Is the field moving so fast that it's destined to repeat the mistakes of earlier technological revolutions?

Nanotechnology Grows Up

ANAHEIM, CALIFORNIA—Forget the futuristic visions of molecular-scale devices that seek out and destroy cancer cells and repair faulty heart valves. The truth is that nanotechnology is already here. Intel and other computer-chip companies already sell tens of billions of dollars worth of chips every year packed with electronic circuitry patterned down to the nanoscale. Computer hard drives, LED-based traffic signals, CD players, and low-friction coatings account for billions more in sales.

So it was only natural that, at a meeting of the American Chemical Society (ACS) here in March, you could almost hear the collective groan when Eva Oberdörster, a toxicologist at Southern Methodist University in Dallas, Texas, told nanoscience researchers that water laced with all-carbon nanoparticles called buckyballs could damage cell membranes in the brains of fish. The story was picked up by newspapers around the globe (as well as *Science*'s daily news Web site *Science*NOW). Researchers and policymakers fretted that such coverage could poison public perception of all things nano—including the vast majority of applications that have nothing to do with buckyballs—and put the field on the same path as previous abortive scientific revolutions such as agricultural biotechnology and nuclear power.

Nanotechnology has not gained that level of notoriety yet. And perhaps it won't. But the field stands at a critical crossroads in public perception. "Nanotechnology is growing up," says Vicki Colvin, a nanotechnology researcher at Rice University in Houston, Texas. Government funding, research, and private investment in the field are all booming, boosting nanotech's visibility as well as scrutiny from outsiders. Regulatory agencies, researchers, and health and environmental watchdogs are investigating how nanoscale materials affect human health and the environment.

Many observers worry that the field may be growing up too fast for its own good and that regulators can't keep pace with the release of new nano-based products. A lag, they say, ups the risk that news about environmental dangers from one form of nanomatter could spark a public backlash against the whole nanotechnology enterprise. "Nanotech is in danger of becoming another Frankenfood controversy," says Julia Moore, a senior adviser in the National Science Foundation's (NSF's) Office of International Science and Engineering in Arlington, Virginia, who closely tracks nanotechnology's progress and is writing a book about the backlash against genetically modified food. The fears are rooted in a basic conundrum: The property that makes nanoparticles so promising—that they behave very differently from bulk forms of the same material—also makes their potential health and environmental effects maddeningly difficult to predict.

Averting disaster. Nanotechnologists hope to avoid the furor that erupted over genetically modified foods (*above*) and the remediation headache of asbestos (*right*).

Protean promise

Nanotechnology isn't as much a discipline, like chemistry or physics, as a tool kit for manipulating matter at its finest scale. The nanoscience boom grew from the recognition that the properties of materials can change drastically as their size is whittled down from the bulk material to small clusters of atoms. Gold, for example, is inert in bulk but becomes highly reactive at the nanoscale, making it a potentially valuable catalyst. Electrical, optical, thermal, and other properties of materials may undergo similar shifts. Such changes typically arise from two effects. First, a nanoparticle's small size means that most of its atoms are on the surface, so the behavior of its surface atoms dominates the particle's chemistry and physics. Also, squeezing atoms' electrons into smaller-than-typical spaces can change properties such as the color of the light they emit and a nanocluster's chemical reactivity.

That protean nature, coupled with new tools for studying small-scale materials, has transformed the kinds of questions scientists can ask, says John Marburger, who heads the White House Office of Science and Technology Policy. "The capability to image, manipulate, and visualize all materials at the atomic level potentially touches every human aspect in the world around us," he says.

The upshot is that by just about any measure, nanotechnology is one of the hottest areas of science around. In just

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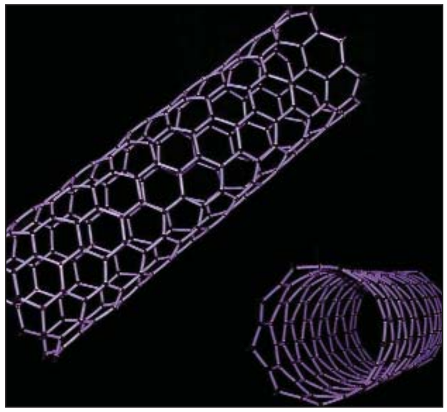
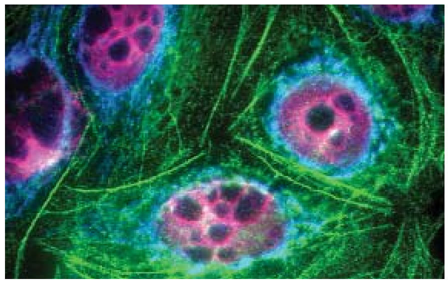
5 years, nanotechnology has catapulted from being a specialty of a relative handful of physicists and chemists to a worldwide scientific and industrial enterprise. In the United States, funding for the National Nanotechnology Initiative (NNI), which started at $270 million in 2000, is now set to approach $1 billion in 2005. Worldwide, government-funded nano research has ballooned sevenfold, from under $500 million in 1997 to over $3.5 billion in 2004. The U.S. government alone has funded 22 new nanoscience research centers since 1991. And the number of papers and patents mentioning nanotechnology has skyrocketed.

The interest isn't only academic. In May at an NNI conference in Washington, D.C., Steve Crosby, the publisher of *Small Times*, a nanotech industry magazine, said that 775 companies and organizations in the United States alone are engaged in nanotechnology. And the March/April issue of *Small Times* noted that venture capital funding in the nano area rose from virtually nil in 1997 to $300 million in 2003, accounting for over 5% of all VC funds distributed. The list of large firms pursuing nano research reads like a *Who's Who* of the Fortune 500, including General Electric, Lucent, Philips, Matsushita, Intel, Advanced Micro Devices, and Merck. In April, Merrill Lynch launched a nanotechnology index to track the stock performance of the emerging sector. According to David Rejeski, who directs the Foresight and Governance Project at the Woodrow Wilson International Center for Scholars in Washington, D.C., companies have already released 130 different nano-based products onto the market. And according to U.S. government estimates, the nanotech economy will be worth a whopping $1 trillion by 2012.

Beyond "gray goo"

This race for the spoils of the nanoworld has some worried that the field may careen into the sort of unintended consequences that shadowed the introduction of genetically modified foods and other industrial and technological revolutions. They aren't talking about far-future "gray goo" scenarios popularized by Sun Microsystems cofounder Bill Joy and others (*Science*, 24 November 2000, p. 1526), in which speck-sized self-replicating robots devour the planet. Making such devices would be "difficult if not impossible," says Rice University nanoscientist Richard Smalley, and most nanoscientists agree. A somewhat more plausible threat, they say, is that nanoparticles released from coatings or other products will create a new type of chemical pollution. What they want to avoid is a repeat of the experience with asbestos, the one-time miracle fiber that's now a convicted killer and multibillion-dollar remediation headache. Unlike



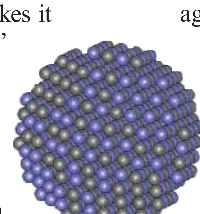


Good and evil. Carbon nanotubes, quantum dots (shown inside cells), and nanoparticles have enticing electrical and optical properties, but toxicologists worry that they might harm organisms.

CREDIT: K. L. KELLY *ET AL., COMPUTING IN SCIENCE AND ENGINEERING* 3, 67 (2001)

asbestos, however, the properties of nanoparticles vary with their chemical makeup, sizes, and interactions. "We know very little about the health and environmental impacts [of nanomaterials] and virtually nothing about their synergistic impacts," Rejeski says.

Over the past couple of years, about a dozen toxicology reports have suggested that nanoparticles pose a unique risk to everything from bacteria to mammals. In addition to Oberdörster's large-mouth bass report, recent studies have found that carbon nanotubes, when washed in a suspension into the lung tissue of rats, can agglomerate, causing tissue damage, respiratory problems, and even death. As well, Colvin reported at the ACS meeting that nanocrystals of buckyballs dissolved in water at a concentration of 1.5 parts per million killed one-half of the *Escherichia coli* bacteria in the water. "That makes it an extremely effective antibiotic," Colvin says.



Exactly how various nanomaterials appear to harm cells is still being worked out. Colvin notes that buckyballs—all-carbon molecules with chemical formula C_{60}—are powerful electron sponges, readily swiping loosely bound electrons from nearby molecules. That makes them highly sought-after for use in electronic devices such as solar cells, where they can help steer electrons into a circuit. But if they find their way inside cells, that same ability may convert oxygen and other molecules into highly reactive radicals that can tear apart cell components. At the ACS meeting in March, Colvin reported that when her team exposed human fibroblast cells to nanocrystalline C_{60}, they found that the cell membranes were degraded and that the cells jacked up their production of glutathione, a small protein antioxidant that snuffs out free radicals.

Just what that means for higher organisms is not yet clear. Although Oberdörster found a similar degradation of lipid membranes surrounding brain cells when she exposed fish to nanocrystals of C_{60}, she did not find unusual amounts of glutathione in the gills or liver of fish, as would be expected. Yet she did find higher levels of other detoxifying enzymes known as P450s.

Other nanoparticles are also raising concern. At the ACS meeting, physiologist Anna Shvedova of the National Institute for Occupational Safety and Health (NIOSH) in Morgantown, West Virginia, announced that exposing human keratinocytes and bronchial epithelial cells to a mixture of straw-shaped carbon particles called nanotubes and nano-sized iron particles increased levels of cell damage and apoptosis, or programmed cell death. And mice forced to breathe the particles suffered significantly more damage to their lung tissue than controls that breathed in silicon particles. "We're talking much higher toxicity," Shvedova says.

"Over the last year, there have been a lot of concerns raised about the potential health and environmental impacts of nanotechnology," says Clayton Teague, who directs the National Nanotechnology Coordination Office in Washington, D.C. Still, he adds, "these are very early pieces of data. It's very hard to draw conclusions about the risk" when there has been so little exposure to specifically engineered nanoparticles.

Most other observers agree that it's too early to start regulating nanoparticles, but some say their concerns are growing. "All of these [studies] say there is a yellow light here," says Pat Mooney, executive director of the ETC Group (formerly known as RAFI), which spearheaded efforts against agricultural biotechnology. "It's a basis to say 'Hold it, you've jumped the gun.' " Faced with so many unknowns, the ETC Group is calling for a moratorium on releasing new products containing nanoparticles and on lab-based research using nanomaterials until health officials come up with standards for dealing with nanomaterials. They aren't the only ones tugging on the reins. In a forward to a report on nanotechnology last year, Greenpeace's chief scientist, Douglas Parr, a physical chemist, wrote: "With cause for concern, and with the precautionary principle applied, these materials should be considered hazardous until proven otherwise." Even Britain's Prince Charles chimed in recently with concerns that nanotechnology could create a new class of environmental damage.

Mihail Roco, who heads NNI, agrees that caution is in order in dealing with new nanomaterials. Since its inception, he says, NNI has funded studies of the social, ethical, and environmental implications of nanotechnology. To date the U.S. Environmental Protection Agency (EPA) has sponsored three extramural grant programs, funding a total of 32 studies, most of which focus on the use of nanomaterials to address environmental problems. NSF backed Colvin's Center for Biological and Environmental Nanotechnology at Rice with $10.5 million to explore, among other areas, the effect of nanomaterials on aquatic systems. The National Toxicology Program is also ramping up studies on the toxicology of nanomaterials, on which Teague estimates the program will spend approximately $5 million a year by 2008. NIOSH has also established a nanotechnology research center and has an internal 6-year research program on nanoparticle toxicology. All told, Roco says, NNI now spends 11% of its budget, or $106 million a year, on environmental studies (see figure).

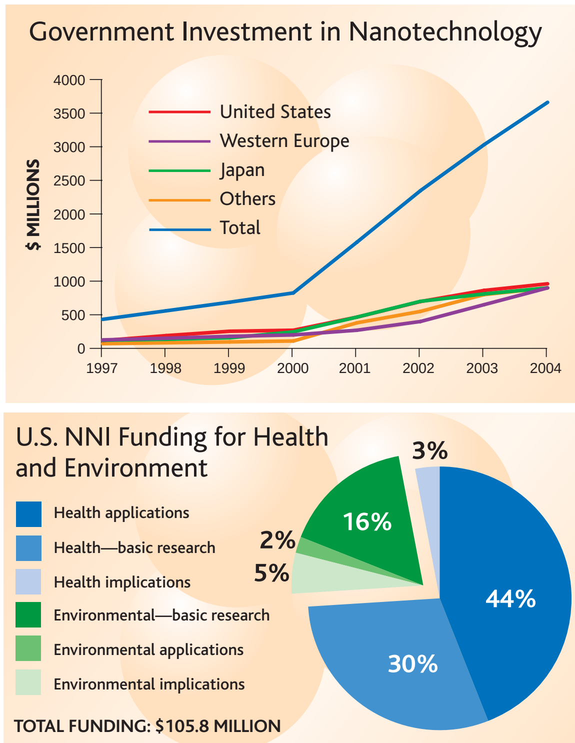
Some observers aren't impressed. Mooney points out that most of the NNI money is aimed at using nanotechnology to address environmental problems, such as remediating pollution sites. Grants for university-based nanotoxicology studies, Oberdörster adds, account for only about $5 million out of the current $961 million budget. "That's on the silly side almost," Oberdörster says. "If you're anticipating a $1 trillion industry, you should take a small fraction of that and put it into toxicology."

Still, Teague says, researchers are hardly starting from scratch. "There is a large body of research on the toxicity of ultrafine [particles]," he says—including extensive studies of carbon soot from power plants, welding fumes, diesel exhaust, paint pigments, and carbon black–based toner in photocopiers. And the federal government—through regulations such as the Toxic Substances Control Act and Clean Air Act, and agencies such as EPA and NIOSH, which sets chemical exposure limits for workers—already has the legal authority to monitor exposure to such particles and set safety standards. Because of what's already in place, adds Marburger, "it seems unlikely the system for identifying and controlling hazardous substances will need to be changed very much" to deal with nanoparticles. The most likely strategy, Teague says, will be to update those regulations to take account of different-size nanoparticles.

Getting it right

That may be easier said than done. Currently, regulators assess the safety of new compounds based on their chemical composition. Yet nanomaterials often change their properties when their size changes, even if their composition remains constant. The upshot is that carbon nanotubes and fullerenes are now regarded as essentially the equivalent of graphite, a typically innocuous form of carbon. Even deciding how to test nanoparticles for toxicity isn't straightforward, Colvin says. Should regulators investigate 1-nanometer, 10-nanometer, or 50-nanometer particles? Should they look at all three and everything in between? The problem quickly becomes unwieldy, she admits.

Predictive models, which assess a new substance's safety by comparing it with well-studied materials in the same chemical family, may also falter when properties change with size. Federal agencies, which already rely heavily on such models in evaluating 1500 to 2000 new chemicals a year, may soon find themselves without one of their most important tools in assessing the safety of new compounds, Rejeski says. "The innovation system is moving incredibly fast. It could get out in front of the regulators."



Big time. As funding for nanotech skyrockets, the U.S. National Nanotechnology Initiative devotes 11% of its budget to health and environmental studies.

SOURCES: (TOP TO BOTTOM) MIKE ROCO/NSF/NNI; CLAYTON TEAGUE/NNCO

Corporations that invest heavily in the field are also scrambling to get a handle on the safety of nanomaterials. DuPont, for example, is funding toxicology work on nanomaterials, and other companies are backing university research at Rice and elsewhere. "[Companies] have a vested interest to make sure the train doesn't go off the track. The last thing they want is to make a massive investment and have nano turn around and bite them," Rejeski says.

Behind such efforts loom the specters of a new generation of environmental cleanup sites, or, much worse, the same downward spiral in public confidence that blighted agricultural biotechnology and nuclear power. "If the public loses confidence, support can wither away," says Senator George Allen (R–VA), who helped craft an authorization bill passed by Congress and signed by President George W. Bush last fall, which affirmed long-term support for nanotechnology. Mooney agrees. Novel technologies based on nanotechnology might someday drastically lower the cost of generating electricity from solar power, purify water, and clean up past environmental contamination, he says—but researchers must be careful. "If people are too blasé about nanotechnology and it gets off on the wrong foot, then it's a problem. It's critical that scientists get it right."

For starters, NSF's Moore says, companies should let consumers know up front which products contain nanomaterials. By showcasing the benefits of the technology while letting individuals choose whether to consume it, she says, companies can avoid the sort of consumer backlash Monsanto suffered after it fought labeling its genetically modified crops. Another key step, says David Goldston, staff director of the U.S. House of Representatives Science Committee, is that scientists should not dismiss public concerns as uninformed or unrealistic. "The message should be one of engagement rather than simply countering their concerns with rhetorical counterattacks," he says. Finally, Roco adds, NNI must continue to back studies on environmental and other impacts of nanotechnology and disseminate them widely. "The best approach is to be open from the beginning and provide as much information as possible. If you don't provide information, there is a perception that something is wrong," he says. That perception may turn out to be the only thing that can knock the nanotechnology train off its tracks.

–ROBERT F. SERVICE