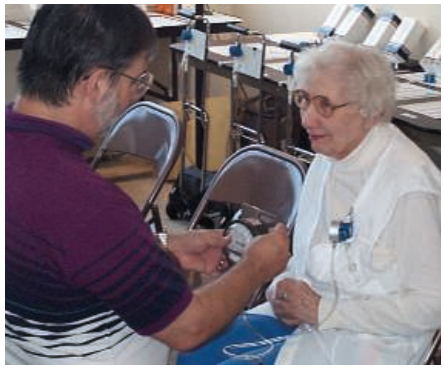
Particle air pollution clearly causes substantial deaths and illness, but what makes fine particles so toxic—the size, the chemical compound, or both?

# Mounting Evidence Indicts Fine-Particle Pollution

Talk about heart-stopping news: Spending time in traffic may triple some people's risk of having a heart attack an hour later. That's what German researchers reported last October in the *New England Journal of Medicine* (*NEJM*), based on responses from 691 heart attack survivors about their activities in the days before they fell ill. The study seemed to support the notion that tiny air pollution particles from tailpipes, along with stress, could help trigger a heart attack. Yet in another recent study in which volunteers in upstate New York breathed in lungfuls of these so-called ultrafines, particles less than 0.1 micrometer (μm) in diameter, the effects were minimal. If ultrafines were the main culprit, "you would have expected to see something more," says Daniel Greenbaum, president of the Health Effects Institute (HEI) in Cambridge, Massachusetts.

The discordant studies illustrate the dilemma posed by fine particle air pollution. The term refers to particles of dust, soot, and smoke consisting of hundreds of chemicals that are defined by their mass and size—2.5 μm in diameter or less, or about one-30th the width of a human hair. They are known collectively as $PM_{2.5}$. Hundreds of studies have suggested that breathing fine particles spewed by vehicles, factories, and power plants can trigger heart attacks and worsen respiratory disease in vulnerable people, leading to perhaps 60,000 premature deaths a year in the United States. In response, the U.S. Environmental Protection Agency (EPA) in 1997 added new regulations to existing rules for coarser particles ($PM_{10}$), issuing the first-ever standards for $PM_{2.5}$. But the move came only after a bitter fight over whether the science supported the rules and a mandate from Congress for EPA to expand its particle research program.



**At risk.** Studies with elderly volunteers have shown that slight changes in outdoor particle levels can change heart rate variability.

Now the issue is getting another look as EPA faces a December 2005 deadline for revisiting its $PM_{2.5}$ standard. EPA scientists, after reviewing piles of new data implicating $PM_{2.5}$ in health effects, have proposed tightening the 1997 standard to further reduce ambient concentrations of fine particles. Some scientists and industry groups remain skeptical, noting that researchers still haven't pinned down what makes particles dangerous—whether it's mainly size, and that the tiniest particles are most potent; or chemistry, such as metal content; or some combination of the two. Despite 8 years and some $400 million in research, finding out exactly how fine particles do their dirty work has proved frustratingly elusive, researchers say. "We've gotten glimpses, but we don't yet have enough systematic coverage of the problem," says epidemiologist Jon Samet of Johns Hopkins University in Baltimore, Maryland.

### Unmasking a killer

Although the evidence against fine particles, initially circumstantial, has grown stronger, gaps still remain. It began with epidemiologic studies finding that when levels of particulate matter (PM) edged up in various cities, hospital visits and deaths from heart and lung disease rose slightly, too. Two landmark studies

## How Dirty Air Hurts the Heart

A decade ago, most cardiologists never suspected that breathing tiny particles of soot and dust could damage their patients' hearts, let alone trigger a heart attack. Today "there's no doubt that air pollution plays a role in cardiovascular disease," says cardiovascular researcher Robert Brook of the University of Michigan, Ann Arbor.

Fine particles seems to affect the heart in two ways: by changing the heart's rhythm and by causing systemic inflammation. Many studies—from animal experiments to tests in which retirement home residents wore heart monitors—have shown that breathing particle pollution can slightly quicken the pulse and make the heartbeat less variable. The mechanism isn't yet known, but one possibility is that airway receptors stimulate nerves in the heart. A less variable heart rate, in turn, makes the heart more prone to arrhythmia (irregular heartbeat), which can presage cardiac arrest.

People don't usually die from arrhythmias unless they are very ill already, Brook notes. But particles also penetrate the lung's alveoli and cause inflammation and oxidative stress. The lung cells then pump proteins called cytokines into the bloodstream. This apparently sparks other immune responses that promote blood clot formation and the constriction of blood vessels. These effects, in turn, may cause deposits of lipids known as plaques to rupture and block blood flow to the heart. "If these things all come together, somebody who's vulnerable might be pushed over the edge" and have a heart attack, says epidemiologist Annette Peters of the National Research Center for Environment and Health in Neuherberg, Germany.

Over the long term, inflammation from breathing particles may also contribute to atherosclerosis, or hardening of the arteries, in the same way that secondhand tobacco smoke is thought to inflict





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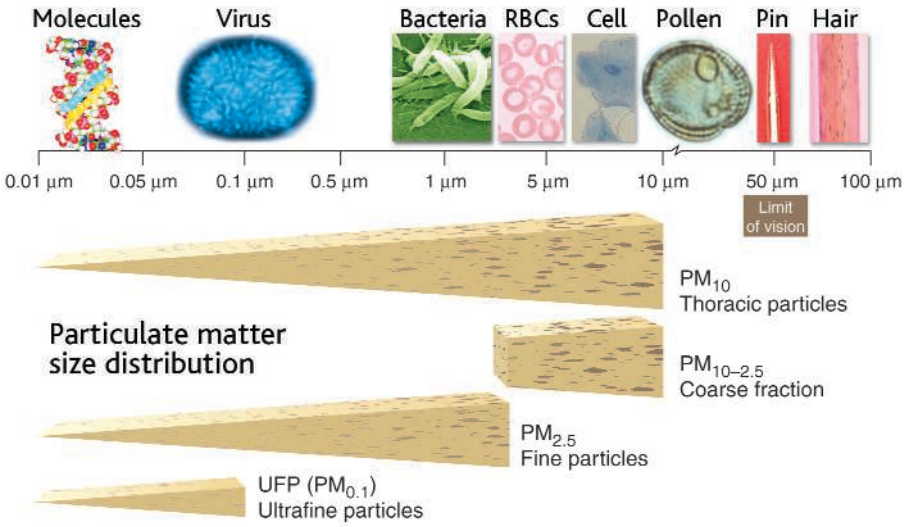
in the early 1990s that tracked more than half a million individuals in cleaner and dirtier cities for many years suggested that PM was shortening the lives of 60,000 people each year. EPA generally regulates air pollutants by chemistry—ozone, sulfates, and mercury, for example—but the 1970 Clean Air Act also regulates total particles. In 1987, EPA switched from controlling total particles to coarse particles 10 μm or less in diameter. These new observations suggested, however, that the rules, which are based on the total mass of particles (liquid or solid) with a diameter of 10 μm or less, weren't enough. The $PM_{10}$ rule was not catching fine particles that aren't readily expelled by the lungs and can penetrate deep into airways.

But when EPA proposed the $PM_{2.5}$ standards in 1996 (along with tighter ozone standards), industry groups and some scientists cried foul, arguing there was no direct evidence that these fine particles were killing people. Congress agreed to the regulations only on the condition that EPA would re-review the science before implementing the rule. Lawmakers also mandated that the National Research Council (NRC) oversee a long-term EPA particle research program funding both in-house scientists and extramural researchers.

Those and other new studies have firmed up the fine particle–death link. Larger studies and new analyses verified the key epidemiological studies, which held up despite a statistics software problem that lowered the short-term risks slightly. Deaths per day are now estimated to tick upward 0.21% for each 10 micrograms/meter$^3$ increase in $PM_{10}$ exposure, and long-term risks of dying rise 4% for each 10 μg/m$^3$ rise in annual $PM_{2.5}$. Similar patterns were reported in Europe: After Dublin banned soft coal in 1990 and levels of black smoke and sulfur dioxide (both contributors to PM) dropped, death rates from heart and lung disease declined as well. Another study found that people living near busy, polluted roads in the Netherlands had twice the risk of dying from a heart attack over an 8-year period than people living in cleaner areas. Although the epidemiologic studies cannot completely disentangle $PM_{2.5}$ effects from those of other pollutants, such as carbon monoxide, most researchers say the link with $PM_{2.5}$ is robust. "There's an association with particles that doesn't go away," says Greenbaum.




Meanwhile, the list of health effects linked to fine particles keeps growing. An American Cancer Society study found that chronic exposure to $PM_{2.5}$ is on par with secondhand smoke as a cause of lung cancer (*Science*, 15 March 2002, p. 1994). Particles of various sizes have been tentatively linked to low birth weight, preterm birth, and sudden infant death syndrome. A study last year in *NEJM* found that children who grow up in parts of southern California with higher $PM_{2.5}$, nitrogen dioxide, and acid vapor pollution levels have less developed lungs. Earlier this year came a report that the newborn babies of New York City mothers exposed to $PM_{2.5}$ containing higher levels of polycyclic aromatic hydrocarbons (PAH), a carcinogenic chemical, had more chromosomal damage that can later lead to cancer than did the babies of mothers with lower PAH exposures. Another report, published in *Science*, found that fine particles from traffic can cause DNA mutations in male mice that are passed on to their offspring (*Science*, 14 May 2004, p. 1008).

Others studies have tightened the link by showing that $PM_{2.5}$ can cause heart and lung health effects in lab animals with conditions such as heart disease that make them susceptible, as well as subtle effects in human volunteers. Studies in which heart monitors were attached to elderly people, for example, have found that their heart rhythm becomes less variable when outdoor particle levels rise—which makes the heart more vulnerable to cardiac arrhythmia. Researchers are now searching for the mechanisms behind this phenomenon (see sidebar, p. 1858).

### Mass confusion

But researchers are still grappling with what makes fine particles toxic. $PM_{2.5}$ consists of hundreds of liquid and solid chemicals, including carbon, nitrates, sulfates, metals, and organic compounds, produced by sources ranging from diesel

**Hardhearted.** The aortas of mice prone to atherosclerosis developed more lipid plaques (red) when they breathed concentrated particles for 5 months than did the same strain of mouse breathing clean air.

damage. For instance, a report in the 15 April 2005 issue of *Inhalation Toxicology* found that mice engineered to be prone to atherosclerosis develop lipid plaques over 57% more area in the aorta if they breathe concentrated ambient particles instead of filtered air for up to 5 months. "This is the first animal study mimicking" long-term exposures of people, says lead author Lung-Chi Chen of New York University.

Although particle pollution is a minor risk factor for heart disease compared to, say, high cholesterol, the impact is large because so many people are exposed. A recent examination of cause-of-death data from a long-term study tying particle pollution to mortality revealed that few extra deaths are from pulmonary disease; the majority are from cardiovascular disease. Citing the body of evidence, an American Heart Association scientific panel in last June labeled fine particles a "serious public health problem" and urged the Environmental Protection Agency to consider "even more stringent standards."

—JOCELYN KAISER

## Regulations Spark Technology Competition

The clampdown on particle air pollution in the United States (see main text) and similar regulations expected in Europe are forcing diesel vehicle manufacturers and industries to update technologies and look for new ones. "In the next 5 years, the diesel industry will clean itself up as much as the car industry has done in 30 years," predicts Richard Kassel, director of clean vehicle projects at the Natural Resources Defense Council (NRDC) in New York.

In the United States, efforts are mainly focused on trucks, buses, and larger diesel engines, which produce a major fraction of fine-particle emissions known as $PM_{2.5}$. Several Environmental Protection Agency (EPA) diesel regulations issued since 2000 will steeply reduce emissions by 2015. Besides requiring low-sulfur fuels, which reduce sulfates (a $PM_{2.5}$ component), the rules mandate that the heavy diesel fleet (including buses) be retrofitted with particle filters; EPA estimates costs at $400 to $1000 per vehicle. EPA expects that the majority of new diesel vehicles in 2007 will have particle filters. The devices generally work with a combination of a metal catalyst and a very hot multichannel trap in which soot particles burn off.

During the past 5 years, the U.S. diesel industry has put almost $5 billion into the development of better technologies. For example, researchers are working to find materials that are more resistant to the high temperatures needed to burn off the particles so the filters will last longer.

Car manufacturers are further ahead in Europe, where diesel cars are more common. The French company Peugeot launched its first diesel car with a catalyst particle filter 5 years ago; over 1 million Peugeots are now equipped with these filters, which burn off 99.9% of the particles. Mercedes-Benz also offers an optional filter in new diesel cars for 580 euros ($800). Some U.S. car manufacturers, such as Ford, are about to follow suit in anticipation of future regulatory requirements.

Industries that produce $PM_{2.5}$, such as coal-burning power plants, have the option of using off-the-shelf technologies—usually a combination of electrostatic filters and bag filters to catch the finest particles. These filters are quite expensive—in the range of $1 million to $2 million for a small power plant using low-sulfur fuel. Some U.S. plants are also adopting a newer device called an agglomerator, developed in Australia, that reduces emissions of both $PM_{2.5}$ particles and mercury, enabling them to satisfy two regulations. The agglomerator uses a so-called bipolar charger to separate the dust and give half of it a positive charge and the other half a negative charge. It then switches the charges and mixes the particles, which causes even the smallest particles to form agglomerates that are then easily captured by an electrostatic filter.

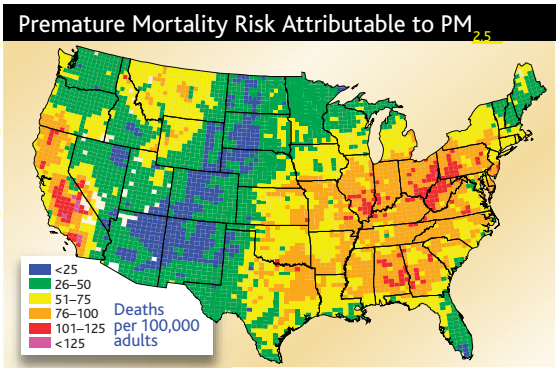
Utilities and other industries will need to install such technologies to comply with a March 2005 regulation to control nitrogen oxides, sulfur dioxide, and particles by 2010. As these and other new regulations controlling $PM_{2.5}$ emissions kick in, EPA predicts that $PM_{2.5}$ levels will fall 10% to 20% over the next decade. **–MARIE GRANMAR**

Marie Granmar is an innovation journalism fellow.

**Culprit.** The heavy diesel fleet in the U.S. is a major source of fine particles.

engines to soil blown from farmers' fields. But efforts to sort out which are the most potent components—or whether it's some combination of size and chemistry—have fallen short.

One reason is that in their animal studies, EPA and academic scientists have often used high doses of particle mixtures such as metal-laden exhaust from oil-burning power plants. These are convenient, but they differ from what people are exposed to. Researchers have also typically inserted the particles directly into the animals' tracheas, which isn't the same as inhaling them. And academic researchers who got grants from EPA have used different protocols or animal models, which makes it difficult to compare experiments to each other and to EPA's. "Lots of the research was relevant, but it wasn't systematic because of the nature of how we do research," says Samet, who chaired a final NRC review that last year pointed out this problem.




**Danger zones.** Risks of premature death from $PM_{2.5}$ pollution are highest on the West Coast and in the Midwest.

So far, the evidence on which components are the most dangerous remains confusing. Researchers have, at least, decided that crustal dust, particles on the large end of $PM_{2.5}$, seem fairly harmless. Particles of various sizes containing metals such as zinc and copper, on the other hand, can cause lung inflammation and heart damage in lab animals. The metals theory got a boost in 2001 from an unusual study. Researchers dug up stored air filters from the Utah Valley during the mid-1980s, when epidemiologists had observed a drop in hospital admissions for respiratory problems that coincided with a 1-year closure of a steel mill. The filters from when the mill was open were richer in metals, and these extracts caused more health effects in lab animals and human volunteers—suggesting that the metals explained the jump in hospital admissions. Still, in general, the amount of metals needed to see toxic effects in lab animals is much higher than the levels in the air people breathe, says EPA toxicologist Daniel Costa.

Other suspects seem relatively harmless when examined in isolation. Sulfates cause only minimal health effects in animals, and these acids don't seem linked to health effects in short-term epidemiologic studies. The power plant industry—which produces most of the sulfates—has cited these studies as evidence that they're not the problem. Yet sulfates are clearly associated with health effects in some studies following people over many years.

Others suspect that it's size that determines toxicity, and that ultrafine particles smaller than 0.1 μm in diameter are the culprits. Toxicologists have found that if coarser particles are ground up into ultrafines, they are much more toxic, most likely because the smaller particles have a greater surface area to react with tissues. And ultrafine particles can get into lung tissue and possibly the blood and even the brain. A few epidemiologic studies, such as the one last fall in *NEJM* on heart attack survivors from epidemiologist Annette Peters's group at the National Research Center for Environment and Health in Neuherberg, Germany, have pointed toward ultrafines, whatever their chemical composition, as the most toxic $PM_{2.5}$ component. Peters's study didn't find an association with ambient air pollution, only with time spent in cars, buses, trams, or on bicycles or motorcycles; traffic pollution contains more ultrafines than air in general. Yet when Mark Utell and Mark Frampton's team at the University of Rochester in New York had 28 resting or exercising volunteers breathe small amounts of carbon ultrafines, they saw only very slight

CREDITS (TOP TO BOTTOM): JUPITER IMAGES; DONALD MCCUBBIN/ABT ASSOCIATES USING 2002 $PM_{2.5}$ MONITORING DATA ADJUSTED FOR BACKGROUND LEVELS; RISK CALCULATION BASED ON POPE *ET AL.*, *JAMA* **287**, 1132 (2002)

changes in measures such as heart rhythm and white blood cells—even in asthmatics, whose damaged lungs contained up to six times as many particles as healthy people.

The explanation may be that it's not size or chemistry alone. The ultrafines used in the Rochester study were pure carbon black, but ultrafines in the real world are likely coated with metals and organic compounds, Frampton says. (Also, the researchers may need to test people with cardiovascular disease.) Likewise, sulfates may form the core of a particle that also contains nastier compounds such as metals, or they could change the chemistry of metals so they're more soluble in blood. Larger particles may irritate and inflame airways, exacerbating the toxicity of PM constituents such as organics and metals, says Costa. And particles may have different effects in the short term and after years of exposure. "It's far more complex than trying to decide which chemicals are toxic," says toxicologist Joseph Mauderly of Lovelace Respiratory Research Institute in Albuquerque, New Mexico.

Newer experiments are seeking to use more realistic mixtures. That became possible only a few years ago when researchers invented devices that can collect ambient air from outside a lab and concentrate the particles for use in experiments. Others are looking at pollutants from a range of sources. For example, Mauderly's group at Lovelace is conducting animal studies comparing particles from diesel engines, gas engines, wood smoke, cooking, road dust, and coal to pin down which type is most toxic. HEI, meanwhile, is sponsoring epidemiologic and toxicology studies that will take advantage of a new monitoring network at 54 sites that measures a finer breakdown of the chemicals in particles, such as sulfates, elemental carbon, and trace elements, than has been gathered previously. And EPA recently launched a $30 million, 10-year study led by University of Washington researchers that tracks correlations between these finer air pollution measurements and the health of 8700 people over age 50.

Down the road, this new information should help guide regulations—for instance, if carbon particles from wood burning were the main problem, or diesel engines, EPA could specifically target those sources. Controlling only mass, as EPA does now, might actually be counterproductive. For example, if larger $PM_{2.5}$ particle levels go down but levels of ultrafines do not, "that could make things even worse," Frampton says. That's because ultrafines tend to glom onto larger $PM_{2.5}$ particles, so they don't stay in the air as long when the larger particles are around.

### Time to act

Those results won't be available for years, however, and EPA is under a court order to decide whether to tighten the current $PM_{2.5}$ standard by the end of 2005. EPA scientists in January recommended that the agency consider tightening the standards from the current annual average of 15 μg/m³ to 12 to 14 μg/m³, and the daily average from 65 μg/m³ to as low as 25 μg/m³. They also suggested replacing the $PM_{10}$ standard with a new one for particles between $PM_{10}$ and $PM_{2.5}$ to better target coarser particles between those sizes. In April, EPA's clean air advisory board will weigh in.

$PM_{2.5}$ levels have already dropped at least 10% since 1999 due to acid rain regulations and new diesel engine standards (see sidebar, p. 1860). They will fall further thanks to additional cuts in sulfates and nitrates from coal-burning power plants through new regulations issued this month and possibly the Administration's proposed Clear Skies program. But a tighter standard could trigger additional controls in areas with the highest particle levels, such as Los Angeles and the Northeast. Environmental and health groups as well as many scientists say that, as with tobacco smoke and lung cancer, policymakers can't wait for all the scientific answers before taking action to prevent deaths from dirty air.

—JOCELYN KAISER

## U.S. Education Research

# Can Randomized Trials Answer The Question of What Works?

**A $120 million federal initiative to improve secondary math education hopes to draw on an approach some researchers say may not be ready for the classroom**

When Susan Sclafani and her colleagues in Houston, Texas, received a $1.35 million grant from the National Science Foundation (NSF) to work with secondary math and science teachers, nobody asked them to demonstrate whether the training improved student performance. "All we had to do was produce qualitative annual reports documenting what we had done," she says. Sclafani thought that wasn't nearly enough and that NSF should be more concerned about whether the project helped students learn. Now, a decade later, she's in a position to do a lot more. And that's exactly what worries many education researchers.

As assistant secretary for vocational and adult education at the Department of Education (ED), Sclafani is championing a $120 million initiative in secondary school mathematics that is built in part on money shifted from the same NSF directorate that funded the Houston grant. The initiative, included in President George W. Bush's 2006 budget request for ED now pending in Congress, will give preference to studies that test the effectiveness of educational interventions in the same way that medical researchers prove the efficacy of a drug. Randomized controlled trials (RCTs) of new approaches to teaching math, Sclafani says, will help school officials know what works, and they can then scale up the most promising new curricula and teaching methods. "Randomized studies are the only way to establish a causal link between educational practice and student performance," she says.

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**Prove it.** The Department of Education's Susan Sclafani wants to see more experimental evaluations in math and science education.

But some researchers say that such trials won't tell educators what they need to know. And they believe their discipline is too young to warrant a large investment in experimental studies. "Rushing to do RCTs is wrongheaded and bad science," says Alan Schoenfeld, a University of California, Berkeley, professor of math education and adviser to both NSF and ED. "There's a whole body of research that must be done before that."

The proposed math initiative at ED would be a competitive grants program to prepare students to take Algebra I, a gateway course for the study of higher mathematics and the sciences. Applicants will be encouraged to use RCTs and quasi-experimental designs to measure whether the reform works, Sclafani



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