

# Nanomaterial Health Effects—Part 1: Background and Current Knowledge

*Maria C. Powell, PhD; Marty S. Kanarek, PhD, MPH*

## ABSTRACT

Nanotechnologies are among the fastest growing areas of scientific research, and have important applications in a wide variety of fields. At the same time, scientists and regulators are concerned about the potential health and environmental risks related to the widespread production and use of the nanomaterials created by these technologies. Several recent animal and cell culture studies have suggested that some engineered nanomaterials may have biological effects similar to ultrafine particulates. This paper describes what nanomaterials are and why they might be toxic, and then reviews existing toxicological studies on engineered nanomaterials.

## INTRODUCTION

In recent years, governments and industries worldwide have invested billions of dollars in nanotechnology research and development, and proponents predict that it will offer numerous benefits to society.<sup>1</sup> At the same time, scientists, government agencies, insurance companies, and non-governmental organizations in the United States and Europe have raised concerns about potential health and environmental risks from the widespread production and use of engineered nano-sized materials, or “nanomaterials.”<sup>2-4</sup> In this paper, we describe what nanotechnologies are and why nanomaterials might be toxic. We then review some of the key toxicological studies completed on engineered nanomaterials.

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This work was supported by NSF grant no. DMR0425880. Dr Powell is a research associate with the University of Wisconsin La Follette School of Public Affairs' Initiative on Nanotechnology in Society. Dr Kanarek is a professor with the Department of Population Health Sciences and Gaylord Nelson Institute for Environmental Studies, University of Wisconsin. Please address correspondence to: Maria Powell, PhD, 1225 Observatory Dr, Madison, WI 53706; phone 608.890.0394, 608.240.1485; fax 608.240.1485; e-mail powell@wisc.edu.

## WHAT ARE NANOTECHNOLOGIES AND NANOMATERIALS?

Nanotechnologies are defined as activities that include “the manipulation, precision placement, measurement, modeling, or manufacture of sub-100 nanometer scale matter...”<sup>3</sup> Some call nanotechnology a “general purpose technology”—much like the Internet, electricity, or steam power—because it is expected to have broad impacts across multiple sectors and products. Others call it an “enabling” technology because it is likely to improve existing technologies in almost every field.

Nanomaterials are typically defined as materials that have at least 1 dimension <100 nanometers. They have properties that make them useful for many applications—such as high conductivity, strength, durability, and reactivity. Engineered nanomaterials can be made from nearly any substance. Many are carbon-based materials, but silicon and titanium are also common. Several nanomaterials are made of metals or metal oxides, including zinc, iron, cerium, zirconium, gold, silver, copper, lead, cadmium, germanium, and selenium. Key nanomaterials currently in production include metal oxides, fullerenes, carbon nanotubes, and quantum dots.<sup>4</sup> Moreover, a variety of different kinds of nanotechnologies and nanomaterials, often called “bionanotechnologies,” are being developed for biomedical purposes. Bionanotechnologies are modeled after biological substances and structures, or combine nanomaterials with biological substances. They include materials such as biochips, drug release systems, nanofibers and hybrid nano-bio devices, molecular electronics, and biomimetics (synthetic genes, proteins, and viruses).<sup>5</sup>

## WHY MIGHT NANOMATERIALS BE TOXIC?

Many of the properties that make nano-sized materials so useful can also make them toxic to cells and organisms. Nano-sized materials have high surface-to-vol-

ume ratios, so a high proportion of their atoms are on the surface, allowing them to more readily react with adjacent atoms and substances. These properties also make them more likely to react with tissues in the body and cause cellular and tissue damage. Moreover, nanomaterials are transported readily through body and environmental barriers, and when inhaled they can translocate to other organs, including the brain.<sup>2,4</sup>

Numerous epidemiological studies have associated exposures to small particles, such as combustion-generated fine particulate matter in air pollution, to lung cancer, heart disease, asthma, and/or increased mortality.<sup>6,7</sup> Ultrafine particles (smaller than 100 nanometers) can be more toxic than larger particles for several reasons. While larger particles tend to deposit in the upper airways, ultrafine particles deposit in the alveolar region where gas exchange takes place. Once deposited, the higher reactivity of nano-sized particulate matter makes it more likely that it will absorb endogenous substances, react with molecules such as proteins and enzymes, and generate inflammatory responses—potentially initiating a series of toxic responses far from the initial site of deposition.<sup>7</sup>

Nano-sized particulates in ambient air pollution may have a variety of systemic effects in addition to lung effects because they can translocate to the blood, liver, spleen, kidney, heart, and brain after deposition in the lungs. A growing body of toxicological and epidemiological evidence indicates that exposures to ultrafine particles via inhalation are associated with increased blood viscosity, atherosclerosis, cardiac arrhythmias, vascular thrombosis, and myocardial infarction.<sup>8,9</sup>

### **TOXICITY STUDIES ON INTENTIONALLY ENGINEERED NANOMATERIALS**

Currently, a variety of types of nanomaterials are being purposely engineered for consumer and industrial applications. Below, we broadly review toxicity studies on some of the engineered nanomaterials currently in production—titanium dioxide, fullerenes, carbon nanotubes, and quantum dots. Although there are numerous other kinds of nanomaterials currently in production, few toxicological studies have addressed these materials to date.

#### *Titanium Dioxide*

Micrometer-sized titanium dioxide has been widely used in a variety of products such as sunscreens, cosmetics, toothpaste, paper, plastics, and pharmaceutical tablets. In recent years, ultrafine or nanometer-sized titanium dioxide has been used in some of these products because it is transparent rather than white, making it more aesthetically pleasing.

Titanium dioxide is not inherently toxic, but because of its small size and low solubility, it can have toxic effects. Exposures to titanium dioxide have been associated with a variety of pulmonary effects in rats, including inflammation, pulmonary damage, fibrosis, and lung tumors.<sup>10,11</sup> Further, ultra-fine titanium dioxide particles can impair macrophage function and increase pulmonary retention, enter the epithelium faster, and translocate to the subepithelium space more readily than fine particles.<sup>12</sup> Several studies show that ultrafine titanium dioxide can also cause mitotic disturbances, DNA damage, and apoptosis.<sup>13,14</sup>

Concerns have also been raised about the use of nano-sized titanium dioxide in cosmetics because they are placed directly on the skin and there is evidence that nanoparticles can penetrate dermal tissues.<sup>2</sup> The titanium dioxide in sunscreens, when exposed to sunlight, can catalyze oxidative damage to DNA in vitro and in cultured human fibroblasts. Moreover, there is evidence that the oxidizing properties of titanium dioxide cause free radical reactions that can lead to the degradation of other organic products in sunscreens, forming further reactive radical intermediates that may be cytotoxic.<sup>14-16</sup>

#### *Fullerenes*

Carbon fullerenes are byproducts of combustion processes and are components of ultra-fine particulate matter in air pollution. In 1985, scientists learned how to isolate fullerenes from soot, and by 1990 they had learned how to create them intentionally in mass quantities by vaporizing or combusting graphite. Engineered carbon fullerenes are hollow balls of carbon arranged in hexagonal and pentagonal panels. The most well known type is C60, also called the “buckyball.” Other fullerene forms include C70, C76, C84, and buckyballs with shells (“bucky-onions”). Fullerenes are currently being used (or being considered for use) as catalysts, copolymers and composites, lubricants, drugs and drug delivery systems, cosmetics, health care products, and sporting goods.

Researchers have been exploring the potential drug uses of fullerenes since the early 1990s. They have strong oxidizing and anti-oxidizing properties (depending on the light and chemical conditions), are highly reactive with biomolecules, and can cross the blood-brain barrier. These properties make them attractive for delivery of AIDS medications, anti-bacterial drugs, and cancer and neurodegenerative disorder treatments.<sup>17</sup>

Because of their strong oxidizing properties, however, scientists raised concerns about the potential dermal and inhalation effects of fullerenes during research and production in the early 1990s.<sup>18</sup> A few short-term

screening studies in the 1990s examined the potential toxicity of fullerenes and did not find significant problems.<sup>19</sup> However, other studies done during the same period showed that when exposed to light, fullerenes can have cytotoxic effects, cleave DNA, affect embryo development, and/or distribute rapidly to many tissues in the body, where they are retained for a long time.<sup>20-22</sup>

More recent studies suggest that fullerenes' cytotoxic effects may be due to lipid peroxidation of cell membranes and resulting "leakiness" of the membranes.<sup>23</sup> They are highly lipophilic and tend to localize to cell membranes.<sup>24,25</sup> In the first study of fullerenes' potential effects on wildlife, largemouth bass were exposed to pure fullerenes, resulting in lipid peroxidation in their brains.<sup>26</sup> Interestingly, in this study, fullerenes also increased water clarity in the fish tanks, possibly because of their strong antibacterial properties. Fullerenes' toxicity levels appear to vary depending on the form of fullerenes; the least derivatized (most pure) forms of water-soluble fullerenes seem to be more toxic than more derivatized forms.<sup>27</sup>

#### *Carbon Nanotubes*

Like fullerenes, carbon nanotubes already exist in the environment in soot, air pollution, and other combustion byproducts. First isolated in 1991, they are intentionally produced using a carbon feedstock (usually graphite) and a metal catalyst (usually iron or nickel). Carbon nanotubes have a range of applications in composites, polymers, sensors, electronics, and display devices as well as in biomedical, pharmaceutical, food and agricultural, and sporting goods applications. Until recently, they were available commercially in only limited quantities, but much higher quantities are now available.

Engineered carbon nanotubes are similar to rolled-up sheets of graphite with single or multiple walls. They have very high physical strength, flexibility, and electrical conductivity, and are extremely insoluble and non-biodegradable. The length-to-width ratio (aspect) of carbon nanotubes, which can be 100 or greater, qualifies them as fibers, like asbestos. Individual nanotubes are usually around 1nm in diameter and can be several microns in length—but because of their high electrical conductivity, they tend to agglomerate into bundles or "nanoropes" that are usually about 20-50nm in diameter and can be more than a millimeter in length.<sup>28</sup> They often contain iron or nickel, which can contribute to toxicity.

Several recent animal studies suggest that carbon nanotubes can have significant pulmonary effects.<sup>29</sup> A Dupont study, for example, found that exposures to

single-wall carbon nanotubes produce immediate (but transient) non-dose-dependent inflammation and granulomas in mice lungs.<sup>30</sup> Other studies, including several done by the National Institute for Occupational Safety and Health (NIOSH), found that nanotubes produce persistent and dose-dependent inflammation, oxidative stress, granulomas, and fibrosis; effects were stronger than those produced by equal doses of carbon black and silica.<sup>31-33</sup> One of these studies found that multi-wall carbon nanotubes produce inflammation and fibrotic reactions that persisted in mouse lung tissue and stimulated the production of a pro-inflammatory cytokine (TNF- $\alpha$ ) that is related to the pathogenesis of particle-induced lung diseases and pneumoconioses.<sup>32</sup> Notably, this study found that for some respiratory effects, nanotubes produce reactions comparable to or stronger than those produced by asbestos. Paralleling recent studies on ultrafine particulates in air pollution, carbon nanotubes have been associated with cardiovascular effects such as aortic DNA damage, platelet aggregation, and enhanced vascular thrombosis.<sup>29,34</sup>

Supporting *in vivo* findings, studies have also shown that nanotubes produce cytotoxic, inflammatory, and fibrogenic responses in macrophages and other pulmonary cell lines.<sup>35</sup> Others found that nanotubes resulted in oxidative stress, cellular toxicity, and loss of cell viability and/or structural, genetic, and morphological changes in keratinocyte cell cultures.<sup>36</sup>

#### *Quantum Dots*

Quantum dots, first developed in the early 1980s, are crystalline semi-conducting nanoparticles comprised of a metalloid crystalline core and a "cap" or "shell" that shields the core and renders the dots biologically compatible. Cores are typically made of cadmium or lead, but can be made of various other semiconductor, noble, or transition metals. They are coated with a variety of materials such as polyethylene glycol, zinc sulfide, or polyacrylate.<sup>37</sup> Quantum dots are used in composites, paints, inks, solar cells, and opto-electronics. Because they can fluoresce, they are also used for labeling in medical and scientific research and for a range of different kinds of sensors for surveillance, medicine, agriculture, military, and business purposes.

Cadmium and lead used in quantum dot cores are well-known toxins to vertebrate systems, even at relatively low concentrations.<sup>38,39</sup> Studies suggest that quantum dot shells can degrade and expose toxic metal cores when exposed to oxidizing conditions and UV light, and there is also evidence that some capping materials may be toxic.<sup>37</sup> The potential toxicities of quantum dots, therefore, depend on the stability of their shell coatings

in cells, during synthesis and storage, and in the environment over the long term.

Toxicity studies on quantum dots have shown inconsistent results. Although some short-term studies found no acute cytotoxicity, they found that quantum dots can affect cell growth and viability.<sup>37</sup> Other studies found the dots were cytotoxic to cell cultures to varying degrees depending on their coatings, can be incorporated into cells via endocytosis, and target cell membranes. Some in vivo studies suggest that quantum dots accumulate in a variety of organs and tissues, including lymph nodes, kidneys, liver, lung, bone marrow, and spleen.<sup>37,40</sup>

## CONCLUSIONS

The growth of nanotechnologies is skyrocketing worldwide, promising a variety of applications in electronics, health and medicine, research, agriculture, information technology, environmental applications, and much more. At the same time, a growing number of studies suggest that some engineered nanomaterials can cause toxic effects in animals and cell cultures. These findings raise concerns about the potential long-term public health and environmental effects of the increasing use of engineered nanomaterials in consumer products, pharmaceuticals, and industrial materials. Production of these materials is currently estimated to be in the thousands of tons per year worldwide, and is expected to increase substantially in coming years.<sup>1</sup> Workers in nanotechnology industries and researchers in labs may be exposed to nanomaterials as production ramps up, and consumers may be exposed as more nano-based products enter the market. Eventually, engineered nanomaterials may end up in the environment, adding to existing combustion-generated nanomaterials. Some of these materials (eg carbon nanotubes) are known to be very resistant to biodegradation. Consequently, they are likely to remain in our environment for a very long time and may build up in the food chain.

Although there are significant uncertainties and unknowns about potential risks related to newly engineered nanomaterials, analogies between the health effects related to engineered nanoparticles and those associated with existing ultrafine materials and fibers are compelling. The weight-of-evidence to date—including numerous toxicological and epidemiological studies on ultrafine particulates and asbestos—suggests that exposures to fibers and materials at the nano-scale can cause significant public health consequences, such as heart and lung disease. In addition, it is well known that the heavy metals used in certain nanomaterials (eg, lead and cadmium) are toxic to humans, particularly developing fetuses and children.

Given this evidence, newly engineered nanomaterials

### University of Wisconsin-Madison's Nanotechnology in Society Project

Scholars with the University of Wisconsin's Center for Nanotechnology in Society\* are establishing a network of toxicologists, epidemiologists, environmental engineers, health and safety experts, and social scientists to examine the environmental and health effects of engineered nanomaterials. (See [www.lafollette.wisc.edu/research/Nano/](http://www.lafollette.wisc.edu/research/Nano/) for more information.) The objectives of this network are to bring interdisciplinary expertise to bear on key questions and data gaps in the evaluation and assessment of new and emerging nanotechnologies and to provide insights relevant to developments in local, state, and federal policy. The network also plans a public outreach program to help inform citizens of Wisconsin about issues of nanotechnology, health, and the environment.

\* The Center for Nanotechnology in Society at the University of Wisconsin-Madison is a component of the Center for Nanotechnology in Society, a national center of excellence for research on the societal implications of nanotechnology led by Arizona State University. The Center is funded by the National Science Foundation and affiliated with the Nanoscale Science and Engineering Center.

should be treated with precaution as production levels increase. Research institutions, industries, and government agencies should develop risk management strategies as soon as possible to prevent worker exposures and broader public health problems such as those resulting from the widespread use of asbestos and lead. In Part 2 of this paper (in the next issue of the *Wisconsin Medical Journal*), we discuss some of the uncertainties and data gaps that need to be addressed to develop adequate risk assessments and risk management policies for emerging nanotechnologies.<sup>41</sup>

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