum dots that are made of semiconductor materials like cadmium selenide that are particularly useful because of their optical properties. If they are excited by light, they emit a relatively narrow wavelength emission that can be changed simply by varying the size of the nanoparticles. The phenomenon of photoluminescence is explained by resorting to quantum mechanical reasoning. More recently, various forms of carbon have attracted a great deal of attention. Carbon nanotubes are being exploited because of their unique mechanical, thermal and electrical properties. They can behave as semiconductor materials, or they can behave as insulators. Their mechanical strength is exceptionally good. These materials are now finding their way into consumer products. Nanoscale silver is also finding wide application in commercial products, often as a bactericide. Graphene is a new form of carbon that has excited many researchers, once again because of its unique properties. It is essentially a single layer of carbon atoms arranged in a graphitic structure. The potential health effects of many of these materials are not well understood, in large part because of the wide range of different properties that may have an impact on toxicity. The size of the materials is obviously an important factor, but so also is the morphology, the surface composition, and the inclusion of potential impurities.

Dr. Kent Pinkerton from the University of California Davis provided an overview of recent trends in understanding the potential toxicity of nano materials. He distinguished between particles that are generated unintentionally in the atmosphere, often as the result of combustion processes, from particles that are intentionally engineered for particular technological functions. The latter materials may present new issues for toxicity. Although the precise mechanism of toxicity for these new materials is not well established, it is believed that oxidative stress plays an important role. Pinkerton focused particularly on the toxicity of carbon nanotubes and some of its similarity to well-known hazardous materials such as asbestos. Frustrated phagocytosis may play an important role in causing inflammatory responses when cells are presented with long thin particles such as carbon nanotubes. The role of metals may also be important, as these are often used as catalysts for the production of nanotubes.

Dr Danielle Carlin of the National Institute of Environmental Health Sciences (NIEHS) described the current activities at NIH with regard to evaluating the toxicity of engineered nano materials. These activities include both intramural and extramural research. The NIEHS National Toxicology Program plays an important role in evaluating a number of nano material classes in comprehensive toxicology studies. The NIEHS also supports an extensive extramural research grant portfolio that includes the Nano Grant Opportunities program and the NIEHS centers for Nanotechnology Health Implications research consortium. The latter program involves collaborating research between multiple universities. In addition to these funding opportunities, the NIEHS also supports research into nano material toxicity through the Superfund Research Program that supports a network of universities, small businesses and training grants. Recently, the NIEHS has established a working education program that enlists universities to undertake to train people who are engaged in nanotechnology development and research at all levels, from the university laboratory down to the local community worker and persons involved in remediation of hazardous materials, in the safe handling, assessment and remediation of nanoscale materials.

Dr. Laura Van Winkle of the University of California Davis, reported on studies with respect to the toxicity of inhaled combustion-derived ultrafine particles. Her particular interest is the impact on neonatal animals, and highlighting the difference between toxicity in the neonate and in the adult, as a result of differences in lung development. She focused on studies using organic-rich particles that contained large amounts of polycyclic aromatic hydrocarbons. The studies showed that cellular toxicity was distributed in different lung regions in the neonates compared to the adult animals. Exposure to these particles caused activation of the aryl hydrocarbon receptor and up-regulation of CYP 1A1. The response in neonates was delayed in comparison with adults. Although both neonatal and adult animals exhibited oxidative stress, only the neonates had a precipitous drop in lung glutathione levels following exposure. Dr. Van Winkles's group concluded that neonates have an impaired ability to respond to nanoparticles. The exposure of young animals to these materials increases lung cytotoxicity and can lead to enhanced susceptibility to particles which may lead to abnormal airway growth.

Dr. Ian Kennedy, the University of California Davis, described a novel experimental system for the study of inhalation toxicology of engineered nano materials. Using an aerosol synthesis route, his group produces nanoparticles that consist of lanthanide elements doped into an oxide crystal host. Lanthanides are especially useful for studying the distribution and deposition of particles in the lungs as well as the translocation to distant organs because the lanthanide elements can be measured with great sensitivity using inductively coupled plasma mass spectrometry (ICP MS). The particles are delivered via inhalation chamber to rats. Concentrations in the animal lung can be measured down to a level of a few parts per trillion. With this level of sensitivity, it was possible to find particles that translocated to other organs such as the heart, liver, kidney and others. In addition to the sensitivity that the lanthanides offer using ICP MS, these particles are also optically luminescent. Lanthanides provide yet another key property that can be made use of for spectroscopic measurements that indicate the presence of intact particles. If particles dissolve in biological fluids, they lose their optical emission. This has been used to study the dissolution rate of particles at various pH in buffers and in biological fluids. The measurement of particle fluorescence showed that the particles do not dissolve in biological fluids at relevant pH, and persist as nanoparticles in animals that are exposed to this material. Sensitive detection via ICP MS reveals the presence of translocated nanoparticles, not dissolved metal ions. The engineering of these novel materials offers an exceptionally valuable tool for studies of nano particle toxicity.

Dr. Evan Gallagher, the University of Washington, demonstrated that heavy metals, in particular cadmium, can induce olfactory injury in fish. His studies help to elucidate the mechanisms for this injury and reveal new biomarkers of exposure. The study uses coho salmon and zebrafish. His very interesting results showed that the coho salmon exhibited a loss of the ability to detect predators after exposure to cadmium. Obviously, a decrease in the ability to detect predators bodes ill for the future of the fish, but significantly, this effect is persistent after the cessation of exposure. Exposure to high levels of cadmium causes persistent olfactory damage and a more extensive loss of normal olfactory behavior. Genes that encode the olfactory G-protein coupled receptors, and antioxidant response genes, were found to be sensitive biomarkers of this olfactory injury. Zebrafish were also found to exhibit similar decreases in sensory responses. These fish models can provide relevant biomarkers for monitoring of Superfund hazardous waste sites.

Jorge Gonzalez-Estralla and collaborators at the University of Arizona have studied the role of sulfide in attenuating zinc oxide nanoparticle inhibition in anaerobic sludge treatment. Methanogens are a key participant in anaerobic digestion that can be potentially affected by nanoparticles. They investigated the possibility that the inhibitory effect of zinc oxide nanoparticles on acetate-utilizing methanogens could be attenuated through precipitation of the toxic Zn^{2+} by biogenic S^{2-}. They found that biogenic sulfide attenuated the inhibitory effect of zinc oxide nanoparticles on acetate-utilizing methanogens. Their measurements indicated that residual free soluble Zn^{2+} in sulfate free and in sulfate rich assays caused the inhibition of acetate-utilizing methanogens. However, in sulfate rich conditions more than 0.4 mM of zinc was required to achieve a free soluble concentration that could affect acetate utilizing methanogens. On the other hand, without sulfate present, only 0.02 mM of zinc caused an adverse effect. Their results show that zinc oxide nanoparticle toxicity is caused by its solubilised zinc and this can be prevented through the formation of zinc sulfide minerals. This can be a potentially useful means of mitigating the adverse impact of unintentionally released zinc oxide nanoparticles that end up in water treatment plants.