I am certain that nanotechnology holds huge promise. . . . But unless environmental, health, and safety issues are addressed in a way that fosters public understanding and support for nanotechnology, that potential is in jeopardy.

Senator Ron Wyden (D–OR), coauthor of the 21st Century Nanotechnology Research and Development Act

RESEARCH INITIATIVES

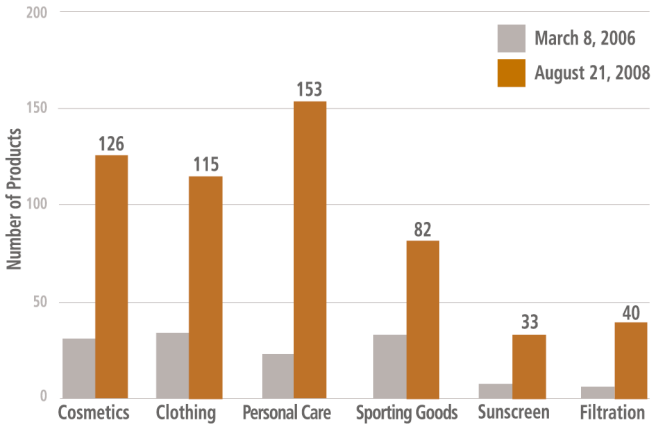
What Lies Ahead for Nanotechnology?

Nanotechnology, the engineering of functional materials at an atomic or molecular scale, has been among the fastest growing fields of science and technology. Worldwide sales of products incorporating nanotechnology are projected to total $2.6 trillion by 2014, according to a 2004 report from Lux Research titled *Sizing Nanotechnology's Value Chain*. But with the increasing use of nanomaterials in many consumer products has come growing concern about potential environmental, health, occupational, and general safety hazards. At the 2009 annual meeting of the American Association for the Advancement of Science, scientists held a seminar titled "Driving Beyond Our Nano-Headlights?" to discuss recent nanotoxicologic research as well as health and environmental policy implications of the use of nanomaterials.

Speaker Agnes Kane, a medical professor at Brown University, revisited the analogy between chrysotile asbestos fibers and carbon nanotubes (CNTs), a concept first introduced in 1998. In collaboration with fellow Brown University researcher Robert Hurt, Kane has compared the two materials and found similarities in surface area, physical properties, and geometry, raising the possibility that CNTs may show asbestos-like behavior in the human body. Also, using a newly designed cell culture model, Vanesa Sanchez, a graduate student in Kane's laboratory, found that very low doses of CNTs (1 μg/mL) appeared to cause lesions known as granulomas similar to what occurs with asbestos fibers. Moreover, the CNTs formed a cage-like structure that Kane suspects might promote granuloma formation.

Kane also cited research by Ken Donaldson and colleagues of the University of Edinburgh in which the mesothelial lining of the mouse body cavity was exposed to CNTs. (In humans, asbestos is known to cause mesothelioma, a rare form of cancer of this lining.) As Donaldson's group reported in the July 2008 issue of *Nature Nanotechnology*, this exposure resulted in asbestos-like pathogenic effects that included inflammation and granuloma formation.

Sanchez's new cell culture model is one of the few that can screen for potential adverse health effects of nanomaterials. Along these lines, the various challenges of conducting nanotoxicologic research are a central focus for Sally Tinkle, senior science advisor in the Office of the NIEHS Director. Tinkle said the shape and manufacture of a nanoparticle will have a profound impact on the particle's reactivity, as well as how it interacts in the body. "Nanomaterials hold incredible promise to solve significant world problems, like the need for energy and clean water, but these new materials have novel physical and chemical properties, and we don't know yet what their interactions with biological systems will be," she said.



Health and fitness products lead the way in terms of nanotechnology market growth. Between 8 March 2006 and 21 August 2008, the number of "nano-enabled" health and fitness products on the market approximately quadrupled.

Source: The Project on Emerging Nanotechnologies, http://www.nanotechproject.org/inventories/consumer/

Tinkle noted various problems with the interpretation of toxicologic data for nanomaterials. Citing correspondence published in the February 2007 issue of *EHP* by Günter Oberdörster and colleagues at the University of Rochester, she pointed out that toxicologic data could be interpreted differently depending on whether you looked at the nanomaterial's mass or surface area. Moreover, in six common toxicology assays on the same nanomaterial sample conducted by Nancy Monteiro-Riviere and colleagues at North Carolina State University, Tinkle noted that some assays showed a significant effect of exposure whereas others showed none. CNTs were also found to compromise the accuracy of the assays, but nanotoxicologists have yet to identify adequate positive and negative controls that would better reveal the presence and effects of such interference.

Norris Alderson, associate commissioner for science at the U.S. Food and Drug Administration (FDA), raised a related issue in the manufacturing domain—that of guaranteeing consistency (primarily in terms of size, shape, and purity of composition) from batch to batch of nanomaterial to ensure safety and efficacy. "Let's say you've got a nanoscale material for which the majority of particles is 50 nm," said Alderson. "But if there's variation on both sides of that, how much can you vary that distribution and still procure a material with the same characteristics or safety and efficacy?"

Establishing appropriate standards for nanomaterial production is a salient concern for Travis Earles, National Science and Technology Council representative on the nanotechnology portfolio in the White House Office of Science and Technology Policy. Earles stated that such standards were still a work in progress, both nationally and internationally. "It's a little bit of the Wild West in the standards development side of things," he said. "The standardization effort is quite crucial because it ultimately will be the context through which we can successfully or unsuccessfully innovate nanotechnology into commercial use."

Despite these and other challenges, Earles was able to sound a note of optimism for scientists who are looking toward whatever might lie beyond the nano-headlights: Federal funding allocated specifically for environmental, health, and safety research in nanotechnology has grown from $34.8 million in 2005 to $58.6 million in 2008. The multiagency National Nanotechnology Initiative anticipates that funding for the current year will increase to $76.4 million, well above the amount of direct investment made by any other country. –Graeme Stemp-Morlock

REGULATION

Cleaner Air, Longer Life

Since the 1970s, a variety of measures for air pollution control have been introduced in an effort to improve air quality throughout the United States. Many epidemiologic studies already support the view that substantial health benefits—including a lower risk of cardiopulmonary disease and death—are derived from better air quality. A new study now suggests that improvements in U.S. air quality during the early 1980s and late 1990s increased life expectancy by several months.

First author C. Arden Pope III, a Brigham Young University economics professor, and colleagues Douglas W. Dockery and Majid Ezzati of the Harvard School of Public Health focused on particles smaller than 2.5 micrometers in diameter ($PM_{2.5}$), which are created by fuel combustion in vehicles and power plants, among other sources. Pope says vehicle emissions tend to be the greatest local source of $PM_{2.5}$, whereas power plants act more regionally because pollutants from smoke stacks travel farther. Numerous studies have linked $PM_{2.5}$ with increased respiratory and cardiovascular illness and premature death.

As part of an extended analysis of the American Cancer Society prospective cohort study, the team collected air-quality data from two 5-year time periods for 51 U.S. metro areas spanning all geographic regions of the nation. The first data set was collected under the U.S. Environmental Protection Agency's (EPA) Inhalable Particle Monitoring Network from 1979 through 1983. The second set, obtained through the EPA's National Ambient Air Quality Standards for $PM_{2.5}$, was collected from 1997 through 2001. Statistical regression models were used to evaluate changes in $PM_{2.5}$ pollution and life expectancy, as well as to account for declines in cigarette smoking and other factors known to affect life expectancy.

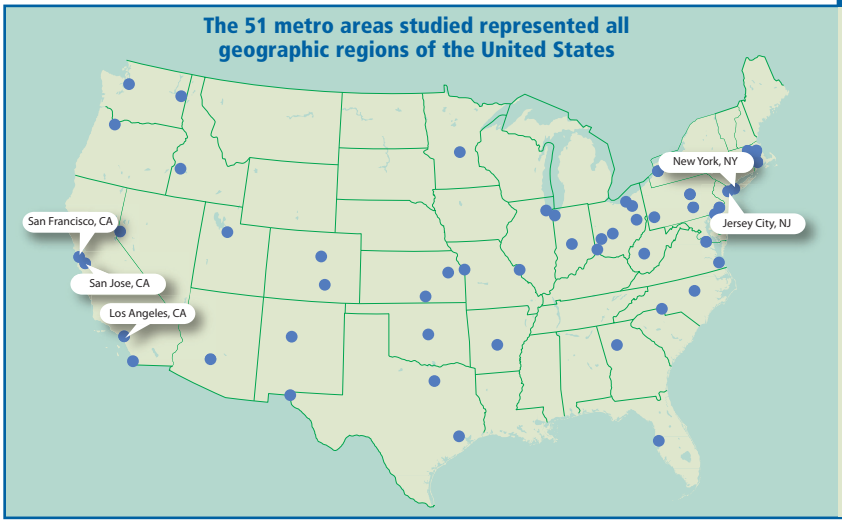
As reported in the 22 January 2009 issue of the *New England Journal of Medicine* (*NEJM*), the team found that when $PM_{2.5}$ averaged over 24 hours dropped by 10 μg/m^3 between the two study periods, life expectancy rose by about 7 months, with a range of 6.6–12.1 months depending on the statistical model used. In those cities with the greatest drop in $PM_{2.5}$ pollution (up to 14 μg/m^3), life expectancy increased by almost 10 months. Overall, life expectancy increased by an average 2.7 years across the time frame studied.

"Any way you model this reasonably, you get roughly the same results," Pope says. A 7-month increase in life expectancy "is stunningly large when you consider no medical intervention took place," he adds.

A variety of national and local events led to reductions in $PM_{2.5}$ since levels were first monitored in 1980. For instance, all cities in the study benefited from emission controls on vehicles such as catalytic converters, which target pollutants that are precursors to $PM_{2.5}$. Regulation of wood-burning stoves and fireplaces helped to clean up the air in the Pacific Northwest. Until now, communities nationwide could only assume that air-quality regulations would translate into increased longevity. "[This study] provides evidence that when actions are taken to reduce particulate air pollution in communities, it increases predicted life expectancy," says environmental health professor Michael Brauer of the University of British Columbia, Vancouver.

An even larger study of the same ACS cohort, published in the 12 March 2009 issue of *NEJM* by Pope and coauthors including Michael Jerrett of the University of California, Berkeley, followed nearly 450,000 people for the same two-decade period but this time covered 96 U.S. metro areas. After analyzing associations between the risk of death and levels of both ozone and $PM_{2.5}$, the researchers concluded that "the risk of dying from a respiratory cause is more than three times as great in the metropolitan areas with the highest ozone concentrations as in those with the lowest ozone concentrations." The report also reiterated the $PM_{2.5}$ findings reported in the earlier *NEJM* article.

The studies' findings affirm the benefits of regulatory efforts aimed at limiting exposure to both ozone and $PM_{2.5}$. Of the first article, Dan Costa, EPA national program director for air research, says, "This study shows that PM reductions due to responses to regulatory actions are having the impact desired—protecting public health. It provides plenty of winds to our sails that we are doing the right thing, and monies spent on regulations have been worth it." –Carol Potera



U.S. Metro Areas with the Highest Increase in Life Expectancy Associated with $PM_{2.5}$ Reductions

Metro Area	Reduction in $PM_{2.5}$ levels (μg/m^3)	Change in Life Expectancy (yr)
New York, NY (4 counties)	9	4.6
Jersey City, NJ (1 county)	4.7	4.5
San Francisco, CA (3 counties)	3.9	4.5
San Jose, CA (1 county)	3.2	4.2
Los Angeles, CA (1 county)	6.6	4.1

Adapted from: Pope CA III, Ezzati M, Dockery DW. Fine-particulate air pollution and life expectancy in the United States. N Engl J Med 360:376–386 (2009).

REPRODUCTIVE TOXICOLOGY

Study Associates PFOS and PFOA with Impaired Fertility

Recent decades have seen a substantial decline in the number of children being born to women in developed countries. Much of this decline is likely attributable to sociocultural changes and increased access to birth control. But some studies suggest that exposure to environmental pollutants may play a role, perhaps by impairing fecundity, the ability to bear live children. Now a study by researchers at the University of California, Los Angeles (UCLA) has found that women who took longer to become pregnant were more likely to have higher blood levels of two common perfluorinated chemicals, perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA).

PFOS and PFOA are persistent manmade pollutants widely found in fabrics, carpets, food packaging, shampoo, nonstick cookware, insecticides, fire-fighting foam, and other household products, as well as in industrial surfactants and emulsifiers. Potential major sources of PFOA in the environment include the degradation of fluorinated alcohols used in these products. Animal studies have associated both PFOS and PFOA with increased pregnancy losses and disruption in sex hormone homeostasis and sexual maturation. Although previous studies have linked pollutants such as pesticides and polychlorinated biphenyls with delayed time to pregnancy, the UCLA study is the first to demonstrate a similar relationship with perfluorinated chemicals.

In the current study, the researchers measured maternal blood concentrations of PFOA and PFOS in 1,240 pregnant women who participated in the Danish National Birth Cohort from 1996 to 2002. Blood samples were drawn from weeks 4 through 14 of pregnancy, and women were asked at approximately week 12 how long it had taken to conceive and whether the pregnancy was planned.

Median maternal blood levels of PFOA and PFOS were 5.3 ng/mL and 33.7 ng/mL, respectively. Women were assigned to four quartiles of exposure, with the lowest quartile serving as the reference group. Women in the three higher quartiles were about twice as likely to have taken longer than 12 months to achieve pregnancy or to have required infertility treatments to become pregnant, compared with the reference group. They were also slightly more likely to report irregular menstrual periods. The results, which are slated to appear in the May 2009 issue of *Human Reproduction*, were published online 28 January 2009.

The blood concentrations measured in the Danish women were similar to those found in other Western populations, "so the findings probably [are applicable to] other affluent Caucasian societies," says study leader Jørn Olsen, chairman of the Department of Epidemiology at the UCLA School of Public Health. However, "it's important for someone else to replicate the study in another group of women," he notes. It's unknown how PFOS and PFOA may contribute to infertility; it is possible the chemicals interfere with sex hormones, delay ovulation, or contribute to unrecognized miscarriage (the authors of the 2004 text *Clinical Gynecologic Endocrinology and Infertility, 7th Edition* estimate that 20–40% of women miscarry before they even realize they are pregnant).

The UCLA study "is the first study ever in humans on this topic, to the best of my knowledge," says David Savitz, director of the Disease Prevention and Public Health Institute at Mount Sinai School of Medicine in New York City. The study "gives a limited first look at the issue," Savitz says, "but does encourage continued evaluation of the reproductive toxicity of PFOA and PFOS."

In 2006 the U.S. Environmental Protection Agency (EPA) asked manufacturers to voluntarily reduce PFOA emissions and product content by 95% no later than 2010 and to eliminate the chemical by 2015. Olsen says the new data could help strengthen arguments to eventually regulate PFOA and PFOS or phase them out. Meanwhile, a study by Antonia M. Calafat and colleagues at the Centers for Disease Control and Prevention, published in the November 2007 issue of *EHP*, found significant reductions in human blood levels of PFOA and PFOS (25% and 32%, respectively) from 2003 and 2004 compared with data for 1999 through 2000. The authors of that study suggested that successful efforts by government and industry to reduce usage and emissions of these chemicals are the most likely reason for the downward trends. –Carol Potera

The Beat | by Erin E. Dooley

No Cap and Trade for Mercury

On 23 February 2009, the U.S. Supreme Court upheld a lower court ruling to dismiss a Bush-era appeal to support a controversial plan to establish a cap-and-trade program for mercury emissions. Most U.S. mercury pollution derives from coal-fired power plants, cement kilns, and incinerators. Utilities had supported the plan, believing it would foster innovation in pollution control; but critics argued that the tradable credits could enable polluters to actually increase their mercury emissions. The 1,100 facilities that would have benefited from the plan account for the largest unregulated industrial source of mercury pollution nationwide.

Lead: Down but Not Out

Public health efforts to reduce lead exposure have resulted in a dramatic drop in average blood lead levels for U.S. children. A report in the March 2009 issue of *Pediatrics* now concludes that the number of children with blood lead above the CDC's level of concern of 10 µg/dL has dropped by 84% since 1988. Although this estimate includes children in historically high-risk groups, the report also notes that levels continue to be disproportionately elevated in these groups—notably non-Hispanic blacks living in housing built before 1950. Indeed, most U.S. children continue to have low-level lead exposure. Because no safe blood level has been established for lead, the authors point to the need to continue identifying and managing sources of lead, the single most important step in controlling blood lead levels.

B Vitamins May Cut AMD Risk

Age-related macular degeneration (AMD) is the leading cause of blindness in elderly Americans. Recent research has associated levels of homocysteine—a metabolic by-product linked with meat intake and blood vessel damage—

istock photo/amygdala imagery; Joseph Tart/EHP

CHEMICAL TESTING

Developmental Immunotoxicity in Review

Much of the current knowledge regarding the adverse effects of environmental pollutants is based on laboratory evaluations performed using adult animals. But new clues now suggest that many diseases—including allergies, asthma, type 1 diabetes, atherosclerosis, leukemia, and autism—may originate in immune system damage caused by exposure to toxicants in early life, possibly even before birth. The routine conduct of safety screens on adult animals misses potential windows of unparalleled immune vulnerability in early life, writes immunotoxicology professor Rodney Dietert of the Cornell University College of Veterinary Medicine, in an invited review of the developmental immunotoxicity (DIT) literature published in the January 2009 issue of *Chemical Research in Toxicology*.

A central tenet of DIT is that the prenatal and perinatal immune systems are uniquely sensitive to toxic insult. For instance, prenatal exposure to dioxin causes immunotoxicity at a dose approximately 100-fold lower than the exposure that causes damage in adults, as Dietert and colleagues reported in the January 2006 *Journal of Toxicology and Environmental Health, Part B Critical Reviews*. Moreover, different immune processes are at work in different life stages. Disease-fighting T cells, for example, develop in the thymus during early life, but by adulthood are produced largely in other tissues. Also, some chemicals produce only transient immune system changes with adult exposure but produce lasting changes with fetal or early neonatal exposure.

Some safety screens are conducted across the life span, but DIT testing is usually initiated only after adult data suggest immunotoxicity. "Dietert's review makes the important point that DIT testing is a complementary approach to toxicology testing in adult immune systems and should be considered when developing immune systems are likely to be exposed to xenobiotics," says Fred Miller, chief of the NIEHS Environmental Autoimmunity Group. "However, DIT testing raises important questions regarding the appropriate doses, periods of exposure, and routes of exposure that should be tested at different phases of immune system development, all of which would depend on the expected human exposure."

Such questions regarding how to implement DIT testing have been debated worldwide for nearly a decade. But further work is needed to refine the details of screening protocols for DIT testing, says Susan Makris, a toxicologist with the Environmental Protection Agency. Screening procedures may need to be tailored to individual chemicals. "For example, consideration must be given to the pharmacokinetics of the chemical [how the chemical is metabolized] in terms of how it's being administered," she says. Otherwise, testing may not closely simulate real-world exposures.

Michael Holsapple, executive director of the Health and Environmental Sciences Institute at the International Life Sciences Institute in Washington, DC, says that what is really needed is development and implementation of DIT testing protocols, including studies to determine "triggers" that would prompt the implementation of such protocols. One such trigger might be the ability of a test compound to cross the placenta or be secreted in milk. "If the fetal or neonatal exposure seems so low as to be basically inconsequential, this could mean that DIT studies would be of little use in assessing risk," he explains. "These and many other considerations would seem to challenge the premise that DIT testing should become a global policy."

Once protocols are complete, regulatory change must occur across many agencies. "But even where there is agreement on what kind of testing needs to be done, implementing those studies, chemical by chemical, will be very much driven by the regulations that are enforced for each of those groups," says Makris.

Perhaps the biggest obstacle to normalizing DIT testing is that of finding reliable ways to generate clear evidence for an impact of early-life exposures on human health outcomes in adult life. "Discovering and characterizing the connections between chemical exposure during early-life stages and disease onset and progression during later-life stages will only come from developing and implementing DIT testing protocols," says Holsapple. "And the complexity of these protocols, if they are to cover the full gamut suggested by Dr. Dietert, will be considerable indeed." –Angela Spivey

with elevated risk of AMD. A report in the 23 February 2009 *Archives of Internal Medicine* now suggests that treatment with certain B vitamins—namely B_6, B_{12}, and folic acid—may ward off AMD by lowering homocysteine levels. Women assigned to the B-vitamin group had a statistically significant 35–40% decreased risk of AMD compared with controls. The association began to show up after about 2 years and persisted throughout the 7-year trial period.

Winners in Cooling the Planet

The winners of the U.K. Institution of Mechanical Engineers Cooling the Planet challenge were announced 5 March 2009. The competition was meant to inspire young scientists to develop engineering methods to reduce atmospheric greenhouse gas levels. The winner in the category of Mitigation—who also won the overall competition—proposed converting organic waste from landfills to biochar through a network of pyrolysis plants; the biochar, in turn, would enrich soils and sequester carbon [for more on biochar, see *EHP* 117:A70–A73 (2009)]. The winner of the Geoengineering category proposed a system of artificial "trees" covered with chemical scrubbers. The scrubbers would use lye to remove CO_2 from surrounding air. Calcium oxide would remove the CO_2 from the scrubbers, after which the developers propose underground storage.

Concept for artificial trees to capture atmospheric CO_2

Institution of Mechanical Engineers

A U.S. Ban for BPA?

Growing evidence links bisphenol A (BPA), an endocrine disruptor, to a range of adverse health effects. On 13 March 2009 companion bills were introduced into the U.S. House and Senate proposing to ban the use of BPA in all food and drink containers. Days earlier, 6 U.S. baby bottle manufacturers had announced they have stopped or plan to stop using BPA in bottles sold in the United States. However, at least one of the manufacturers has publicly stated its intention to continue selling BPA-containing baby bottles overseas.

EPA to Monitor Air Near Schools

Recent media coverage (e.g., *EHP* 116:A474 [2008]) has called attention to high levels of air pollution found around at least one in three U.S. schools. On 2 March 2009, the EPA announced a novel program to measure air pollution near 100 at-risk schools across the country, with monitoring to be performed by state, local, and tribal government personnel. The agency expects monitoring to begin at some schools as early as April 2009, and results will be made available to the public. Because children are more vulnerable than adults to the toxic effects of many pollutants, strategies to minimize their day-to-day exposure levels are urgently needed.