Nanotechnology to Nanotoxicology: A New Cause for Concern

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Nanotechnology using ultrafine particles (UFP) has been hailed as the next industrial revolution, but like many other industrial processes such as chemical manufacturing, human toxicity and ecotoxicity are studied well after their release into the environment. Early studies show that some nanoparticles can have significant long-term toxic effects due to their shape, small size, structure, biopersistence, and attachment to the product. These are, unfortunately, the very properties that give nanoparticles their unique functionality.

The first nanoparticles created were thin film in 1974. Carbon soccer ball shapes, called "fullerenes," were developed in 1986. (41) Since the early 2000s, nanoparticles have found their way into over 1,200 consumer products including electronics, sunscreen, food packaging, and health drinks. They have also found their way into recycled wastewater and farming soil. There is no requirement for labeling of products with nanoparticles. Many government agencies, both in the U.S. and abroad, have concerns about the safety of this technology. To date, there is no organized effort to monitor the chemicals or set responsible regulations for the protection of public health or the environment.

The information in this article is taken from both peer reviewed journals as well as a comprehensive report from the University of San Francisco and California's Office of Environmental Health Hazard Assessment. (1) It is hoped by many governmental and non-governmental scientists that action will be taken now to identify, monitor, and strictly regulate nanoparticles instead of following the path of our failed chemical policies.

What Is Nanotechnology?

The word nanotechnology is derived from the Greek word "nanos" which means dwarf. Nanotechnology creates and manipulates a new class of materials on the scale of atoms and molecules. As currently defined, these particles are from 1 to 100 nanometers and can only be seen with an electron microscope. One million nanometers equals one millimeter. A flea is 1million nm. A red blood cell is 7,000 nm. A bacteria is 1,000 nanometers. Nano scale particles are close in size to biological molecules such as DNA, proteins, and viruses. Their small size enables nanoparticles to be inhaled or ingested and taken into cells. With transcytosis, they can cross epithelial cells and endothelium entering into blood and lymph circulation. (38)

Nanomaterials can contain one or more nanoparticles in different shapes and can have a metal base such as silver, titanium, or gold. They can also have a complex structure, such as in Quantum dots with a metal core of zinc, cadmium, or lead, and a biologically-friendly outer

shell. Carbon-based nanomaterials can be in the shape of tubes (carbon nanotubes) or in the shape of a ball frame with hundreds of carbon atoms (fullerenes or "buckyballs"). Dendrimers and Polymeric nanomaterials refer to a large range of particles which branch out from a central core, which may be a metal such as gold. Dendrimers are typically highly biologically active or biocompatible. Because their use is highly specialized in pharmaceutical applications, there is a low public-health risk, whereas other nanoproducts in wide consumer use are much more of a concern at this time.

What Makes Nanoparticles So Special?

The small size of nanomaterials with a high surface area affects their electronic, optical, fluorescent, and chemical reactivity. Certain carbon-based nanotubules can behave as semiconductors, like metals. Nanotubes can also be valuable in instrument manufacturing and medicine. Manufactured nanoparticles usually serve as additives or ingredients to existing products such as silver impregnated fabrics, antifogging coating to glass, or paint dispersives. The science of nanoparticles spans every physical discipline. California has three of the five leading centers in nanotechnology in the U.S. which combine academics, research, non-governmental, and industry organizations. Nanotechnology is a rapidly growing big business. It is estimated that by 2014, nanotechnology-enabled products may be worth $2.9 trillion. (2)

What Consumer Products Contain Nanoparticles?

There are a variety of applications for nanomaterials. In some instances, the particles are "fixed" in the product and thus are less likely to be of concern. In other products, the nanomaterials are free floating and can then disperse in the environment and can be absorbed into living systems.

In electronics, nanoparticles are used in batteries, memory, and display modules. In sporting goods, carbon fibers are an integral part of the structure making tennis rackets and bicycles lighter. Nanoparticles are used in pigments, car coatings, antifog coatings, anti-fingerprint coatings, and on solar panels. In agriculture, nanoparticles are used to make pesticides and fertilizers adhere and persist. In medicine, nanoparticles, such as dendritics, are used for drug delivery, and in cellular regeneration, on various matrices. Silver nanoparticles are used as antibacterial coatings or additives for wound dressings. Nanoparticles are used for imaging and displays in medical devices.

In personal care products, nanoparticles are now widely found in cosmetics. Titanium dioxide nanoparticles are used as a sunscreen to help disperse the product so it is not seen and also confer increased UV protection. These are "non-chemical" sunscreens with titanium dioxide that is "micronized." Nanoparticles are used as glidants in mineral-based and other makeup, now totally over 160 personal care products.

Nanoparticles are also used in nutraceuticals and as dietary supplements. They claim enhanced absorption and bioavailability of medications and vitamins. (16) Silicone dioxide, magnesium oxide, and titanium dioxide are used to coat confectionary products (Mars Bars) to increase shelf life. (16) Nanoclay polymers mix nylon, polystyrene, polyurethane, and other chemicals, and are now used to coat the interior of beer bottles (Miller Brewing Co. and Hite Brewing Co.). (16)

Nanosilver is the largest material being utilized in household products. It is used in silver non-

stick surfaces and utensils, nanosilver coatings on children's products (i.e., baby bottles, pacifiers, wet wipes, and stuffed animals all claiming antibacterial properties), washing machines, and antibacterial socks, to mention a few. (23) The project for emerging technologies inventories products with advertised nanoparticles. (42) There is no requirement for labeling, thus many more products may contain them.

How Are Nanoparticles Harmful? Size Matters

Studies have shown that nanoparticles elicit different toxic cell responses and target different organs, depending on their size, shape, surface functionality, stability, and reactivity. Nanoparticles can enter the body via inhalation, ingestion, or with dermal exposure through injured and sometimes normal skin. Metal nanoparticles can bioaccumulate in the kidneys or liver. Unlike conventional chemicals, nanoparticles may trigger phagocytosis, whereby the cell membrane surrounds the particle, transports it to the center of the cell in order to break it down. Bacteria and viruses can be destroyed, however, nanoparticles may not be changed with normal biological processes and may accumulate in the cell and cause chronic irritation of the cell to the point of cell death. Nanoparticles can also cross cell membranes via diffusion or adhesion. Inside the cell, they can react with proteins, organelles, and DNA increasing their toxic potential. (26) Like some chemicals, they cannot be broken down, thus persist in the body.

Scientists studying the mechanisms of action of toxins state the simple dose response curve does not always apply. Cell death after exposure to a toxin is a very complex interaction. The chemical or material may directly injure the cellular processes, but may also interfere with the immune system and tumor surveillance, thus causing cancer from long term exposure. Another method of cell death is called aptosis. Some call this cell suicide. It is a natural and programmed cell death found in normal development and initiated by the cell itself. Recent studies have shown that a variety of environmental contaminants, including heavy metals (copper, cadmium, mercury, lead), can cause aptotic cell death. (39)

Engineered nanoparticles have been shown to induce aptotic cell death of macrophages after inhalation of single-walled nanotubes. (39) There is growing concern, as neurodegeneration is seen in some nanoparticle animal studies.(43)

Nanoparticle Effects on the Lungs

We know that exposure to complex mixtures of air pollutants produces inflammation in the upper and lower respiratory tract. Interest has risen in recent years with regards to the potential effects of ultrafine particles on pulmonary function. Nanoparticles have a much higher inflammatory potential than larger particles. When inhaled, they are efficiently deposited in all regions of the respiratory tract and they can translocate out of the respiratory tract to other parts of the body as well. (36)(38)

Inhalation studies demonstrate that these smaller particles create oxidative stress, free radical formation, inflammation in cell culture, and in vivo in the lung. (26)(27)(28)(29)(30)(31)(32) Titanium dioxide nanoparticles have been shown to induce inflammation in the lungs in animal studies. (51)

Carbon nanotubes have toxicologically significant structural and chemical similarities to asbestos. Multiple inhalation and injection studies have shown that carbon nanotubes act like the long fibers of asbestos and get stuck in the pleural lining causing pulmonary inflammation, granuloma formation, and fibrosis, which like asbestos could lead to mesothelioma. (33)(34)(35)(49)(50)(57) All these studies point to a potential for increased lung disease in populations already facing rising chronic pulmonary disease from chemical and air pollution.

Intestinal Absorption of Nanoparticles

Particulate uptake across the intestinal cells and into the bloodstream has been well documented since 1926. (58) Ingested nanoparticles are absorbed, depending on morphology, and charge through or around normal intestinal cells or through Peyer's patches (PP). Peyer's patches are aggregates of lymphoid tissue in the small intestine which are responsible for immune surveillance and response. Particulates, once in the sub-mucosal tissue, are able to enter both lymphatic and capillaries to other organs.(58)(59)(60) Jani found increased uptake with smaller diameter. Nanosized polystyrene particles were much better absorbed than larger particles. (61)(62) The GI tract is an efficient delivery system for vaccines and drugs, thus is well studied.

An increasing route of exposure to nanoparticles is through consumer products, food additives, packaging, and drugs. "For those nanoparticles designed to stabilize food or to deliver drug via intestinal uptake, other, more demanding rules exist and should be followed before marketing these compounds." Dr. Hoet (55)

Nanoparticles: Destination Brain

We have known for years that air pollution causes chronic lung disease. But recent studies now show brain damage from air pollution. Calderon-Gardciduenas, et al., found significant inflammatory neurodegenerative changes in the olfactory bulbs, olfactory mucosa, and cortical and subcortical brain structures in dogs from a heavily polluted area in Mexico City, whereas these changes were not seen in a less polluted rural control city. (52) As it turns out, the nasal cavity, olfactory bulb, and respiratory epithelia are a common portal of entry to the brain and targets for toxicological damage. (36) This circumvents the very tight blood brain barrier. Oberdörster, in 2002, reported the translocation of inhaled nanoparticles via the olfactory nerves. (38) A translocation pathway from the respiratory tract to the brain was demonstrated over 60 years ago for polio viruses. Herpes virus travels long distance in a similar pattern along the axon. Transport velocity for nanoparticles in nerve axoplasm has been shown to be 2.4mm/hour. (36)

A Japanese study, in 2009, showed that titanium dioxide nanoparticles could transfer from pregnant mice to their offspring and cause nervous system damage and reduced sperm production in the male offspring. (44) Sárközi, in 2009, instilled manganese nanoparticles into the airways of adult rats and found that manganese had access from the airways to the brain with resulting behavioral, electrophysiologic, and toxicologic effects. (45) In vivo studies of fish indicate that nanoparticles already in use can have adverse effects on wildlife. Oberdorster studied carbon based lipophilic fullerenes, which are now being manufactured by the tons and used in cosmetics and face creams. (65) He found oxidative brain damage in large mouth bass. (46) The cumulative effects of these increasing exposures are unknown. (68)

Trickler, in 2010, studied silver nanoparticles effects on rat brain. He found inflammation and an increase in the blood brain barrier with smaller nanoparticles. He states that "if left unchecked, these events may further induce brain inflammation and neurotoxicity."(67) Wang found that titanium dioxide nanoparticles instilled intranasally directly entered the brain through the olfactory bulb in the whole exposure period, and deposited more heavily in the hippocampus region where spatial navigation and both short term and long term memory are located. Toxicity was seen via oxidative damage leading to an inflammatory response. (86)

There is great cause for concern as more research indicates that inflammation of the brain can directly cause Alzheimer's disease.(66)

Reactive Oxygen Species and Cardiovascular Effects of Nanoparticles

Reactive Oxygen Species (ROS) are highly reactive chemical molecules in living organisms implicated in many disease states including aging, DNA damage, brain dysfunction, cell damage, organism stress, inflammation, Alzheimer's disease, to name a few. Reactive Oxygen Species are the normal byproduct of metabolism and function to signal cells for apoptosis (cell death), immune stimulation, and platelet aggregation. Chemicals and heavy metals can increase ROS in our bodies. Our bodies make natural antioxidants to combat free radical formation (ROS). These are chemicals like glutathione and enzymes such as superoxide dismutase that scavenge the free radical before much harm can be done. If there is excessive ROS, these free radicals damage cellular DNA, oxidize proteins, inactivate enzymes, signal inflammation, or cell death. Oxidative stress is believed to be one of the major deleterious consequences of exposure to nanomaterials. (29)(30)(56)(40)

Radomski, in 2005, showed that some carbon nanoparticles and microparticles have the ability to activate platelets and enhance vascular thrombosis. (48) Other studies have shown similar effects. (75)

Lifecycle of Nanoparticles : Entrance Into the Soil and Water Cycle

What is the fate of nanoparticles in our sunscreen, powdered makeup, microbe proof teddy bear, or silver impregnated socks once they are washed down the drain? The solids that go to the treatment plant are put on agricultural fields as fertilizer and the liquid is used for irrigation in landscaping and agriculture, with the rest pumped into local rivers or bays. Soon, we will be drinking this reclaimed water and paying a lot more for it, as we are approaching serious water shortages.

Will we be able to remove nanoparticles in sewage treatment? Good question, considering we are not removing many persistent toxic chemicals now such as flame retardants, pharmceuticals, estrogenic synthetic compounds from primary wastewater treatment, which are effecting fish and other aquatic organisms. (89)(90)(91)(92)(93)(94)(95)(96)(97)(98)(99)(100)(101) We have yet to control known toxins in the environment, as we add newer emerging contaminants to the list. Studies have shown that nanoized copper causes acute toxicity and gill injury in Zebrafish. (82) Silver particles are known to be toxic to freshwater fish and have now become a major pollutant in San Francisco Bay and other surface waters from wastewater discharge. (85) (5)(6)(7)(8)(9) Nanoparticles are already in our soil and wastewater.

Beneficial Bacteria at Risk: Antibacterials Gone Awry

While we need antibacterial products in medicine, too much of a good thing can cause disruption in healthy ecosystems including our gastrointestinal tract. Studies have now shown that E. Coli bacteria strains were greatly inhibited by even small amounts of titanium dioxide nanoparticles. Most of these are beneficial friendly bacteria that keep the gut healthy by preventing establishment of pathogenic bacteria and producing vitamin K.

Titanium dioxide particles have been considered non-toxic, as they do not incite a chemical reaction. Nanoparticles of titanium, however, interact with living organisms in a much different way. They can travel through the body and cause oxidative stress. Schiestl exposed mice to titanium dioxide in their drinking water. By the fifth day, they began to show genetic damage with double stranded DNA breaks and signs of inflammation. (76)

Silver has broad spectrum antimicrobial activity towards many pathogens and it has been used in the past for medicinal purposes. The bactericidal activity of silver, however, inhibits soil microbial growth at levels below the concentrations of other heavy metals. (77)

The antimicrobial effects of silver nanoparticles also have impacts at the ecosystem level affecting beneficial soil organisms (bacteria and fungi) that "feed" nutrients to plants. Researchers grew plants in biosolids with and without the addition of ecologically relevant silver nanoparticles. These levels of silver nanoparticles were within the range that the U.S. Environmental Protection Agency reported finding in a recent survey of biosolids from water treatment plants. The nanoparticles reduced the growth of one of the tested plant species by 22 % compared to silver-free biosolid treatment. Similarly, microbial biomass was reduced by 20%. (80) Considering nanoparticles do not degrade, are biologically active, and bioaccumulate, this has serious implications for the future of agriculture. Canada, in 2010, joined several other countries banning nanotechnology as a prohibited substance or method in organic food production. (81)

Hijacking Wastewater Treatment

Sewage treatment is a several step process of removing contaminants from wastewater prior to discharge into local waterways or for non-potable uses. In southern California, sewage effluent is used as drinking water after additional treatments. Usually, there are three steps. Primary treatment involves separating solids from liquids. Secondary treatment involves biological degradation of the suspended organic matter in the effluent by microorganisms. Tertiary treatment occurs when additives are used to clean the water if discharged into a sensitive ecosystem or if used for non-potable uses, such as golf courses.

Nanoparticles have been shown to inhibit bacteria that are used to help degrade the organic matter in sewage treatment plants. (88)(89) Preliminary studies to evaluate removal of nanoparticles in wastewater show that it is not as easy as predicted. (83)(84) Dr. Limbach states "results indicate a limited capability of the biological treatment step to completely remove oxide nanoparticles from wastewater." (83)

Next Steps in Growing a Sustainable Nanotechnology Industry

While there has been an avalanche of research and development in commercial nanotechnology,

there has been a sharply contrasted lack of data with regards to human and environmental safety testing. The emerging science of nanotoxicology has identified some real concerns for some nanoparticles with regards to public health and the environment, including wildlife, fragile aquatic, and soil ecosystems.

"The current state of oversight regimes should raise serious concerns for policymakers tasked with the challenge of encouraging nanotechnology innovation in a responsible and sustainable manner," says David Rejeski, Director, Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars.

Many government and non-governmental organizations have written extensive reports with regards to the concerns of nanotechnology and its oversight.

The conclusion of these reports is that there is inadequate data on toxicology of these diverse particles, exposure data, and biomonitoring, as well as a lack of adequate regulation.

A comprehensive 2011 report by the Office of Environmental Health Hazard Assessment Cal/EPA and the University of California San Francisco titled "Recommendations for Addressing Potential Health Risks From Nanomaterials" discusses these issues, and specific goals for government agencies were suggested. (1) Many lessons have been learned about chemical contamination too late. It is hoped that earlier action will prevent major public and environmental health problems. Below are some policy recommendations from the report.

UCSF-OEHHA Recommendations for Addressing Potential Health Risks From Nanomaterials

1) Traditional mass-based dose models may not be sufficient to characterize toxicity. New traits or properties will need to be defined and considered.

2) Heeding early warnings and using environmental monitoring is integral to identifying, evaluating, and monitoring potential hazards.

3) Persistent and/or bioaccumulative materials should be identified early, as build-up of exogenous chemicals are usually detrimental in some way.

4) Targeted research in the area of biological transport and distribution of nanomaterials, including sources, routes of contact, and internal distributions. Integrate this with the information gathered on exposure potential.

5) Require sufficient toxicological testing information to assess safety of risks to consumers, including susceptible subpopulations such as infants preferable premarket, and post-market as necessary.

6) Require testing of release and exposure potential for nanomaterials in consumer products that have widespread use, such as titanium dioxide, silver nanoparticles, and carbon nanotubes. Testing must be completed for products to remain on the market.

7) Collect information on fate and transport of nanomaterials, including monitoring in environmental and biological media. Require centralized reporting mechanisms, and maintain them in a systematic manner.

8) Susceptible sub-populations should be characterized in risk assessment and considered in decision-making.

9) Implement a labeling system that requires labeling products that contain nanomaterials.

10) Support a publicly accessible clearinghouse and inventory of products and sources of nanomaterials, requiring disclosure of where nanomaterials are manufactured, in what quantities, and for what new or existing products such as through product labeling.

11) Develop a framework for making policy and regulatory decisions based on nanomaterials' use, exposure potential, and exposure to susceptible subpopulations, while weighing public health or societal benefit.

12) Integrate nanomaterial safe handling practices into standard lab safety training for academic, industrial, and other laboratory workers and students.

13) Continue to include provisions for public input and comment during the decision-making processes.

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