Nanotechnology

Is there cause for concern?

By Brian McShane

NANOTECHNOLOGY is a fast-growing field that U.S. government officials have cited as "the foundation for the 'next industrial revolution' worth an estimated trillion dollars within the coming decade" (Weiss 1). While the field of nanotechnology is in its infancy, products containing nanomaterials—from car bumpers to stain-resistant clothing and cosmetics—are finding their way into the marketplace. As the demand for these materials increases, so, too, will the frequency of occupational exposures in the workplace, particularly in research and manufacturing facilities. While most occupational exposures to nanomaterials will likely not be hazardous, a significant body of evidence concerning exposure to ultrafine particles (UFPs) and some preliminary toxicology findings concerning free nanoparticles describes unusual potential health effects that should be cause for concern.

Understanding UFPs & Nanotechnology

No standard definitions have been established for the terms UFPs and nanoparticles, which has led to some confusion because the words are often used interchangeably. For this article, nanoparticles are defined as engineered particles not exceeding 100 nanometers (nm) in at least one dimension. The term "ultrafine particle" has been used primarily by researchers in atmospheric science and exposure assessment. UFPs are defined as having diameters of less than 100 nm. Generally, they are from naturally occurring sources or are unintentional byproducts of anthropogenic processes. To put the size of particles below 100 nm into perspective, 1 nm is approximately the width of 10 hydrogen atoms (Feder C1). Cold viruses are generally 50 nm in length (Rotman 72). Therefore, nanoparticles and UFPs approach the size limits of matter.

The concept of nanotechnology has been on the minds of scientists for centuries. In 1871, Scottish physicist James Maxwell imagined tiny demons that could move atoms (Keiper 2). It was not until Dec. 29, 1959, however, that the concept of nanotechnology was clearly defined in a speech given by Nobel Prize winner Richard Feynman. In that speech, entitled "There's Plenty of Room at the Bottom," Feynman talks of a class of minute materials beyond the scale of miniaturization in which atoms are rearranged to make small switches and machines.

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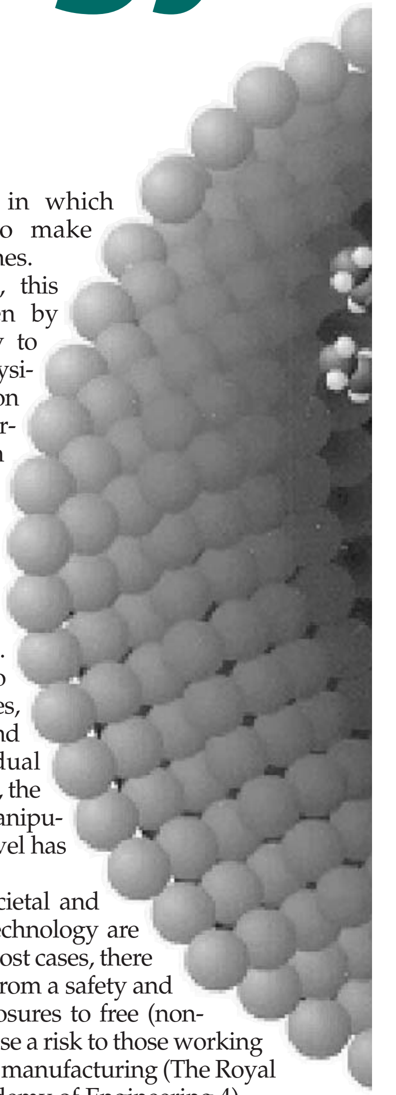
As Feynman predicted, this technology is now driven by humankind's recent ability to visualize, measure and physically manipulate matter on the atomic scale. The watershed moment occurred in 1981 when a team of IBM scientists invented the scanning tunneling microscope. The device uses a fine needle and extremely low electric current to detect the height of individual atoms. This microscope was able to not only visualize molecules, but also contact, move and precisely place individual atoms (Keiper 3). Since then, the ability to visualize and manipulate matter on the atomic level has steadily improved.

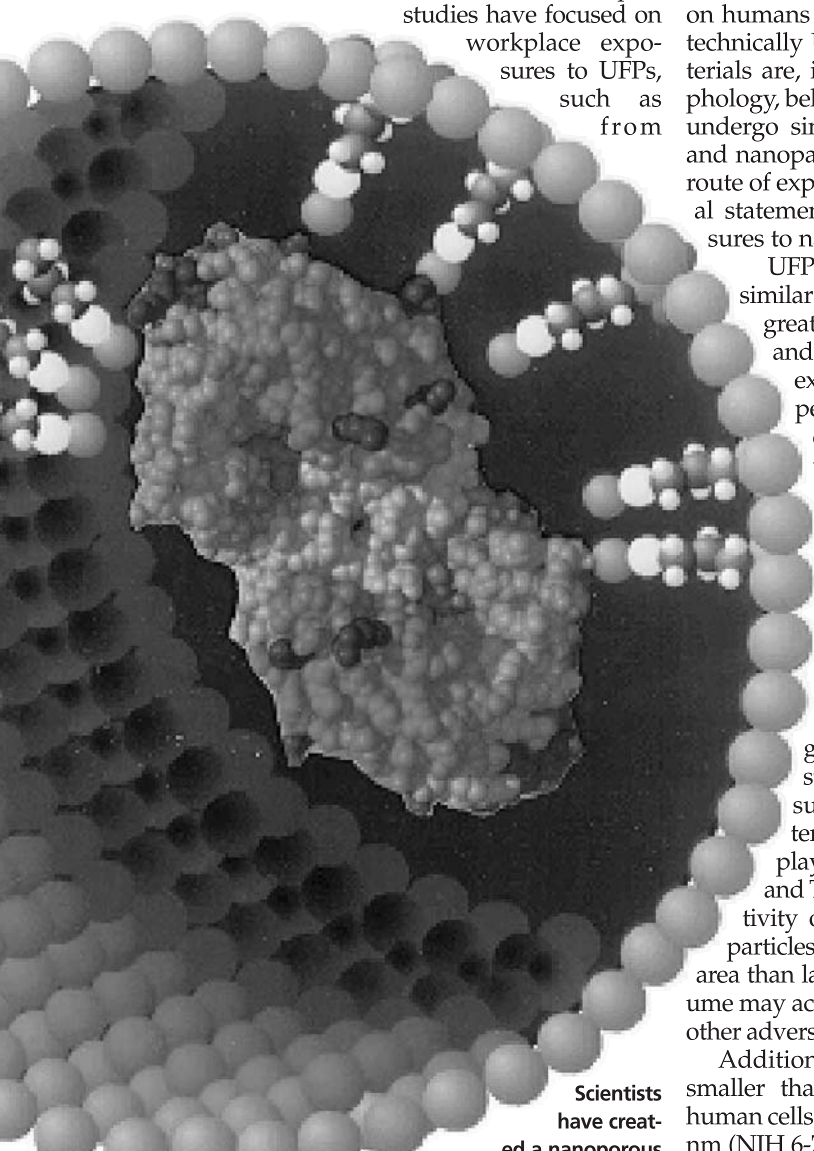


While the economic, societal and scientific impacts of nanotechnology are expected to be positive in most cases, there has been growing concern from a safety and health standpoint that exposures to free (nonfixed) nanoparticles may pose a risk to those working in research laboratories and manufacturing (The Royal Society and The Royal Academy of Engineering 4).

The properties of nanomaterials that are a function of their size are what distinguish them from other materials. At the macromolecular level in which these constructs exist, "quantum effects can begin to dominate the behavior of matter at the nanoscale—particularly at the lower end—affecting the optical, electrical and magnetic behavior of materials" (The Royal Society and The Royal Academy of Engineering 2).

For example, carbon nanotubes exhibit unusual quantum properties which can serve as wiring for molecular computers at scales of size so small that ordinary electrical current flow is not possible (Akin 3). Concerns have been expressed that the very properties of nanoscale particles being exploited in certain applications (such as high surface reactivity and the ability to cross cell membranes) might also have negative health and environmental impacts.

Exposure to nanoscale materials is not new. For example, humans have been exposed to the products of combustion since fire was harnessed. While past studies have focused on workplace exposures to UFPs, such as from metal fumes, it has recently become apparent that ambient exposures to UFPs in the atmosphere from man-made and natural sources have resulted in significant increases in mortality in susceptible portions of the population (G. Oberdorster 1).



Scientists have created a nanoporous silica that increases enzyme activity and stability by binding part of an enzyme to the walls of a 30-nanometer pore using a covalent linker molecule. The binding stabilizes the enzyme.

IMAGE BY PACIFIC NORTHWEST NATIONAL LABORATORY

Examples of ambient particulate matter include soot from combustion engines, forest fires and power generation, dust from geological processes, agriculture, construction and demolition, as well as secondary particulates formed from the transformation of acidic gases to particulates in the atmosphere (Brook, et al 2656). In response to concerns regarding potential public health impacts, a significant body of research has developed that includes information on the effects of UFPs on laboratory animals and also on humans through epidemiological studies. While technically UFPs are not manufactured as nanomaterials are, in many cases, UFPs have similar morphology, behave similarly aerodynamically and may undergo similar processes within the body. UFPs and nanoparticles also share inhalation as the main route of exposure into the body. Thus, several general statements can be made about potential exposures to nanoparticles through analogy to UFPs.

UFPs are thought to be more reactive than the similar amounts of larger particles because of the greater number of particles per unit of mass and greater surface area of the materials. For example, "to obtain 10 μg/m^3 (micrograms per cubic meter) of 2 μm (micrometer) diameter particles, you only need 1.2 particles per ml (milliliter) of air and a total surface area of 24 μm^2 /ml; the same airborne mass concentration of 20 nm particles requires 2.4 million particles with a surface area of 3,016 μm^2 /ml" (Donaldson and Stone 406).

According to Jefferson and Tilley, it is also the relatively high proportion of surface atoms that makes these particles so interesting; for example, for a 50 nm singlet particle, one in six atoms will be at the surface (64). "Such a high proportion of surface atoms ensures that, in general terms, nanoparticles of this size regime display vastly increased reactivity" (Jefferson and Tilley 64). Thus, the increased surface reactivity of UFPs coupled with larger amount of particles presenting a significantly higher surface area than larger particles of equal mass per unit volume may account for the enhanced inflammation and other adverse effects observed from exposure to UFPs.

Additionally, nanoparticles, particularly those smaller than 50 nm, can readily penetrate most human cells, which range in size from 10,000 to 20,000 nm (NIH 6-7). These particles can also move relatively freely into and within the body or penetrate deep enough into it, as in the case of alveolar deposition (The Royal Society and The Royal Academy of Engineering 41), enhancing compound potency. They may interfere with macrophage motility within the lung by penetrating into these cells and compromising their ability to clear the alveoli of deposited particulates and bacteria (Renwick, et al 125).

After inhalation, if these particles are not cleared by phagocytosis in the lung, they can penetrate the interstitium and be actively transported throughout the body by the circulatory system or lymph system (Ferin, et al 383; G. Oberdorster 7). Nanoparticles smaller than 20 nm were also found to "transmit out of blood vessels" (NIH 7) and are then free to interact with adjoining tissues. In the short term, these

Abstract: *This article reviews safety and health information available regarding ultrafine particles (UFPs), including nanomaterials. It covers the characteristics of free nanoparticles/UFPs as well as health effects observed from exposures to these materials. Routes of exposures are discussed as are several manufacturing processes that present the potential for occupational exposure to UFPs. The state of current regulation covering occupational exposure is reviewed as is the need for a precautionary approach to these materials until such time that risk assessment information becomes available.*

exposures can cause decreased pulmonary function, increased incidence of cardiac events and inflammation (Brook, et al 2666; Donaldson and Stone 409). The hazards of these materials to specific segments of the population involving those with impaired pulmonary functions has also been documented and can be further exacerbated by exposure to endotoxin and/or ozone, which were found to have a synergistic inflammatory response when coupled with UFPs to affected tissues (G. Oberdorster 6). Chronic inflammation has been shown to promote other diseases such as cancer (Locke 117).

Additionally, UFPs, particularly those at the lower end of the nanoscale, may penetrate into the brain. They have been found to circumvent the blood/brain barrier of various animal models (via the olfactory bulb in rats), potentially causing neurotoxic effects by inducing inflammation that may result in neurodegenerative diseases such as Alzheimer's, or promote cancer (Calderon-Garciduenas, et al 386; E. Oberdorster 1060-1061; Oberdorster, et al 444). Thus, using the preliminary nanomaterials exposures in animals and UFP research, it can be extrapolated that nanomaterials may pose a significant and possibly much different occupational risk to workers in research and manufacturing than what has been seen before.

Products Currently Containing Nanomaterials

End User Applications
- tennis balls and rackets;
- clothing;
- cameras;
- respirators;
- razor blades;
- cosmetics;
- sunscreens;
- beer bottles.

Therapeutic Systems
- drugs;
- sprays;
- burn dressings;
- medical equipment components.

Components
- transistors;
- fillers;
- catalytic converters;
- fenders;
- mirror housings;
- fuel cells;
- step assists;
- polarizers/wave plates;
- displays (OLEDs).

Software
- modeling;
- controllers for microscopes;
- computer-aided design navigation.

Capital Equipment
- positioners;
- cantilevers;
- coaters;
- probers;
- manipulators;
- lithography masks.

Imaging
- microscopes;
- electron beams;
- X-ray.

Source: EPA(a).

Routes of Exposure

Little research has been performed to characterize potential routes of exposure to various engineered nanoparticles. However, in general, inhalation is identified as the major route of exposure in the occupational setting for free nanoparticles; skin contact follows as the next most common route of exposure (The Royal Society and The Royal Academy of Engineering 36).

Ingestion of nanomaterials and their effects on the gastrointestinal tract may also be an issue, but little research has been conducted in this area, with the exception of lead exposures involving hand-to-mouth exposure and contamination of foodstuff in certain industries (Aitken, et al 15). As a result, ingestion exposure is expected to be directly related to skin exposure. A secondary ingestion exposure may also occur as inhaled particles are swallowed after being cleared from the lungs by the mucociliary escalator (ICRP).

Studies also suggest that nanoparticles may enter the body through the skin, although additional research is needed on this issue [NIOSH(a)]. Evidence has also been reported that skin contact from nanotubes rather than inhalation may be an important route of exposure in occupational settings (Maynard, et al 106). Unrefined single-walled carbon nanotubes (SWCNT) with significant amounts of transition metals present were found to be toxic to human dermal cells [Shvedova, et al(a) 1924]. The mechanism of toxicity involved the creation of free radicals that oxidized the cells, leading to inflammation which, as previously stated, may be a promoter for cancer.

SWCNT may pose a potential hazard causing respiratory tract inflammation if made airborne and inhaled. Using SWCNT containing up to 30 percent iron and "neutralized" or reduced unrefined SWCNT with human bronchial epithelial cells, researchers found diminished cytotoxicity from the reduced SWCNT indicating that the transition metal catalyst may be primarily responsible for the observed cytotoxicity in direct contradiction to an earlier study by Brown, et al [Shedova, et al(b) 100]. In the study performed by Brown, et al, ultra fine carbon black particulates (UFCB) were found to be more proinflammatory than fine carbon black particles; however, no statistically significant difference was found between the UFCB coated with the reactive transition metal Fe(III) and uncoated UFCB (Brown, et al 690). Additional studies are required to separate the cytotoxic effects of the transition metals from those of the carbon nanomaterials.

The health effects of water-soluble, polyalkylsulfonated C_{60} fullerenes in rats were also investigated. Fullerenes are hollow spheres approximately 1 nm in size; they are composed of a geodesic latticework of 60 carbon atoms and are viewed as likely candidates for drug delivery (The Royal Society and The Royal Academy of Engineering 9). It was established that for rats ingestion of these materials is not harmful; however, intravenous or intraperitoneal injection of these constructs will eventually cause damage to the kidneys as the fullerenes are metabolized (Chen, et al 150). Fullerenes were also found to bind strongly to DNA suggesting that they may negatively impact "the structure, stability and biological functions of DNA molecules" (Zhao, et al) if they can penetrate into the cell nucleus.

Quantum dots made from cadmium were found to be toxic when surface coatings break down and a portion of the metal was released (Kalaugher 1) as may occur in the acidic environment of the stomach after ingestion. Thus, based on the limited evidence gathered, some nanomaterials may pose a significant safety and health risk to humans through exposures to free nanoscale materials in the occupational setting.

Manufacturing

The two basic approaches by which nanomaterials can be made are the bottom-up and the top-down manufacturing. Top-down manufacturing is actually a form of miniaturization, and it is currently how most nanomaterials are manufactured "producing very small structures from larger pieces of material, for example by etching to create circuits on the surface of a silicon microchip" (The Royal Society and The Royal Academy of Engineering 3). Examples of this include industrial processes in the semiconductor and microchip industries that are continually striving for more effective methods of miniaturization. Mechanical attrition, another top-down approach, uses processes such as grinding, milling and alloying to produce smaller particles from larger ones. The processes primarily involve wet milling of materials such as clays and metals. The suspensions can be produced at the rate of tons per hour, which must be stabilized to prevent agglomeration (Aitken, et al 26).

The bottom-up approach, sometimes referred to as molecular manufacturing, involves using atoms or molecules to arrange themselves into a structure due to their natural properties. The first bottom-up approach is the gas-phase synthesis in which the raw material is evaporated using a furnace, laser or plasma evaporation "followed by a homogenous nucleation and a further condensation and coalescence of particles (Gleiche and Hoffschulz 29). Gas-phase synthesis includes flame pyrolysis used in the production of fumed silica and ultrafine titanium dioxide. Of the manufacturing processes noted, "only the gas-phase processes have the potential to cause exposure to primary nanoparticles by inhalation during the synthesis phase" (Aitken, et al 57).

The colloidal method, another bottom-up process, involves wet chemistry precipitation reactions that are relatively inexpensive to perform and are a reliable and well-established means of producing nanomaterials (Aitken, et al 25). The sol-gel process is a wet chemical process in which a semi-solid or "sol" is produced to form a solid structure or "gel" when dried. "Different drying procedures will form a glassy or ceramic structure, whereby thin coatings, fibers, aerogels and powders can be obtained" (Gleiche and Hoffschulz 29). Colloidal methods may also involve the use of ultrasound radiation to induce chemical reactions (Aitken, et al 26).

The vapor deposition method is a process in which "vapor is formed in a reaction chamber by pyrolysis, reduction, oxidation and nitridation . . . to deposit thin films of silicon and other semiconductors on to semiconductor wafers" (Aitken, et al 25).

Nanotech Web Resources

NIOSH Safety and Health Topic: Nanotechnology: www.cdc.gov/niosh/topics/nanotech/default.html.

Sample interim guideline based on the NIOSH information from Texas A&M Engineering: http://engineering.tamu.edu/safety/guidelines/Nanotechnology/NANO_SafeGuideline.pdf.

National Science Foundation Nanocenter HS&E Guide from Columbia University Nanoscale Science and Engineering Center: www.cise.columbia.edu/nsec/safety/?subsection=guide.

A Best Practices Approach to Minimizing EHS Risk in Nanotechnology Manufacturing from *Occupational Hazards* E-News: www.occupationalhazards.com/articles/14129.

External Review Draft Nanotechnology White Paper from EPA: www.epa.gov/osa/nanotech.htm.

National Nanotechnology Initiative Environment and Health Safety Issues: www.nano.gov/html/society/EHS.htm.

Practical Safety Guidance

NIOSH recently published some practical preliminary guidance in draft form online. Major points from the Exposure Control Procedures web page include:

- The principle of existing general aerosol control technology can be applied to engineering controls for nanoparticles following ACGIH ventilation guidelines.
- High-efficiency particulate air (HEPA) filters should work in controlling exposures to unfixed nanoparticles. Further research continues.
- Frequent housekeeping, using HEPA-equipped vacuums and wet techniques, to reduce workplace contamination is important.
- Personal hygiene is a key element; no food consumption in work areas, dedicated work clothes, hand washing and showering facilities must be available and used.
- Information on effective protective clothing is lacking.
- Respiratory protection is recommended if engineering and administrative controls are inadequate.

Source: Adapted from NIOSH (<http://www.cdc.gov/niosh/topics/nanotech/nano_exchange_control.html>).

It has been determined that there is potential for exposure to agglomerated nanomaterials in all of the cited manufacturing processes, the gas-phase, vapor deposition, colloidal and attrition processes "which may potentially result in exposure by inhalation, dermal or ingestion routes . . . during recovery, powder handling and product processing" (Aitken, et al 57).

Additionally, other potential processes are emerging. For example, atoms can now be moved manually; however, while "positional assembly" offers greater control over construction, it is currently very laborious and not suitable for industrial applications (The Royal Society and The Royal Academy of Engineering 3). Other scenarios that have yet to be realized involve using nanomachines to create materials one atom at a time in precise order and configuration (Arnall 16). It is expected that bottom-up manufacturing will begin to dominate the field of nanotechnology as more precise and intricate manufacturing processes are developed. It is also where the more-exciting properties of nanomaterials are seen due to the effect that quantum mechanics has at the atomic and molecular level which "gives them bizarre but useful physical properties"(Akin 134).

The full potential of nanotechnology has not yet been realized—in part due to the difficulties in manufacturing a standardized product whether it be to a particular size or discrete uniform unit. In most applications, nanomaterials are usually embedded in a matrix, such as titanium dioxide added to glass to make it more dirt-resistant or in car bumpers to add strength. Although as yet unproven, the likelihood of nanoparticles or nanotubes being released from products in which they have been fixed or embedded (such as composites) is low (The Royal Society and The Royal Academy of Engineering 4), "but in some, such as those used in cosmetics and in some pilot environmental remediation applications, free nanoparticles are used" (The Royal Society and The Royal Academy of Engineering 3). It is these free nanomaterials that may pose the greatest risk of adverse exposure, not only as consumer products but also farther up the pipeline during the manufacture and processing of these materials and initially as exposure issues in the research and development lab.

At this time, relatively limited manufacturing capacity is available for the production of nanomaterials. Thus, regulators must "get a handle" on this issue in order to develop a uniform method for identifying hazardous properties of these materials, communicating this information, developing effective controls to limit exposures when necessary, and a means to effectively promote compliance in a flexible manner that will allow for innovation and growth necessary for the state of the technology to advance and its containment to remain effective.

Regulation

Currently, no regulations in place in the U.S. specifically address the unique issues nanoparticles present, nor have they been characterized as hazardous materials. Additionally, within the U.S., no regulatory requirements mandate tests of nanomaterials for safety, health and environmental impacts (NIEHS).

Currently, OSHA would use its chemical hygiene standard, Occupational Exposure to Hazardous

Elements of an Effective Nanotech Safety Program

- Establish in-house procedures that identify tasks which may present an exposure risk (job hazard analysis).
- Provide training on proper handling of nanomaterials, including health effects, if known, and potential routes of exposure, exposure control methods, etc.
- Install and use effective engineering controls where exposures are likely.
- Provide documented guidance (SOPs and written safety programs) on the type and proper use of PPE and engineering controls, spill control, waste handling, etc.
- Provide strict oversight and frequent auditing of program activities.

Source: Adapted from NIOSH and NSF Nanocenter.

Chemicals in Laboratories (29 CFR 1910.1450), for research laboratories (Kulinowski) and presumably its Hazard Communication standard (29 CFR 1910.1200) and the general duty clause for enforcement in manufacturing facilities, provided that nanomaterials are classified as hazardous.

Also, EPA, which is concerned primarily with environmental risk, could use the Toxic Substances Control Act (TSCA) "as a means for exercising its own regulatory authority to minimize workplace exposures" (IOMA 4) since "EPA has the power to prohibit and or limit the manufacture of particular chemicals based on risk assessments" (Wardak 3). Unfortunately, it may be years before scientifically meaningful information will be available to perform a rigorous risk assessment. For example, only in October 2005 did NIOSH announce its plan to address exposure to nanomaterials in the workplace [NIOSH(b)].

Potentially thousands—and in the future, possibly millions—of people will be working with these materials that if handled improperly could pose a significant health risk to exposed individuals. While not all constructs will be found to be hazardous, as the industry grows, more types of compounds will be created that will both provide a wide range of benefits and present new risks. As a result, a regulatory framework must be set up that is both effective and flexible enough to allow for innovation not only in the creation of new nanomaterials but also in the control of their exposures.

Conclusion

While adequate information is available to raise questions concerning the safety of occupational exposures to free nanoparticles, the current state of knowledge concerning the exposure risks associated with nanotechnology is poor. Several preliminary toxicological studies have been performed using nanomaterials, but none have been associated with actual human exposures.

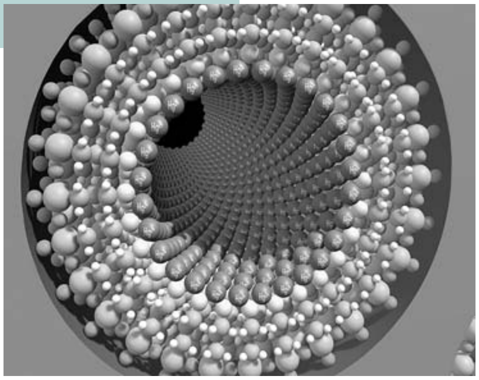
The majority of evidence concerning the potential health effects comes from the work performed with UFP exposures. Results from these studies suggest significant pulmonary and cardiovascular effects, such as decreased pulmonary function, increased incidents of adverse cardiac events and inflammation (Brook, et al 2666; Donaldson and Stone 409), as well as extracardiopulmonary impacts on organs such as the liver occurring as a result of exposure to UFPs entering the bloodstream from inhalation exposures (Borm 316; Ferin, et al 383). Additionally, UFPs are

Best Practices

The following best practices are provided for informational purposes. It is recognized that research is ongoing concerning health effects, engineering controls and air monitoring techniques.

- Employee baseline medical surveillance.
- Effective air monitoring.
- In-house toxicology studies.
- Design and implementation of effective control technologies.
- Capture of potential discharges to the environment.
- Transparency with stakeholders.

Source: Adapted from Cable.



Computer-generated model of Thiol-SAMMS, a nanotechnology with applications in the remediation, water treatment, catalyst, sensor and controlled-release markets.

IMAGE BY PACIFIC NORTHWEST NATIONAL LABORATORY

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able to cross the blood/brain barrier and potentially affect the central nervous system (Oberdorster, et al 444). Thus, significant evidence suggests that UFPs—and by association nanoparticles—may present significant health risks.

It is presumed that once government initiatives complete their missions, a framework will be implemented to address the hazards posed by existing and new constructs of nanomaterials as they are introduced in the workplace. The risk assessment process must be efficient and as effective as possible to meet the demands of this growing field.

Regulation will also be necessary. There appears to be an adequate basis to handle some preliminary problems associated with these materials within the existing regulatory framework. However, specific sets of standards should be developed over time to classify nanoparticulates by hazard and address potential exposure issues in the workplace through the use of appropriate engineering controls and PPE. These standards must be flexible enough to allow for innovation both within the industry itself and in the development of protective measures.

Until questions concerning the safety and health risks of these materials are answered, a precautionary approach must be adopted, and in-house policies and procedures must be developed to protect workers. NIOSH has published draft preliminary guidance (see "Practical Safety Guidance" sidebar on pg. 32). The precautionary approach would assume that unfixed nanomaterials are hazardous and are treated as such until proven otherwise. This would ensure that nanomaterials will be responsibly used and no harm will come to those potentially exposed to them. ■

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