Precarious Promise: A Case Study of Engineered Carbon Nanotubes

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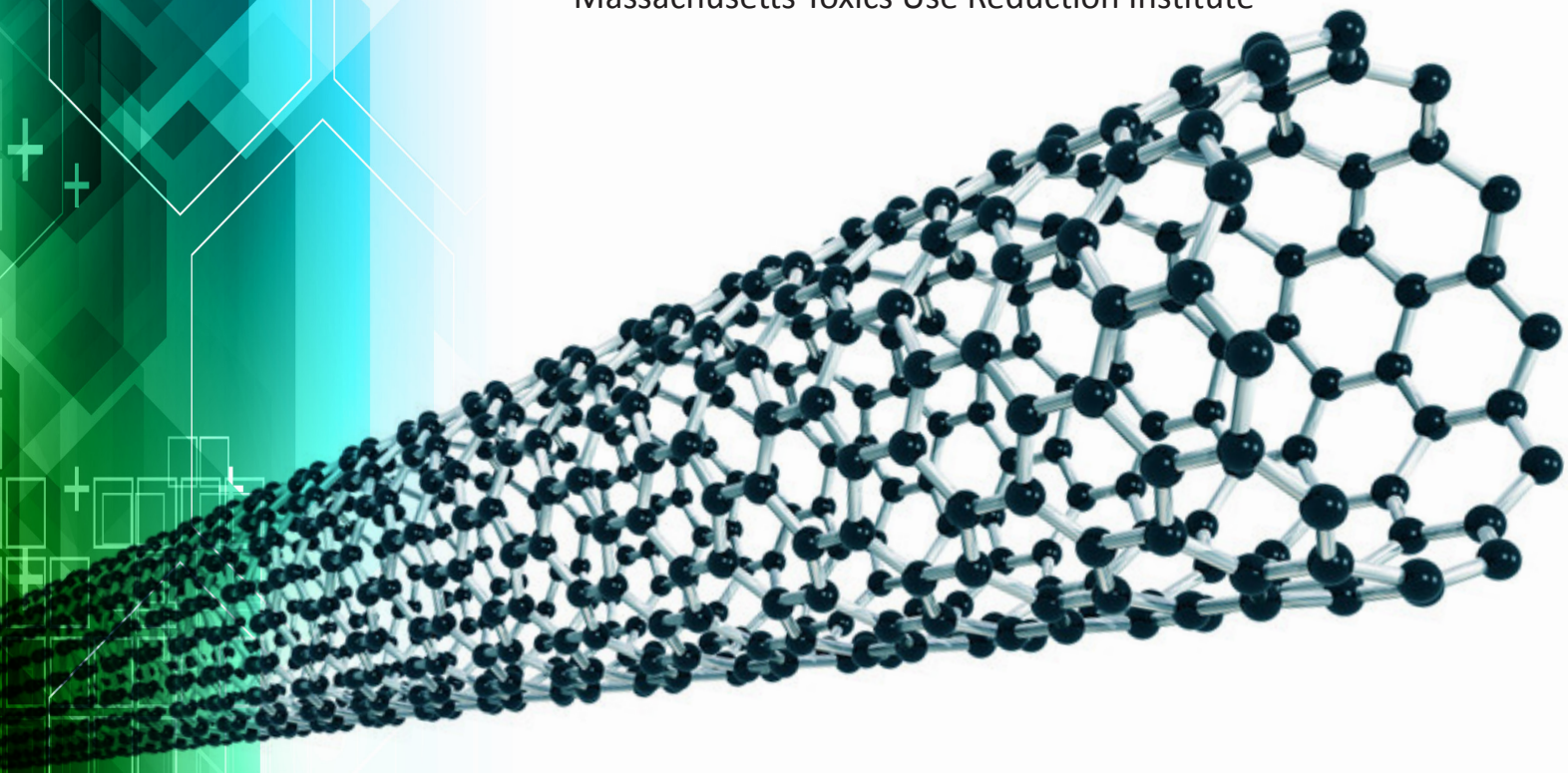

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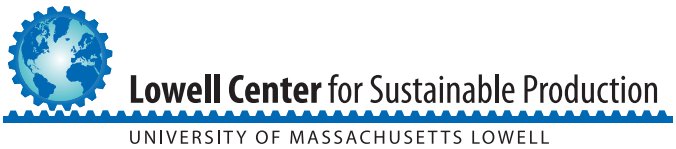

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Summary

In 1991, a researcher with the NEC Corporation identified what is now heralded as one of the most important discoveries of the 20th century: carbon nanotubes (CNTs). One-hundred thousand times smaller than a human hair, these cylinders of carbon can be over 100 times stronger than steel and six times lighter. CNTs are able to withstand repeated bending and twisting, are an excellent conductor of electricity, and can transport heat better than any other known material. With such extraordinary chemical and physical properties, many believe that CNTs have sparked the next industrial revolution.

In just over two decades since the discovery of carbon nanotubes, technologies relying on engineered CNTs have developed at warp speed. Current and anticipated uses of engineered CNTs are numerous and diverse: sporting equipment, solar cells, wind turbines, disk drives, batteries, antifouling paints for boats, flame retardants, life-saving medical devices, drug delivery technologies, and many more. Some have suggested that every feature of life as we know it is or will be impacted by the discovery and use of CNTs.

Despite uncertainty about how these entirely new materials may affect living systems, CNTs have largely been a case of "forget precaution, get to production." Concern for human health and the environment has been overwhelmed by the promise of profits and progress. Financial support for nanomaterial research and commercial development has vastly outpaced funding of environmental health and safety and sustainable design research on these materials. And with limited understanding of how these structures – small enough to penetrate cells – will interact with humans and other life forms, use of CNTs is proliferating with few systems in place to protect people or the environment.

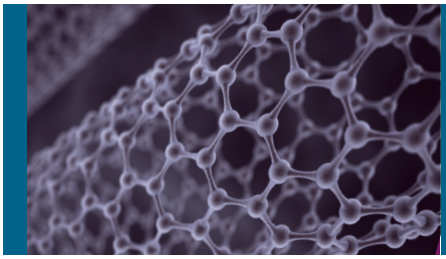
Warning signs have emerged, however. CNTs share important physical characteristics with ultrafine air pollution particles as well as with asbestos fibers – both recognized as seriously toxic. Mounting numbers of toxicological studies now demonstrate irreversible health effects in laboratory animals, but it is unclear whether similar effects have occurred in humans exposed at work or through environmental releases.

The growing literature on toxic effects of CNTs also make clear that the environmental and human health impacts may vary radically, depending on specific chemical and physical characteristics of the engineered nanomaterial. While some CNTs appear to be highly hazardous, it remains possible that others may pose little threat. Is it possible to gain the benefits of CNTs with minimal risk by ensuring the use of the safest alternatives for a particular application?

New technologies such as engineered CNTs, have the potential to bring dramatic benefits to society and will simultaneously present challenges to those charged with protecting health and the environment. When the benefits are clear and profitable while the risks are uncertain and prospective, the momentum to create and use new technologies like CNTs often trumps the urgency of acting to protect health and the environment. CNTs present a compelling case for the need for proactive rather than reactive measures – by government, industry and other stakeholders – to address hazards of emerging chemicals and materials.

A Familiar Story

We've been here before. In the nineteenth century, organic chemists created a radically new direction for their field. Instead of just identifying and using the complex molecules created by life, chemists learned that they could create them. Once they learned to synthesize "organic" molecules (the original meaning was those created in living systems), scientists discovered that they could also synthesize new organic molecules that did not exist in nature. As Barry Commoner wrote, "It was as though a language had suddenly been invented, followed inevitably by a vast outburst of creative writing."[1(p131)]



What resulted remains one of the most rapid bursts of innovation in human history. Thousands of new chemicals were developed, and from those chemicals, tens of thousands more. These new chemicals were enlisted to rapidly develop new technologies that supported the military demands of World War II. Following the war, military technologies transformed the nature and productivity of agricultural and industrial production as well as transportation and communication. Dependence on these chemicals subsequently sky rocketed. And every year since, a new surge of creativity is unleashed; synthetic organic chemistry, born in the nineteenth century, generates thousands of new additional chemicals annually.

Only later was the severe flaw in the foundation of synthetic organic chemistry discovered: "It was like a two-legged stool: well founded in physics and chemistry, but flawed by a missing third leg – the biology of the environment [including people]."[1(p133)] Industrial, agricultural and commercial uses of new synthetic organic chemicals proliferated without attention to public health and environmental impacts. The legacy of this technological revolution is a toxic brew of chemicals that are ubiquitous in the environment and in our bodies, resulting in a litany of environmental and public health problems: cancer, groundwater contamination, hormone dysfunction, asthma, fish kills, birth defects and breast milk contamination. Many of these outcomes can be traced back to the chemists' knowledge, creativity, and market-driven innovation.

At the same time, synthetic organic chemistry resulted in tremendous life-saving and life-improving advances: antibiotics, cancer drugs, plastics, and countless industrial chemicals that enable production of nearly every important technology on which our economies depend. We leave it to historians and ethicists to decide if the explosion in innovation from synthetic organic chemistry was "good." But we believe that society can and should learn from the assumption that each new chemical represented progress and that the undeniable benefits outweighed the risk of environmental and health tragedies.

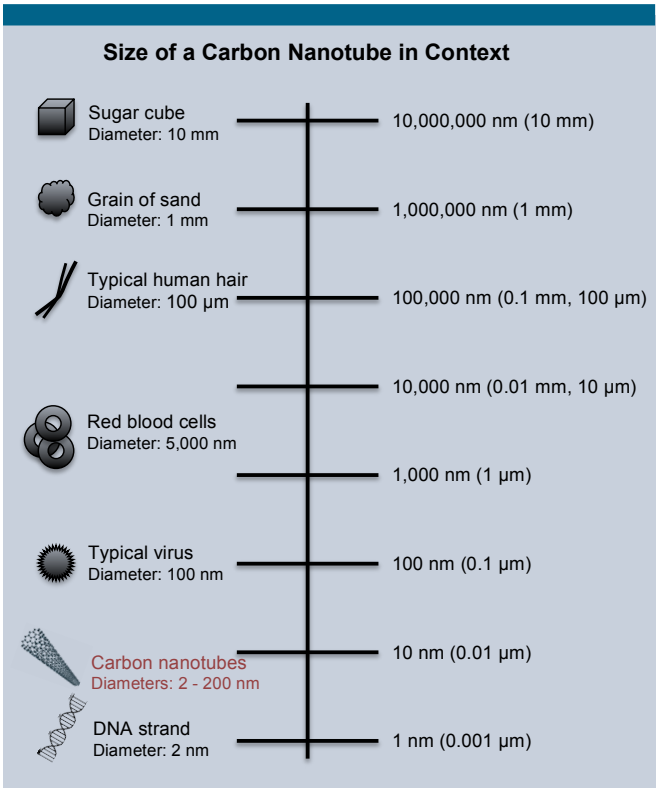
Can we write a different history for nanotechnology – a technological breakthrough with implications no less significant than synthetic organic chemistry? This review of one type of

engineered nanomaterial, carbon nanotubes, demonstrates the need, the challenges, and the urgency of ensuring the responsible and safe development of nanotechnology – undoubtedly at the center of the scientific and industrial revolution of the 21st century.

Carbon Nanotubes: Discovery and Forewarnings

Engineered carbon nanotubes (CNTs) are a class of nanoparticles. These nanoscale – 1 billionth of a meter – tubes of hexagonal sheets of carbon (graphite) resemble miniscule rolls of chicken wire. CNTs are often divided into two overall categories. Single-layered CNTs, which are commonly referred to as single-walled carbon nanotubes (SWCNTs), have diameters of only a few nanometers.[2] Multi-walled carbon nanotubes (MWCNTs) are larger, consisting of one or more single-walled tubes inside the other; their diameters range from 5 nm to 200 nm.[2,3] While the diameters of CNTs are in the nanometer range, their lengths can be thousands of times longer – up to several centimeters.[2]

CNTs are not a single material. It has been suggested that there are up to 50,000 potential combinations of SWCNTs and inevitably more than that number of MWCNTs.[4] CNTs can differ dramatically in size, shape and chemical composition, either by design or as a results of contamination during production.[2,5] CNTs may be straight and narrow, bent or curly, rigid or partly flexible. They can exist as single entities or bundled together in ropes or compact tangles that look and act like particles rather than tubes. They may also be functionalized with a wide variety of chemicals on the surface to enhance desired chemical, biochemical, electrical, or physical properties.



Several reports document discoveries of CNTs by researchers as far back as the 1950's.[6] However the implications of these findings were not fully appreciated within the scientific community until 1991. That year, Sumio Iijima, a Japanese scientist at the NEC Corporation published a paper in *Nature* describing the formation of "nanometer-sized" "needle-like tubes of carbon," now known as MWCNTs.[7] Two years later, Iijima and an IBM researcher, Donald Bethune, independently observed and published papers on the formation of SWCNTs.[6]

Cautions about carbon nanotubes also surfaced in the early 1990s. Just one year after Iijima's initial discovery, the same highly-regarded journal published a letter raising concerns about occupational hazards. In response to an article on the valuable materials characteristics and potential cost savings of the emerging technology, Gerald Coles, an industrial hygienist wrote:

> *"Sir—Attractive though they are, the technical properties of ultra-thin man-made fibres pointed*

out by Paul Calvert (Nature 357 365; 1992) should not hide the potential—at least for those fibres resistant to biological degradation in vivo—for related occupational risks to workers.

…A need for stringent precautions in preventing occupational exposure to the dusts of these thinner materials might well result in cost increases in manufacture that would outweigh the "dramatic reduction in production costs" hypothesized by Calvert."[9]

Over subsequent years, excitement grew as dozens of research papers were published detailing the extraordinary physical and chemical properties of CNTs and ideas for their application. A 1998 article in the prestigious journal *Science* concluded that, "Although they may resemble nothing more glamorous than microscopic rolls of chicken wire, nanotubes have emerged as stars of the chemistry world."[10] The superstar status of CNTs was based on their superior properties. CNTs are now understood to be over 100 times stronger than steel and able to withstand repeated bending, buckling and twisting. They conduct electricity better than copper, are better semiconductors than silicon, and better transporters of heat than any known material.[10,11]

Small batch bulk manufacturing of carbon nanotubes was already occurring by the late 1990's, resulting in the use of CNTs in plastic composites for the automotive and computer industries to help prevent the build up of static electricity.[10] Early speculation envisioned an array of new technologies and new material advances based on CNTs, such as scanning tunneling microscopes, super strong cables, electrodes and charge storage devices in batteries, wires for "nanosized electronic devices in futuristic computers," and light-weight composites, among others.[10,12] One carbon nanotube researcher noted, "If I were to write down all the different applications, I'd have… a book for nanotubes."[10]

Among numerous articles touting the promise of carbon nanotubes during the 1990s, few mentioned potential detrimental impacts. The 1998 article in Science was an exception; it was the first to make a connection between CNTs and asbestos:[13]

"The dangers of asbestos first came to light in the early 1960s, when studies linked exposure to these silicate fibers with mesothelioma – a rare cancer of the lining of the chest or abdomen that's commonly fatal. Asbestos fibers were found to be so small that they could be inhaled into the deep lung, where they could stick around for decades. Once there, metals in the silicate fibers could act as catalysts to create reactive oxygen compounds that go on to damage DNA and other vital cellular components.

Whether nanotubes could reproduce this behavior is unknown: Their toxicity has yet to be tested. But already views on their safety differ sharply. "[Nanotubes] may be wonderful materials," says Art Langer, an asbestos expert at the City University of New York's Brooklyn College. "But they reproduce properties [in asbestos] that we consider to be biologically relevant. There is a caution light that goes on." Most notably, says Langer, nanotubes are the right size to be inhaled, their chemical stability means that they are unlikely to be broken down quickly by cells and so could persist in the body, and their needlelike shape could damage tissue."

While CNTs' structural resemblance to asbestos was raising red flags, so was their small size. For decades, researchers and health professionals have understood that "size matters" regarding health effects associated with airborne particles: the smaller the particle, the more significant the health effect. Unlike larger particles that can be cleared by the lung when inhaled, very small particles can settle in the deepest part of the lungs – the alveolar region – where gas exchange occurs. Here, very

small particles can pass through the thin walls of the lungs, enter the blood stream, and affect more distant organs in the body. By 1997, the Environmental Protection Agency (EPA) began regulating air pollution particles less than 2.5 μm in diameter – not quite small enough to be considered in the nanometer range – based on documented evidence of both respiratory and cardiovascular health impacts in humans. In the early 1990s, evidence showed that particles in the nanoscale range, called ultrafine particles, were demonstrating even greater toxicity than their larger cousins.[14] These effects were suggested in part because of the sheer number of ultrafine particles per unit volume of air capable of crossing of the alveolar air-tissue barrier.[15]

While CNTs' structural resemblance to asbestos was raising red flags, so was their small size.

"Forget Precaution, Get to Production"[16]

As the market for CNTs expanded, the promise of profits and progress overwhelmed concern for human health and the environment. Despite early red flags, dollar signs and excitement over new innovations trumped warning signs and CNT research and development (R&D) continued to progress rapidly.[16] The number of scientific journal publications discussing and reporting on CNT-related research increased exponentially – over a 3-fold increase from 2004 to 2011.[2,17] A steep rise in patents followed.[17]

Just as growth in R&D and commercialization of synthetic organic chemicals was aided by the influx of government resources, so too was the growth in CNT-related R&D. In 2001, the interagency National Nanotechnology Initiative (NNI) was launched by the Clinton Administration to coordinate federal investment in nanotechnology R&D. Twenty federal departments and agencies (the National Science Foundation, the Department of Homeland Security, the National Institute for Occupational Safety and Health, and the Department of Energy, among others.) currently contribute to the NNI mission and financial support for nanotechnolology R&D. In its first year, NNI agencies had committed $500 million to fund research and track progress in nanotechnology globally.[20] Just a few years later in 2005, that figure doubled to $1 billion.[18] However, only 3.6% was allocated for research on the environmental health and safety aspects of nanotechnology.[19]

Other countries were also investing in nanotechnology research – especially in western European and Japan. In fact, Japan was the first government to create a national nanotechnology research program in 1990 – one of the sparks that ignited the establishment of the NNI. By 2005, funding in Japan for nanotechnology research had reached $950 million, a figure just shy of the combined federal and state contributions in the United States. Similarly, European countries were collectively spending $1 billion.[20]

By 2008, the Woodrow Wilson Project on Emerging Nanotechnologies documented a collection of consumer products that contained CNTs, including bike components and sporting equipment such as tennis racquets. Andrew

Maynard, the Project's Senior Research Associate, called these "The tip of the iceberg," given that disclosing nanomaterials during the production of a product was not (and currently is not) required by regulation.[21] Companies that chose to disclose the use of CNTs were doing so to advertise technological advantages over their competitors. Famous achievements in sports helped to showcase these advantages. In 2006, the Tour de France was won by a cyclist riding one of the strongest and lightest bikes ever made – using a frame made with CNTs.[22]

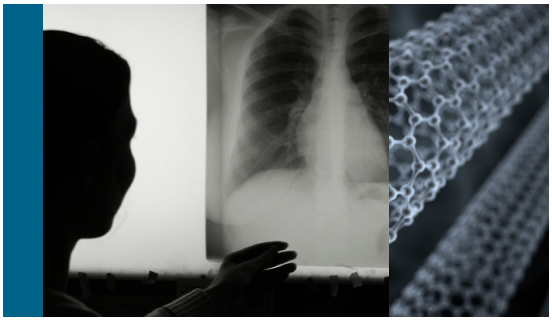
In 2006, the Tour de France was won by a cyclist riding one of the strongest and lightest bikes ever made – using a frame made with CNTs.

According to the Consumer Products Inventory maintained by the Project on Emerging Technologies, by far the majority of commercial products containing CNTs currently available are types of sporting equipment: tennis racquets, golf club shafts and balls, baseball bats, bicycle components, among others (as of December 2012).[23] Additional products include armor and small aircraft frames.[23] All of these applications use CNTs as reinforcements in high strength, light weight, high performance composites and can make use of cheaper bulk MWCNTs that are readily on the market today.[17]

It is worth noting that a wide variety of additional CNT-based products are near commercialization or have been already deployed. Many of these products have the potential to address important global challenges: delivery devices for cancer drugs; CNT-based solar cells; stronger, lighter wind turbine blades; and the provision of clean drinking water with CNT water filters that eliminate bacterial and chemical contaminants (see Table 1).[2] A prudent and responsible approach, however, would ensure that these benefits are not realized at the expense of impacts to human health and environmental quality. As more than one observer has noted, historically CNT production processes have been designed to maximize product yield and to minimize production costs, with little attention paid on minimizing environmental and public health impacts.[17] Research on environmental health and safety is clearly on the NNI agenda, and funding for this research has increased substantially. Yet only 7.1% of the proposed NNI

Table 1: Examples of Carbon Nanotube Products Commercially Available or in Development[2, 17, 23]

Sporting Equipment	golf shafts, bicycle frames and components, hockey sticks, archery arrows, baseball bats, tennis racquets
Automotive	Fuel lines and filters, electrostatic paints for mirror housings
Maritime	Boat hulls, anti-fouling paint
Aviation	Deicing, lightning strike protection & structural health monitoring
Electronics	Electron field emitters (flat screen panels), EMI shielding, transistors, memory chips, super capacitors
Biotechnology	Biosensors [food, military, medical & environmental applications], medical therapies (including drug delivery)
Energy	Wind turbine blades, lithium ion batteries, photovoltaics, thin-film solar cells, hydrogen fuel cells
Other	Water filters, armor



budget for FY 2014 is dedicated to supporting this research – not enough given the magnitude of potential harm.[24]

Since 2006, worldwide CNT production capacity has increased at least 10-fold.[2] While figures vary, global CNT production capacity in 2011 was estimated to be 4.6 kilotons and market forecasters anticipate continued growth.[2] One reason for the dramatic commercial growth is the cost of the material. Although CNTs were initially very expensive, prices have fallen dramatically over the past 10 years, from $45,000 per kilogram to as little as $100 per kilogram for bulk purified MWCNTs.[2,17] Production capacity of SWCNTs is still limited given the detailed processes necessary to ensure that only pure SWCNTs are produced.[17] As a consequence, the price for pure SWCNTs is still prohibitive for bulk use. Prices are expected to fall in coming years, however, given the demand for these materials and continued advances in their manufacturing.

Until the mid-2000s, there was a striking absence of studies evaluating the environmental and human health impacts of CNTs.

Evidence of Harm: Human Health Effects

When engineered CNTs first came on to the scene, it was their revolutionary physical and chemical properties that gave rise to their extraordinary mechanical, thermal and electrical capabilities. These physical and chemical characteristics include size, shape, surface area, surface chemistry, and reactivity among others. Yet researchers understood that these physical and chemical attributes could lead to different toxicological effects. As described above, even before studies began to reveal concerns about impacts on human health and the environment, researchers predicted a range of impacts based on fiber and particle toxicology.

Pulmonary fibrosis

Until the mid-2000s, there was a striking absence of studies evaluating the environmental and human health impacts of CNTs. It wasn't until 2004 that toxicologists at NASA published one of the first studies documenting the development of pulmonary inflammation and lesions in the lungs of mice exposed to SWCNTs (using intratracheal instillation – essentially squirting the material into the lungs, standard procedure when screening dusts for pulmonary toxicity).[25] Additional studies followed that reported similar effects in other animal models and also evidence of "progressive fibrosis" – scarring in the deep regions of the lung.[26,27] These first studies also examined how acute and sub-chronic toxicity of SWCNTs compared to other materials such as carbon

black and quartz that present known pulmonary hazards. These studies concluded that SWCNTs were more toxic than those materials.[25,27]

Toxicological studies found that exposure to MWCNTs results in effects similar to those produced by SWCNTs. For example, animals exposed short-term to MWCNTs developed early onset, persistent and progressive pulmonary fibrosis.[28,29] Of particular concern was the finding that this effect occurs when the animals experience airborne exposures similar to those found in occupational settings.[30,31,32] Studies do suggest, however, that SWCNTs appear to be more potent at causing fibrosis than MWCNTs.[3]

An acute exposure study captured MWCNTs penetrating the mesothelial surface of the pleural lining, considered part of the mechanism by which mesothelioma develops.

What is pulmonary fibrosis? It is an irreversible and severe lung disease, historically associated with exposure to silica, asbestos and other airborne toxins. Particles deposited in the gas exchange (alveolar) region of the lung destroy the macrophage cells that are attempting to engulf and clear the particles. This destruction releases enzymes, which attack lung tissue and lead to scarring, or fibrosis. Pulmonary fibrosis is a progressive disease, meaning that the macrophage destruction and scarring may continue after exposure ceases. If exposure is sufficiently heavy and prolonged, the prognosis can be poor; with limited oxygen supply, pulmonary hypertension can occur, which in turn leads to heart failure. It is important to note that no one knows if workers exposed to CNTs experience these effects. Direct investigation of the health effects in worker populations exposed to CNTs is still in its infancy.

Cancer

Despite the fact that pulmonary fibrosis is a plausible and serious health risk associated with exposure to CNTs, the potential hazards of CNTs did not get much attention in the broader public health community until the word "cancer" was mentioned.

In 2008, two studies of lab animals exposed to MWCNTs found links with mesothelioma, a cancer of the mesothelium.[33,34] Mesothelium is the membrane that forms the outer lining of the lungs (in the pleural cavity), and the outer lining of the abdomen (in the peritoneal cavity). By far the most common cause of mesothelioma is exposure to asbestos fibers. The studies found that when injected into the peritoneal mesothelium of mice, long (greater than 10 μm) MWCNTs caused inflammation and lesions (granulomas) that are considered precursors of asbestos-related mesothelioma in humans. These findings have been supported by additional studies.[35] As with asbestos, the extent of inflammation was proportional to the length of the fibers. These studies strongly implicate CNTs as potential causes of mesothelioma in animals and by extension in humans.

Since 2008, additional studies have confirmed that long straight MWCNTs may be capable of causing cancer. Recent studies show that after pulmonary exposure to MWCNTs, the material can migrate to the pleura, which is where mesothelioma develops.[31,36,37] In addition, an acute exposure study captured MWCNTs penetrating the mesothelial surface of the pleural lining, consid-

ered part of the mechanism by which mesothelioma develops.[38] Penetration by MWCNTs into the pleural lining was observed to be frequent and sustained long after exposure occurred.[38] Studies have also observed additional effects associated with MWCNT exposure, including DNA damage, mesothelial cell proliferation, and mesothelial tumor formation.[34,36,39,40]

SWCNTs have also been reported to migrate to the pleural region of the lungs. However, they have not been shown to penetrate the lining, likely because they are less rigid than MWCNTs, which have multiple concentric walls of carbon. However, researchers have observed that SWCNTs can enter the nucleus of airway epithelial cells and interfere with normal cell division, leading to missing or extra chromosomes.[41,42]

Investigators at the US National Institute for Occupational Safety and Health (NIOSH) recently reported that chronic inhalation of MWCNTs by mice showed an increased incidence of lung tumors. (Asbestos is also a known cause of lung cancer in addition to mesothelioma.) The study showed that MWCNTs have the capacity to promote the development and growth of lung tumors when mice are first exposed to a chemical that is known to initiate the disease. Thus, while this work indicates that MWCNTs have the potential to promote cancer, additional studies are needed to determine if it can initiate the disease as well.[43]

Other Impacts: Systemic Inflammation and Cardiovascular, Reproductive, and Developmental Effects

To a much lesser degree, animal studies have examined other health impacts of exposure to CNTs beyond respiratory effects. These studies have primarily investigated cardiovascular effects and systemic inflammation that are predicted based on known hazards associated with exposure to larger particles, such as fine particulates in air pollution.

Studies have observed that pulmonary exposure to SWCNTs induces systemic responses, including systemic inflammation and cardiovascular effects. Toxicological studies suggest that exposure to SWCNTs can increase inflammatory mediators in the blood, oxidative stress in aortic tissue, and increases in biomarkers and plaque formation that are consistent with atherosclerosis.[44,45] Studies examining the effects of MWCNTs have also observed decreased ability of coronary arterioles to respond to dilators.[46]

Few studies have examined the developmental and reproductive effects associated with CNTs. Two recent toxicological studies identified effects from exposure to various SWCNTs that included fetal death, increased levels of reactive oxygen species in the placenta and in offspring, as well as teratogenic effects including skeletal abnormalities.[47,48] Other studies examining MWCNTs do not report similar effects.[49,50]

Physical-Chemical Hazard Characteristics and Human Health

One of the 2008 studies that first documented a possible link between CNTs and mesothelioma also drew a second intriguing conclusion: the size and shape of CNTs influence the biological effects. As described above, if mice were exposed to MWCNTs that were long and straight, precancerous growths developed. Yet if they were exposed to MWCNTs that were tightly curled together, no effect was observed – no lesions, no inflammation.[33] In addition, short MWCNTs have shown no evidence of a connection with mesothelial tumors.[51,52]

Why might size and shape influence toxicity? The body's immune system clears foreign material via immune cells called macrophages, which engulf the material and remove it by additional immune system responses, including removal through the lymphatic system. It has been repeatedly suggested within the research community that MWCNTs that are small and/or curled and bundled are cleared by the immune system. However, long and rigid MWCNTs that are larger than macrophages cannot be completely engulfed and removed. Moreover, the inability to fully engulf the foreign material (called frustrated phagocytosis) leads to a release of compounds that damage the surrounding cell, leading to inflammation, lesions and progressive scarring (fibrosis).[53]

Long and rigid MWCNTs can cause a "double hit" on the pulmonary system.[54] Long MWCNTs have high aspect ratios: the ratio between the material's length and width. These MWCNTs are nanometers in diameter, yet micrometers in length. CNTs also are highly biopersistent – they do not weaken or dissolve and therefore persist in the lungs if not removed by macrophages and other immune mechanisms described above. These two characteristics – high aspect ratio and biopersistence – contribute to the intrinsic hazard of a compound. These factors were clearly understood even before the health impacts of CNTs began to be researched and published, because these are the characteristics shared with asbestos fibers.[55,54] The "double hit" emerges because long and rigid MWCNTs are more likely to be retained, and more likely to accumulate with ongoing exposure. Secondly, when they make contact with cells, longer MWCNTs are more biologically active than shorter CNTs; evidence demonstrates more pronounced inflammatory and fibrotic effects.

While multiple studies suggest that short MWCNTs are cleared by the lungs, this doesn't appear to be a steadfast rule. There is evidence that short MWCNTs can be retained after short-term exposures and move to the pleural cavity of the lung.[38] Once in the pleural cavity, clearance may be more restrictive, so that even small MWCNTs may not be able to be cleared and may therefore cause harm.[38] In a recent review article, researchers state: "it would be prudent to define a cut-off of 5 μm and above" for the threshold length at which a MWCNT would be considered pathogenic.[53]

Studies have also revealed that the ***CNT surface and chemical composition influence their biological effects.*** Depending on the manufacturing methods, CNTs may contain a variety of catalysts and contaminants. These can include cobalt, iron, nickel, and molybdenum, all of which are known to induce toxic effects because they are highly reactive and biologically active. These metals can activate the release of reactive oxygen species from macrophages.[54] Studies over a decade ago had already demonstrated that metals such as iron in other occu-

pational dust or airborne exposures could cause oxidative stress.[56,57] And sure enough, when this issue was explored for CNTs, study results indicated that iron-rich SWCNTs, as compared to purified SWCNTs, contribute to oxidative stress and associated toxicity.[58,59] Other research has shown that if structural defects in the surface of the CNTs are introduced, for example by grinding MWNCTs, pulmonary toxicity is increased.[60]

When compared to other particles, CNTs tend to have large surface areas.[54] Thus if a CNT contains soluble or reactive material, its greater surface area translates into a greater delivery or biologically effective dose of the compound.[53]

Thus, if a CNT contains soluble or reactive material, its greater surface area translates into a greater delivery or biologically effective dose of the compound.

This characteristic is one reason why CNTs are being studied for their drug delivery capacity – the high surface area and small size of these particles could enable them to efficiently deliver chemotherapy drugs to sites of tumors, for example. Yet the same characteristics of CNTs that may be able to deliver therapeutic chemicals can also deliver toxic effects.

The surface composition of CNTs can also be intentionally modified to accommodate their intended commercial uses. CNTs can be coated or "functionalized" with specific chemicals that enhance their electrical, mechanical or chemical properties. Unfortunately, product designers do not typically consider how changing the surface chemistry of a CNT could influence the toxicity of the material.

Evidence of Harm: Environmental Effects

It goes without saying that the release of CNTs into the environment will increase with rising levels of production and expanding use in industrial and commercial products. CNTs may be released to the environment at different stages of their lifecycle, from manufacture, through use, re-use, recycling and disposal. Similar to the paucity of data on health effects research, there are very limited data on environmental behavior, fate and ecotoxicity of CNTs. The bulk of the existing literature on the topic did not emerge until the late 2000s and is still in its infancy.[61] Though there is a need for ongoing research, studies conducted thus far have identified ecotoxicity concerns, particularly among some aquatic species and microorganisms. Similar to human health studies, the ecotoxicity literature reveals attributes of CNTs that can help predict problematic environmental outcomes, including increased bioavailability of toxic pollutants as well as possible bioaccumulation.

Ecotoxicity studies generally reveal minimal evidence of toxicity for most terrestrial organisms currently studied.[61,62] However, several aquatic organisms appear to be particularly sensitive to exposure to CNTs, including lower pelagic organisms such as algae and fresh water fleas (daphnids), as well as some fish species. Studies demonstrate that SWCNTs and MWCNTs of various lengths and surface characteristics can inhibit the growth of both fresh and marine algae.[61] Effects on a fresh water flea (*Daphnia magna*) were tested with exposures to MWCNTs and SWCNTs of various lengths and surface treatments. The studies document that ingested CNTs may interfere with food intake and movement at low concentrations, and appear to be more toxic after longer exposures.[63,64,65,66] Parameters such as im-

paired growth or reproduction were affected at even lower concentrations for both SWCNTs and MWCNTs.[66,67] Lastly, studies examining effects on juvenile rainbow trout (*Oncorhynchus mykiss*) demonstrate that exposure to SWCNTs dispersed in water caused systemic toxicity, including respiratory toxicity, neurotoxicity and hepatotoxicity, with effects starting at extremely low concentrations (0.1 mg/L), levels consistent with a classification of "extremely toxic to aquatic life" by the Globally Harmonized System of Classifying and Labeling of Chemicals (GHS).[68]

SWCNTs are powerful antimicrobial agents. The direct contact between SWCNTs and bacteria causes bacterial cell death.[69] While the majority of SWCNTs tested demonstrate antimicrobial activity, size, shape, and chemical composition all influence levels of toxicity.[61] For example, the higher the metal content, and the longer the CNT, the greater the bacterial toxicity.[70,71] While MWCNTs also have antibacterial properties, multiple studies demonstrate that they are less toxic to bacteria than SWCNTs.[61] While some R&D efforts are attempting to apply the antimicrobial properties of SWCNTs to commercial applications, release to the environment may have problematic implications, for example processes in waste water treatment plants that depend on microbial activity.[72]

Physical-Chemical Hazard Characteristics and Environmental Effects

CNTs are highly stable and biopersistent. Pure CNTs do not disperse well in water because they are highly hydrophobic and therefore poorly soluble, and also because they often entangle or aggregate/agglomerate. However, the surfaces of CNTs are often oxidized, or functional groups are added for many applications to make them more dispersible in polar solvents, including water. Therefore the solubility of CNTs can vary. Thus aquatic, sediment and terrestrial ecosystems are all relevant targets for the ecotoxicity of the vast array of different types of CNTs.

CNTs have a tremendous capacity to adsorb other chemicals – a feature that is being commercialized in the use of CNTs for drinking water filtration. However, the presence of CNTs in the environment could affect the bioavailability of other environmental contaminants, for example heavy metals or organic pollutants. This has been demonstrated in several studies related to the bioavailability of pharmaceuticals and both organic and inorganic water and soil pollutants in several model organisms.[73,74,65,75] While both SWCNTs and MWCNTs have high adsorption capacities, the capacity of SWCNTs is greater.[73] Ultimately factors such as pH and the presence of organic matter in water as well as the specific chemical characteristics of the material (if and how the CNT is functionalized) can either enhance or reduce the ability of CNTs to adsorb contaminants.[61]

CNTs are highly stable and biopersistent.

Given their persistence, CNTs are reported to be one of the least biodegradable man-made materials known.[76] Their persistence as well as their lipophilic nature (at least pure CNTs) suggest that bioaccumulation could occur. However, a recent review of existing studies demonstrates that CNTs ingested by organisms that inhabit terrestrial, sediment or aquatic habitats are

mostly excreted rather than absorbed.[61,62] Thus, the majority of studies to date suggest no appreciable absorption of CNTs across epithelial membranes (the outer "skin" of an organism).[62]

The potential for bioaccumulation in individual organisms is still being evaluated, however. For example, a recent study shows that CNTs (both MWCNTs and SWCNTs) are able to penetrate an array of plant seeds during germination and plant roots during growth.[77] In some studies, CNTs were able to migrate from the roots into leaves and fruit, albeit in small concentrations.[78] Thus plants (or other organisms) containing CNTs could be a source of CNT exposure when ingested by larger animals.[61] In addition, CNTs can stay in the digestive tract of some organisms in the lower levels of the ecological pyramid, moving up through the food chain as these organisms are consumed.[63]

In studies examining the effects of CNTs on plants, one finding has been described as a "beneficial outcome." When MWCTs or SWCNTs are dispersed in media that increase their solubility or when SWCNTs are functionalized so that they are more water soluble, their penetration of plant seeds and roots results in a significant boost in growth of the plants.[61,79] Researchers are quick to propose potential applications without reference to potential long-term implications, suggesting that "the use of water-soluble CNTs in plant growth can play an important role in the arid areas of agriculture where the supply of water is crucial and requires maximum conservation."[80]

Thus, based on existing ecotoxicity studies, SWCNTs appear to be more toxic than MWCNTs and invertebrates appear to be more sensitive than vertebrates. Findings such as CNTs stimulating increased growth in plants, while also being retained by some plants, raise concerns about pursing yet another application of CNTs without first considering the long-term consequences for the environment or human health.

Safe and Sustainable CNTs: Truth or Fiction?

In summary, recent evidence on a wide array of potential health and environmental impacts of CNTs substantiates early predictions of potential for harm. It also indicates that some CNTs are safer than others. This complexity raises the question of whether policies and practices can or should distinguish among different CNTs. Is it possible to generate only tangle/bundled CNTs without chemical contaminants; treated with additional chemical functional groups to minimize the potential for toxic effects; manufactured or used only in well-controlled settings? Even if so, can we ensure that these same CNTs do not have deleterious effects in aquatic systems, taking into account the extraordinary biological and chemical complexity of those ecosystems? And can we ensure that CNTs are not released to sewage systems where they could impair the microbial activity that makes possible the discharge of safe water into our rivers, lakes and oceans? Is it possible to develop and use only the safest CNTs for a particular application?

Green and Safer Nanotechnology

There is growing interest in "green" nanotechnology – advancing sustainability through prevention-oriented manufacturing, design and application of nanomaterials. Pioneered by researchers at institutions such as the Safer

Nanomaterials and Nanomanufacturing Initiative at the Oregon Nanoscience and Microtechnologies Institute (ONAMI) and the Center for Green Chemistry and Green Engineering at Yale, and supported by new professional societies such as the Sustainable Nanotechnology Organization, there is a growing cohort of scientists who are advancing the concept that nanomaterials can be used in promotion of sustainability – improving society, the environment and human health while minimizing adverse impacts. These researchers are identifying specific properties of CNTs that govern toxicity as well as methods by which toxic properties can be controlled.

Elimination of the hazard is the only method for guaranteeing prevention of disease and environmental damage.

There is reason to hope for success. As described earlier, CNTs promise social benefits, including medical breakthroughs, increased efficiencies in renewable energy generation, and safer drinking water supplies, among countless others. Given their mechanical, thermal, and electrical properties, CNTs could be used as substitutes for a range of known toxic chemicals as well.

Green nanotechnology straddles two disciplines: green chemistry and green engineering.[81,82] Traditional chemists and engineers are not trained to think about the health, safety and environmental concerns of the chemicals and materials they develop or the products they design. These issues are managed after the fact, mainly through environmental and occupational "risk reduction" approaches that seek to manage exposure levels, such as using engineering controls (e.g. working under appropriate ventilation) or using personal protective equipment. Green chemistry and green engineering offer a different approach to the current risk management paradigm, considering hazard across the lifecycle as an inherent property of the chemicals and materials that are under development. Green chemists and engineers see hazard as a design attribute – more specifically a design flaw – to be considered as part of the feasibility equation, on equal footing with technical and economic feasibility considerations. Elimination of the hazard is the only method for guaranteeing prevention of disease and environmental damage. As long as the hazard exists, it can cause harm by some unanticipated or even anticipated event, despite having the best control measures in place.

While the promise of green nanotechnology is technically grounded, green CNT products have not been realized to date, although advances in cleaner and less toxic manufacturing processes are resulting in better control over impurities that impact toxicity.[83] Tailoring the design of CNTs to specific applications that avoid deleterious impacts will require overcoming a number of barriers. Two primary barriers include the lack of engineers and chemists working in product development that have training in green engineering and green chemistry, and the need for clear design rules for CNTs (and other nanomaterials) that protect health and safety.[84,85] Overcoming this latter barrier is a primary objective of the roadmap for green nanotechnology outlined at a summit on the topic in 2010.[86]

Researchers at the Toxics Use Reduction Institute at the University of Massachusetts Lowell have begun to develop a blueprint for design rules for safer nanotechnology. The design rules

include five principles which together follow the acronym SAFER (see Table 2) and focus on aspects such as modifying physical or chemical characteristics of the material to diminish the hazard, considering alternative materials, and enclosing the material within another less hazardous compound.[87] Other researchers have also proposed additional design rules, which include avoiding chemical compositions of nanomaterials that contain known toxic elements, and avoiding compositions of nanomaterials with dimensions that are known to possess hazardous properties.[85] Over time, these principles could evolve as additional information regarding hazard, exposure and performance emerge and are made available, and as the principles are tested by product designers and toxicologists.

Alternatives Assessment and Alternative Testing Strategies

The Principles of Design for Safer Nanotechnology include the concept of identifying and evaluating safer, available alternative materials that reduce and even eliminate the use of hazardous nanomaterials, including some CNTs. Environmental and public health tragedies of the past have revealed the dangers of becoming so captivated by a new technology that we are blinded to options (including non-chemical alternatives) that can achieve the same function.[88] We are risking the same dangers with CNTs. Large sums are being invested to identify CNT applications for a wide array of commercial and industrial products. This is being done without first evaluating the potential health and environmental impacts and asking whether a safer compound or process can be used to achieve the same function or whether the function served by the CNT is even necessary.

The design phase for new applications and products is not the only time when a comparative evaluation of alternatives is needed. According to a recent analysis, one of the key drivers of CNT market growth is the replacement of currently used chemicals and materials with CNTs in a wide variety of applications. For example, MWCNTs are emerging as alternatives to chemicals considered toxic, such as halogentated flame retardant additives used in plastics, and biocide-containing paints.[2]

Alternatives assessment – also called alternatives analysis or substitution assessment – can assist with consideration of the health and environmental impacts of chemicals, materials and technologies at both the design stage and when evaluating substitutes for hazardous chemicals.

Table 2: Principles of Design for SAFER Nanotechnology[87]

#1	**Size, surface and structure**: diminish or eliminate the hazard by changing the size, surface, or structure of the nanoparticle while preserving the functionality of the nanomaterial for the specific application
#2	**Alternative materials:** identify either a nano or bulk safer alternative that can be used to replace a hazardous nanoparticle
#3	**Functionalization:** add additional molecules (or atoms) to the nanomaterial to diminish or eliminate the hazard while preserving desired properties for a specific application
#4	**Encapsulation:** enclose a nanoparticle within another less hazardous material
#5	**Reduce the quantity:** in situations where the above design principles cannot be used to reduce or eliminate the hazard of a nanomaterial, and continued use is necessary, investigate opportunities to use smaller quantities while still maintaining product functionality

As conveyed in the Commons Principles for Alternatives Assessment (Table 3), alternatives assessment is a process for identifying, comparing and selecting alternatives, taking into account hazard as well as performance and economic viability.[89] A primary goal of alternatives assessment is to reduce potential harm to humans and the environment by identifying safer choices. Alternatives assessment can help prevent regrettable substitutions or risk trade-offs, such as replacing a persistent and bioaccumulative chemical with a suspected carcinogen. Businesses and governments are increasingly interested in alternatives assessment as a tool to inform both voluntary and regulatory management of chemicals..

Table 3: The Commons Principles for Alternatives Assessment[89]

REDUCE HAZARD Reduce hazard by replacing a chemical of concern with a less hazardous alternative.
MINIMIZE EXPOSURE Assess use patterns and exposure pathways to limit exposure to alternatives that may also present risks.
USE BEST AVAILABLE INFORMATION Obtain access to and use information that assists in distinguishing between possible choices.
REQUIRE DISCLOSURE AND TRANSPARENCY Require disclosure across the supply chain regarding key chemical and technical information. Engage stakeholders throughout the assessment process to promote transparency in regard to alternatives assessment methodologies employed, data used to characterize alternatives, assumptions made and decision making rules applied.
RESOLVE TRADE-OFFS Use information about the product's life cycle to better understand potential benefits, impacts, and mitigation options associated with different alternatives. When substitution options do not provide a clearly preferable solution, consider organizational goals and values to determine appropriate weighting of decision criteria and identify acceptable trade-offs.
TAKE ACTION Take action to eliminate or substitute potentially hazardous chemicals. Choose safer alternatives that are commercially available, technically and economically feasible, and satisfy the performance requirements of the process/ product. Collaborate with supply chain partners to drive innovation in the development and adoption of safer substitutes. Review new information to ensure that the option selected remains a safer choice.

Central to alternatives assessment is the evaluation of hazard, featured in all of the alternatives assessment frameworks published over the past decade.[90,91,92] Hazard assessment uses available data sources, including structural modeling, to assess and compare the environmental and health hazards of a substance with possible alternatives. Endpoints considered include acute toxicity, sensitization, carcinogenicity, aquatic toxicity, bioaccumulation, etc. Lack of hazard data is a persistent challenge. By highlighting data gaps, alternatives assessment can help prevent unintended consequences associated with the adoption of product designs or the substitution of specific chemicals about which there is little information.

Recent research demonstrates that it is possible to conduct hazard assessments on engineered nanomaterials, although data gaps do exist and the assessment protocols need to be adapted for nanomaterials specifically.[93] Researchers using Greenscreen® – a validated hazard assessment tool used by many companies, NGOs and government agencies – compared the hazards of two types of nanosilver and their bulk counterpart. They determined that while data gaps were an issue in the evaluation, the identification of gaps deemed "critical" was helpful for targeting and stimulating additional research. The research also helped to advance methodological changes to hazard assessment protocols, such as the inclusion of the array of specific physical and chemical characteristics that are known to govern the hazard of nanomaterials (i.e., size, structure, chemical composition, etc.,) but are not currently included in most hazard assessment tools that were originally developed to evaluate conventional chemicals. Additional

differences between the hazard assessment of conventional chemicals and nanomaterials include criteria for categorizing hazard level. In the case of conventional chemicals, hazard level is often based the mass of the chemical, whereas for many nanomaterials, a more appropriate metric is surface area or number of particles.

For alternatives assessment to become more robust and more useful in decision-making about nanomaterials, there is a need to incorporate data and knowledge emerging from research on green and safer nanotechnology into alternatives assessment frameworks, as shown in the nanosilver casestudy. As described earlier, the physical and chemical characteristics of an engineered nanomaterial that are predictive of harm are guiding green design principles. These same design principles can be used in an alternatives assessment framework to compare and evaluate hazards of both CNT and non-CNT alternatives being considered for a specific application.

Given that all CNTs will not impart the same level or type of toxicity, predictive hazard data for specific CNTs are needed for use in alternatives assessments. However, the sheer number of CNTs and other engineered nanomaterials can quickly overwhelm existing toxicological testing resources. Traditional toxicological testing uses costly animal tests that examine the effects of one chemical at a time, and then struggles to extrapolate results to humans. Fortunately, new rapid testing strategies examine toxicity at the cellular or biomolecular level.[94] This high-throughput testing has the capacity to rapidly produce results for batches of chemicals and materials at a time.

For CNTs, which are expected to target the lung, high-throughput testing methods have been developed that target specific cellular mechanisms indicative of pulmonary effects, such as inflammation and fibrosis.[95] High-throughput testing can help screen for other potential health impacts as well, since the expression of specific genes or biological markers are indicative of specific toxicity pathways – carcinogenic, immunological, or developmental effects among others. By using these alternative test strategies, varied CNT compositions can be screened and ranked on specific hazard traits. These data can be then used to plan and prioritize more complex and costly in vivo animal testing.[94]

Fortunately, new rapid testing strategies examine toxicity at the cellular or biomolecular level. This high-throughput testing has the capacity to rapidly produce results for batches of chemicals at a time.

As testing methods develop and data accumulate, it will be important that the information be made publicly available to support efforts such as green and safer nanotechnology design and the use of alternatives assessment. While comprehensive toxicological data for new and novel substances will never be available, baseline hazard screening data derived from rapid testing methods can be used to inform safer product development choices.

One recently developed tool to screen nanomaterials for human health and environmental risks suggests that even the most basic hazard data can reveal important red flags to assist not only the development of nanomaterials that are "safer by design", but also to assist industry and government with implementing more proactive and prevention-oriented measures. The screening tool employs five indicators that the European Environment Agency suggests are "warning signs" of environmental and public

While comprehensive toxicological data for new and novel substances will never be available, baseline hazard screening data derived from rapid testing methods can be used to inform safer product development choices.

health harms, including: (1) novelty, (2) persistence, (3) ready dispersion in the environment, (4) tendency to bioaccumulate, and (5) irreversibility of impacts, including health effects.[96] When CNTs were assessed using this tool, 4 out of the 5 red flags were raised. The only criterion not fulfilled was "readily dispersed" as unmodified CNTs are not water soluble.[97] Had this basic screening of CNTs been employed 10 years ago, it might have sent signals to public and private sector decision-makers to "slow down," lest we repeat our history of two-legged stool technologies: missing the biological considerations of environment, health and safety.

Controlling Exposure: Should We Discourage Some Applications of CNTs?

There are two ways to prevent harm from CNTs. The first is to design a CNT to be safe. The second is to ensure no individual or organism is exposed. With no CNT currently deemed "safe," and given evidence that some CNTs already in use are hazardous, understanding and controlling exposure is important.

Studies have documented that workers can be exposed to CNTs during a variety of operations, including research activities, substance manufacturing and product manufacturing. Performing tasks such as collecting CNTs after synthesis, cleaning the reactor, or transferring, weighing, pouring, blending and mixing powders of CNTs, can cause the light-weight material to become airborne and then inhaled by workers.[98,99,100] Workers cutting or drilling CNTs in composite materials can similarly be exposed.[101] Even "sonicating" – agitating CNTs using ultrasonic frequencies in water containing natural organic acids to help them disperse – can produce high levels of CNTs in the air.[99]

Reducing exposures to reduce risk from CNTs may require rethinking how and in what type of applications we use these materials. A comparison of two uses of CNTs – in tennis racket frames and in advanced electronic memory devices– suggests principles for deciding what kinds of uses might be encouraged or discouraged. Table 4 delineates exposure, hazard and societal benefit attributes of these two uses of CNTs.

The composite material used in the frame of a tennis racket can contain MWCNTs. To create the composite materials, high quantities (grams) of dry CNTs are put into a hopper and fed into the extruder to mix with the polymer, both very dusty operations with a high potential for release of CNTs. The extruded frame must be processed further by grinding, sanding, and cutting – all operations that release CNTs into the air. In contrast, building advanced memory devices – when they advance beyond the basic research stage – likely will involve the suspension of a very small quantity (nanograms) of CNTs in a liquid, which will then be processed so that the CNTs "self-assemble" into the final device. This follows two of the principles for safer nanotechnology (see Table 2): use in an

encapsulated form and in small quantities to minimize the potential for worker exposure.

During consumer use, a CNT polymer composite tennis racket can release CNTs whenever the racket is scratched – by abrasion on the court, for example. While amounts released from the tennis racket will be minimal (especially when compared to releases during the manufacturing and production phases), the release of CNTs from memory devices during consumer use – such as in a cell phone – is not considered likely. Likewise, the potential for release at the end of life is orders of magnitude higher for the tennis racket than for the memory device.

Table 4. Risks and Benefits of Two CNT Products Properties to Consider

Property	Tennis Racket	Memory Device
Importance to society	Low	Very high
Value added to the device	Low	Very high
Quantity used per device	Very high (grams)	Very low (nanograms)
Physical form during device manufacture	Dry powder	Suspended in liquid
Potential for occupational exposure	Very high	Very low
Potential for consumer exposure	Low	Very low
Quantity at end of life disposal	Very high	Very low

The use of CNTs in powder form in large quantities to make minor improvements in a sports device presents different risks and benefits than using minute quantities of CNTs in liquid suspension to make the next generation of advanced memory devices. Clearly, some potential uses of CNTs are low value/high risk, while others are the reverse.

Questions regarding the societal value and the level of risk that society is willing to accept go beyond what scientists or product engineers alone can answer. Broader citizen engagement is necessary given the shared stake in how and under what circumstances a new technology with uncertain risks should be allowed to progress. Currently, no organizational structure for technology assessment is in place that critically appraises the social and ethical considerations of a new or changing technology. Neither is there opportunity for a participatory process that enables laypeople, who are otherwise minimally represented in debates about science and technology, to express judgments about complex topics such as nanomaterials.

Regulation: Necessary but Insufficient

To meet their obligation to protect workers, the public and the environment from the hazards of nanomaterials, governments use existing imperfect worker safety and chemicals management frameworks. In the US, the implementation of the Occupational Safety and Health Act and the Toxics Substances Control Act (TSCA) by the Occupational Safety and Health Administration (OSHA) and EPA, respectively, is widely regarded as slow, expensive and reactive. In Europe, the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) law has improved upon the US approach by requiring hazard and exposure data prior to marketing, but both systems are overwhelmed by the sheer volume of chemicals in use and by gaps in data relevant to assessing risk. These limitations are magnified many fold with regard to nanomaterials. With thousands of types of CNTs alone, for example, the prospect of regulating all of the versions of

nanomaterials, each functionalized with different chemical groups with different implications for toxicity, is daunting. With nanomaterials, "paralysis by analysis" becomes an even greater specter threatening swift regulation. Regarding the parallel drawn between human health risks from CNT exposure and asbestos, one industry-research alliance stated that "an individual evaluation of every single CNT structural model is needed to make a sound scientific assessment."[102]

High throughput testing holds promise for providing some data on which to make decisions. The requirement that some nanomaterials provide pre-manufacturing information to EPA (see below) removes one barrier to health-protective regulation. However, experience thus far with regulating carbon nanotubes affirms the limitations of regulation based on risk assessment as the primary approach for maximizing societal benefits of nanotechnology while preventing detrimental impacts on health and the environment. It corroborates the need for complementary non-regulatory approaches described above – the high throughput toxicological data to inform green and safer design for nanotechnology; the use of alternatives assessment in technology planning; and the need for systematic technology assessment with public participation to evaluate the complex societal issues surrounding the adoption of new technologies.

Occupational Safety and Health

In the US, the main regulatory tool used by OSHA to regulate toxic chemicals are permissible exposure limits (PELs) that establish maximum allowable exposures to specific substances. To date, no PELs for CNTs or any other nanomaterial have been established by OSHA.[103] The only other mechanism that OSHA could use to protect workers from exposure to CNTs is the general duty clause, which states that each employer must "furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employee." OSHA has yet to issue a citation using the general duty clause for exposure to CNTs.[103]

As the federal government's research arm for occupational safety and health, NIOSH is charged with recommending standards and describing exposures that are considered safe. In April 2013, NIOSH issued a Current Intelligence Bulletin in which it reviewed the science on the occupational hazards associated with CNTs.[3] The Institute concluded that CNTs may pose a respiratory hazard for workers based on the existing evidence of pulmonary inflammation and fibrosis, and established a recommended exposure limit (REL) of 1 $\mu g/m^3$ of elemental carbon for an 8-hour time-weighted average. NIOSH established the REL at the lowest level that the elemental carbon analytical method could quantify, rather than at the level NIOSH considers safe for workers. In addition, NIOSH did not include the evidence regarding carcinogenicity of some CNTs in establishing the REL, and warned that "continued efforts should be made to reduce exposures as much as possible" because of uncertainty regarding chronic health effects, including cancer. Some researchers also warn that the current REL may underestimate risks to workers considering the number of individual carbon nanotubes contained in 1 μg/m3, as high a several thousand CNTs/cm3, levels that are significantly higher than OSHA's PEL for asbestos.[103]

NIOSH's Current Intelligence Bulletin includes additional guidance to protect workers, including establishing a process safety management program. An integral part of this program is hazard analysis, which includes identifying the sources of exposure to CNTs so that the process or equipment can be designed or redesigned to minimize exposure. This program aligns with the use of alternatives assessment in technology planning to ensure that health and safety are part of the decision calculus in product development and manufacturing, as described above.

While NIOSH's recommendations are helping to fill a critical void in protecting workers from exposure to CNTs, they are not enforceable; compliance is purely voluntary.

While NIOSH's recommendations are helping to fill a critical void in protecting workers from exposure to CNTs, they are not enforceable; compliance is purely voluntary. Nevertheless, EPA is attempting to give more weight to some of these recommendations by including industrial hygiene provisions in its consent orders and Significant New Use Rules (SNURs) for CNTs as described further below.

Some European countries have issued recommended exposure limits that are more stringent. For example, in 2007, the British Standards Institute recommended an occupational exposure limit for CNTs of 0.01 fiber/cm^3, a limit that is equivalent to the most rigorous exposure limit for asbestos in Britain and in the US. Nano reference values (NRVs) have been recently developed for CNTs to serve as provisional substitutes for occupational exposure limit values and also call for a limit of 0.01 fiber/cm^3. [104, 105] This is the most stringent recommended occupational exposure limit, anywhere in the world there is still no regulatory structure in place to enforce it.

Chemicals Management Regulations

Early attempts by the US and other governments, including the United Kingdom and Australia, to capture information about the types and amounts of nanomaterials being produced and imported were voluntary in nature. It is perhaps not surprising that there were few submissions and the programs were ultimately disbanded.[84]

In the US, most nanomaterials are considered chemical substances and regulated by EPA under TSCA. In 2008, EPA adopted a regulatory approach to gather additional data on CNTs, announcing that companies intending to make or import CNTs must formally notify EPA, provide available data and allow review by the agency.[106] The year before, EPA had classified CNTs as "new substances" thus formally recognizing these substances as different than their bulk counterpart.[107] This was a crucial determination by EPA because under TSCA, designation as "new" versus "existing" has very specific implications: the agency only has authority to require pre-manufacture review of "new" not "existing" chemicals.

With CNTs formally defined as "new" substances, EPA requires companies to submit a Premanufacturing Notification (PMN) to the agency before manufacturing or importing any CNTs. If

a *particular* CNT is not on the TSCA inventory (i.e., an existing chemical) a PMN is required. Thus EPA's requirements recognize the dramatic heterogeneity of CNTs and potential differences in human and ecological toxicity. Yet if even one tenth of the possible CNTs are commercialized, the resource-constrained agency will be unable to effectively review each and every PMN. There is no easy solution, beyond providing EPA with the level of resources required for individual reviews and responses.

A common outcome of EPA's review of PMNs for CNTs has been the issuance of consent orders that are negotiated with individual companies. The consent orders typically require additional reporting and testing of CNTs – 90-day inhalation studies – and mandate specific industrial hygiene practices to mitigate risk to workers.[108] Once a CNT has been listed in the TSCA Inventory (now considered an "existing chemical"), EPA has subsequently issued Significant New Use Rules (SNUR) to capture additional information and to place requirements – similar to those in the consent orders – on companies that are using the engineered nanomaterial beyond the specific uses outlined in the original PMN. More recent SNURs reflect comments submitted to EPA by NIOSH and labor groups to improve protections for workers by mandating the use of engineering controls (methods that are built into the design of a plant, equipment or process to minimize the hazard such as ventilation or physical containment) in addition to the use of personal protective equipment, such as respirators.[109]

EPA's regulatory actions to promote and enforce NIOSH's occupational health and safety recommendations for CNTs through its authority under TSCA are an important development to protect workers and potentially to minimize downstream effects on the environment and consumers. Nevertheless, EPA's current authority to regulate nanomaterials is insufficient to advance green and safer CNTs.

While EPA lacks authority to mandate that only safe nanomaterials be manufactured and used, it can provide guidance materials to help steer research and development efforts in that direction. EPA is currently collecting reams of data from industries complying with its PMN and SNUR requirements. This information should be synthesized to distill lessons learned for industry and the research community to better guide green and safer nanotechnology efforts.

EPA's actions that place the burden of conducting toxicity testing on companies manufacturing or importing specific engineered nanomaterials are also an important development given that EPA does not have the capacity to conduct such studies on every type of CNT being used in the market-place. However the current regulatory process is neglecting one major concern: the potential carcinogenicity of CNTs. While EPA's own summary of

the health and environmental effects of CNTs clearly demonstrates concern for cancer, requirements outlined in EPA's consent orders and SNURs have not addressed the potential for increased cancer risk.[110] EPA specifically rejected adopting NIOSH's REL as its own New Chemical Exposure Limit (NCEL), because "it may not be preventative of all known health effects" and has called for more data to establish a NCEL for CNTs.[109] Yet as we wait for these data, EPA's current regulatory actions may be invoking a false sense of security.

In Europe, the chemicals management legislation REACH is also the first line of defense for protection of human health and the environment from risks associated with nanomaterials. REACH is based on a "no data, no market" principle – the law prohibits the manufacture or sale in the EU of any substance produced or imported in quantities of more than 1 metric ton (2,000 pounds) per year unless it has been registered with the European Chemicals Agency (ECHA). As part of the registration process, manufacturers and importers must submit to ECHA a dossier of information relevant to health and safety.

As of 2008, CNTs are regulated under REACH. Prior to 2008, the law exempted registration of carbon and graphite – the bulk form of CNTs – because of presumed safety. However, the European Commission removed the exemption as it determined that insufficient information was known about the substances, particularly at the nano-scale.[111]

Regulation of CNTs and other nanomaterials under REACH are at a standstill, however, because the thresholds which trigger regulatory requirements are inappropriate for nanomaterials. As noted above, production or import of 1 metric ton per year triggers regulatory requirements under REACH, but the majority of manufacturers of CNTs are likely producing these materials in quantities far below 1 ton. Moreover, a formal risk assessment is not required until a manufacturer produces 10 metric tons and then only if the chemical or material is classified as "dangerous" or assessed to be persistent, bioaccumulative or toxic (PBT) or very persistent or very bioaccumulative (vPVB) – none of which currently applies to CNTs. To date, only 2 registrations have been filed by MWCNT manufacturers (one by a group of manufacturers).[113]

While REACH provisions for nanomaterials are under review as of this writing and revisions are expected, some member states are becoming impatient. For example, in 2012 the French Government issued a decree requiring companies that manufacture, import, or distribute nanomaterials in quantities of more than or equal to 100 grams to submit an annual declaration that includes quantity and use information. The decree applies to "professional users" and research laboratories located in France as well. France is the first government to mandate regular reporting of nanomaterials. Other countries including Denmark, Sweden and Belgium are exploring similar requirements.

Assuming that Europe resolves the threshold issue and requires registration of nanomaterials manufactured in smaller quantities, barriers to assessing risk will remain. In 2009, the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks was asked to assess the appropriateness of existing risk assessment methods for the evaluation of nanomaterials. The Committee concluded that while existing methods are generally applicable, "specific aspects related to nanomaterials still require further development. This

will remain so until there is sufficient scientific information available to characterize the harmful effects of nanomaterials on humans and the environment."[114] The committee further stated, "As there is not yet a generally applicable paradigm for nanomaterial hazard identification, a case-by-case approach for the risk assessment of nanomaterials is still warranted."[114]

This case-by-case approach will fall victim to paralysis by analysis even if a small percentage of the tens of thousands of CNTs become commercially viable. A 2012 WHO report on nanotechnology and the assessment of risk concluded that the vast number of potential combinations of various material and chemical properties of CNTs makes the case-by-case health and ecosystem health assessment for the purpose of regulation so resource intensive and demanding as to be impractical and impossible. This report states, "Developing the capacity to predict the effects of CNTs and other nanomaterials is essential."[4]

Despite regulatory attention to CNTs, there remains no effective mechanism in the US and EU for ensuring that only the safest CNTs are being used. While there is currently more action on CNTs in the US than under REACH, both approaches are limited by structures that were established for conventional chemicals, not nano-scale forms. California's new Safer Consumer Products regulations provide an opportunity for promoting safer CNTs, at least in California, which could have a ripple effect elsewhere. The regulations require that alternatives assessments be conducted for chemical/product combinations that the state identifies as of high concern. Though nanomaterials are not specifically mentioned in the regulation, chemical hazard characteristics including, "particle size" or "fiber dimensions" are. The regulations may also expedite the process of adapting existing alternatives assessment frameworks for the evaluation of nanomaterials.[115]

"Developing the capacity to predict the effects of CNTs and other nanomaterials is essential."

Concluding Remarks

Tens of thousands of chemicals circulate in commerce, a small percentage of which have been tested comprehensively for environmental and human health effects. Even without resolution of debates about whether government should have to demonstrate harm or industry demonstrate safety, there is broad consensus that current policies and testing approaches are unable to manage the volume of conventional chemicals. Enter nanomaterials. With tens of thousands of variations of CNTs alone, nanomaterials dwarf conventional chemicals in the magnitude of the task of comprehensive testing and regulation to protect public health. Challenges in adapting existing regulations to nanomaterials – such as inappropriate tonnage thresholds that trigger reporting requirements – magnify the fundamental limitations of the existing chemicals management systems.

Research on the environmental health and safety of CNTs was late in coming, yet has steadily increased over the last 10 years. Early predictions based on knowledge from the mature science of particle toxicology have turned out to be accurate.

Existing evidence suggests that long and rigid MWCNTs do act like asbestos, for example, and the body of toxicological evidence about many different CNTs raises concerns about pulmonary toxicity, fibrosis and carcinogenicity, among other outcomes. The persistence of CNTs in the environment is also a concern. Though ecosystem impacts remain understudied across the CNT lifecycle, evidence suggests that some aquatic organisms may be at risk. While there have been significant advances in the regulation of CNTs in recent years, the lack of attention to the potential carcinogenic effects of these nanomaterials means that current efforts may provide a false sense of security.

Yet there are reasons to remain optimistic. The emerging field of green and safe nanotechnology holds promise, but the need for resources is urgent given the dramatic increases in CNT manufacturing and product commercialization. High-throughput testing technologies have the potential to exponentially increase knowledge about the hazards of new materials. Data from these tests should be made widely available to assist design processes as well as to better adapt hazard assessment protocols for nanomaterials as part of alternatives assessment. In doing so, alternatives assessment can help distinguish CNTs that may be viable alternatives to high hazard conventional chemicals from those that should be discouraged.

Undoubtedly, use of CNTs will have far-reaching social ramifications. Channeling technological development down healthy rather than unhealthy paths requires stepping into the messy realm of ethics and values. Uncertainty about risks will continue to abound, no matter the stage of scientific understanding. And while we wait for the science on health and environmental effects to advance, does it make sense to encourage the proliferation of CNTs in those applications where the ultimate value to society is low, yet the potential risk is high? Without a formal system and structure to assess the social ramifications of the development and deployment of CNTs – or any new technology for that matter – which includes citizens' perspectives and judgments, we risk entrenching uses of a new technology where the risks outweigh the benefits. Establishing offices of technology assessment in the US and elsewhere would strengthen capacity to respond to and anticipate challenges and opportunities of new technologies.

The environmentalist Barry Commoner criticized the 20th century revolution in synthetic organic chemistry by calling it a two legged stool – "…well founded in physics and chemistry" but lacking in biology. The revolution in nanotechnology promises a transformation in society no less profound, and a demand for "biology" – toxicology, epidemiology, ecology – that is equally urgent. The preliminary data are in, and they are a cause for concern. But a great many uncertainties remain. CNTs illustrate the precarious promise of nanomaterials. We call on advocates and industry, government and universities, to accelerate the development of tools that elevate health in design and decision-making, and to marshal an ambitious shift towards green nanomaterials design.

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Engineered carbon nanotubes (CNTs) present a compelling case for the need for proactive rather than reactive measures – by government, industry and other stakeholders – to address hazards of emerging chemicals and materials. Along with the promise of dramatic societal benefits, the use of a vast array of new technologies like CNTs carries risks, and the sheer volume of them threatens to overwhelm agencies charged with protecting health and environment.

With clear and profitable benefits, and uncertain prospective risks, CNTs demonstrate how the speed of penetration of a new technology often trumps concern for health protection. They also illuminate the need for systematic assessment of alternatives and consideration of hazard at the earliest stages of material design.