HEALTH & CLEAN AIR
newsletter
Winter-Spring 2006

An Inconvenient Reality

All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

Sir Austin Bradford Hill,
"The Environment and Disease: Association or Causation?,"
Proceedings of the Royal Society of Medicine, 58 (1965), 295–300.

The wheels of science, like those of justice, grind exceedingly slow. Seldom does one study, or even two, categorically resolve contentious issues. Yet one recently published effort may do just that. In the process, it also highlights the virtual certainty that tens of thousands of avoidable future deaths and illnesses will occur if the Bush administration persists in its refusal to strengthen a key air quality standard.

The study focuses on the impact of $PM_{2.5}$, tiny pieces of soot, dust, liquids and other matter so small that 30 to 70 could be placed on the width of a human hair. We now know that these are a factor in about 2 percent of the nation's total mortality.[1]

The new study, "Spatial Analysis of Air Pollution and Mortality in Los Angeles," was contributed by Michael Jerrett of the University of California and a team of the field's most highly regarded researchers.[2] They analyzed a sub-group of 22,905 southern Californians drawn from a much larger study of 1.2 million subjects enlisted twenty years ago by the American Cancer Society (ACS). The subjects were enrolled in the study in 1982, and between then and 2000, there were 5,856 deaths. Jerrett compared each death with estimated long-term $PM_{2.5}$ concentrations at the location of each person in the cohort, or study group—this is probably the most finely tuned, highly resolved study ever conducted—and found that particle toxicity had previously been vastly underestimated: the death rates he found were at least two to three times larger than in previous studies using the ACS group.[a] As with all such stud-

[a] For example, the highest estimate from Pope et al. 2002 for all cause mortality is 6 percent. In the Jerrett et al. study, the percent increase for exactly the same model and exposure contrast is 17 percent (nearly 3 times as large). When neighborhood confounders are added to the Jerrett model, the risk is about 11 percent (nearly twice as large).

Jerrett established a link between higher levels of particles and increased rates of death from lung cancer and, especially in diabetics, heart attack, as well as a number of other causes and showed particles to be two to three times more toxic than previous analyses.

ies, Jerrett's findings must be replicated, which can be done in other large cities with sufficient data such as New York City and Boston. At the very least, however, Jerrett's findings are a persuasive, additional confirmation of the toxicity of fine particles, one that is consistent with other long term studies, as well as the short term analyses, laboratory work, and a raft of toxicological evidence in human and other subjects. Taken together, these paint a coherent picture of a major threat to public health, one that starts at birth—or perhaps before it—and continues throughout life.

Jerrett's findings do not change the total number of deaths attributable to fine particles. They do, however, show that people living in polluted neighborhoods are at much greater risk than previously believed. Because the analysis is so finely tuned—it examines mortality reduced to a 25 meter grid, which is very nearly a review of each individual death—and because of its coherence with the many other population, laboratory and toxicological studies, it effectively ends debate as to whether deaths are merely associated with fine particles or literally caused by them.

This larger ACS group has been examined before, once in 1995[3] and again in 2002,[4] to determine whether rates of death and illness were linked to concentrations of fine particles by comparing metropolitan areas to one another. Like the handful of other "longitudinal" studies in which changes in health outcomes are compared over time to assess whether they are connected to air pollution and, specifically, fine particles, the researchers found a clear linkage. Those who lived in cities with higher particle pollution died at higher rates from total, or "all cause" mortality, lung cancer and cardiopulmonary disease.[5] In the 1995 study, scientists were confident that the increases in deaths were not attributable to tobacco smoking, but they were unable to completely rule out "other unmeasured correlates of pollution."[6]

Kriging

Jerrett built on this work, but refined it.

First, Jerrett adapted a technique from the field of geostatistics to air pollution research. Called "kriging," it is a way of using data from monitors to estimate pollutant concentrations even at sites where there are no monitors.[7]

Second, Jerrett took into account 44 other "confounders," or potential causes of death and illness, such as tobacco smoking and diet.[b] Industry critics have claimed since studies linking air pollution to death and illness first began 36 years ago,[8] that factors such as these, not air pollution, might be responsible for deaths and illnesses.[9]

Third, Jerrett compared fine particle levels and rates of death between neighborhoods in a single metropolitan area, rather than between cities. By doing this, he was able to much more precisely determine air pollution levels.

That Jerrett established a link between higher levels of particles and increased rates of death from lung cancer and, especially in diabetics, heart attack, as well as a number of other causes, is unsurprising. Several other analyses had done the same.[10] Truly remarkable, however, was that Jerrett's analyses showed particles to be two to three times more toxic than previous analyses. Indeed, had Jerrett not found such increased toxicity, his results would have been viewed with some suspicion, because as exposure precision increases so, too, should the connection between cause and effect.

Because of the carefulness of his study, its elimination of confounders and the precision with which both health damage and fine particle levels were measured, Jerrett's work, in the view of some, revolutionizes the field of research on the death and illness caused by fine particles. Among those who share this view is the Newsletter's co-editor, Dr. David V. Bates (see For Expert Readers).

Bad Timing for Bush

The Jerrett results arrive at a time when the Bush Administration is refusing to tighten a key air quality standard, placing it and polluters on one side with public health advocates and the science community on the other.

The U.S. Clean Air Act of 1970 requires the Administrator of the U.S. Environmental Protection Agency to place limits on the amount pollution allowed in the nation's air.[11] These ambient air quality standards must protect sensitive populations—children and the

HEALTH & CLEAN AIR newsletter

The *Health and Clean Air Newsletter* is co-edited by Curtis Moore and David Bates, M.D. Reviewers include Drs. John Balmes, Bart Croes, Shankar Prasad and George Thurston. Correspondence may be addressed to HCAN, 1100 Eleventh Street, Suite 311, Sacramento, California 95814. Issues, abstracts and citations may be found at www.healthandcleanair.org

[b] Jerrett intentionally used the same individual covariate controls as the Pope et al. 2002 to promote comparison. The major difference in the level of confounding control related to the neighborhoods' "contextual" variables (e.g., poverty, race, unemployment, education), which were found to reduce the effects.

elderly, for example, in some cases and joggers and construction workers in others—with an adequate margin of safety.[12] The first health-based standards issued for soot and dust regulated "total suspended particulate matter," regardless of the size of individual particles.[13] As it became apparent during the 1970s and 1980s that smaller sized particles were the most dangerous, the Administrator established standards that focused on those ten microns or less, or PM_{10}, sometimes referred to as "inhalable."[14] By the early 1990s, scientists had zeroed in on particles of 2.5 microns or less, including the very smallest of them, called ultrafines.[15]

Standards for $PM_{2.5}$ were established for the first time in 1997, but industry lawsuits delayed enforcement to 2004.[16] However, the Clean Air Act requires health based standards to be reviewed and, if necessary, revised every five years.[17] The Administrator is under court order to issue a new rule for the particle pollution standards by September 27, 2006. The Agency published proposals on December 2, 2005.[c]

What Should be the Annual Standard?

The most contentious issue has been the level at which the annual standard should be set. Currently 15 micrograms per cubic meter ($\mu g/m^3$), EPA's Clean Air Scientific Advisory Committee and the Agency's own staff have recommended a tighter annual limit of 14 to 13 $\mu g/m^3$, and a daily limit of 35 to 30 $\mu g/m^3$. Health and environmental groups, including the American Lung Association, called for an even stronger annual standard of 12 $\mu g/m^3$,[18] which is the requirement in California.[19]

To establish standards for short-term exposures, the Agency relies on the findings of short-term studies, which correlate death and illness with changes in fine particle levels day-to-day or other brief periods. To establish an annual standard, the Agency looks to studies of particle impacts over longer terms, years or even decades. When fine particle standards were first adopted ten years ago, there were only three long-term studies—

- **The Harvard Six Cities Study:** A 1993 comparison of the levels of illness and death among the residents of six cities with varying pollution levels, this was the first large, prospective cohort study to demonstrate the adverse health impacts of long-term air pollution exposure.[20, 21] This study demonstrated that chronic exposure to air pollutants is independently related to cardiovascular mortality. In the group of 8,111 adults with 14 to 16 years of follow-up, the increase in overall mortality for the most-polluted city versus the least-polluted city was 26 percent. Of the 1,401 validated deaths, 646 were due to cardiovascular causes, which was the largest single category of increased mortality.[22]
- **ACS Cancer Prevention study:** The first nationwide examination of the American Cancer Society data in 1995 included approximately 552,138 adults who resided in all 50 states, this study linked chronic exposure to multiple air pollutants to mortality over a 16-year period.[23]
- **AHSMOG Study of Seventh Day Adventists in Southern California:** The Adventist Health and Smog (AHSMOG) study followed cancer incidence and mortality for six years in a group of 6,338 nonsmoking California Seventh-Day Adventists, comparing them to long-term, cumulative ambient air pollution. Again, as levels of particulate rose, so did deaths.[24]

As the U.S. Environmental Protection Agency (EPA) moved toward adoption of a fine particle strategy in 1996, industry mounted a massive campaign aimed at stopping the proposal in EPA, then within the Clinton Administration,[25] next the Congress and finally the U.S. courts, taking the case to the nation's ultimate arbiter, the U.S. Supreme Court.[26] There, by a vote of 9 to 0, the judges upheld the standards, as well as the Constitutionality of the Clean Air Act.[27]

In its efforts to prevent adoption of the standards,[28] industry enlisted sympathetic Senators including Richard Shelby of Alabama, who demanded that Harvard researchers not only reveal the names of the participants in their Six Cities study, but also disgorge confidential data.[29] The scientists refused, setting up an impasse. It was broken when the researchers agreed to allow the Health Effects Institute (HEI) of Cambridge, Massachusetts to undertake an independent reanalysis to see whether the data supported their conclusions on morbidity and mortality caused by air pollution.[30] HEI is funded one-half by the federal government and one half by the auto industry.[31]

Be Careful What You Wish For

In a classic case of the caution to "be careful of what you wish for, because you might get it," the re-analyses of ACS and Six Cities demanded by industry in an attempt to intimidate and discredit the original researchers had the opposite effect.

First, instead of undercutting the original work, the reanalyses bolstered it by reaffirming the quality of the science. Where there had once been only three

[c] The main provisions of the proposal are—

$PM_{2.5}$ 24-Hour Standard: The standard currently limiting daily concentration of fine particles size 2.5 µm or smaller to 65 $\mu g/m^3$ would be tightened to 35 $\mu g/m^3$.

$PM_{2.5}$ Annual Standard: The current $PM_{2.5}$ standard of 15 $\mu g/m^3$ would unchanged.

$PM_{10\text{-}2.5}$ 24-Hour Standard: A standard of 70 $\mu g/m^3$ is proposed for particles between 2.5 and 10 µm. The new $PM_{10\text{-}2.5}$ would include coarse particles that come from sources typically found in urban areas such as high density traffic on paved roads, industrial sources and construction activities. The standard would not cover coarse particles from such sources as windblown dust and soils, agricultural or mining sources.

PM_{10} 24-hour standard: The current daily PM_{10} standard of 150 $\mu g/m^3$ would be revoked, except in urban areas with a population of 100,000 or more.

studies of long-term impacts of air pollution, if the reanalyses are included, there were suddenly more, and their strength was greater.

Second, with the opportunity to revisit the original studies, those conducting the reanalyses were able to improve on them. Oil industry scientists, for example, had argued that the death and illness originally found might result from other air pollutants, a less healthy lifestyle in dirtier cities, or other confounding factors.[32] The team probed the data for more than 30 possible confounders, from altitude to health services, and tested the link "in nearly every possible manner" with various analytical techniques. The results still held.[33]

Third, because of the industry assault on science and the questions that it raised, Congress established and funded a major new research program to reduce scientific uncertainties about particles in the air and their health effects. The combination of new money—the National Academy of Sciences placed six-year spending at $300 million[34]—and the relative glamour of particle research, drew new researchers to the field and, with them, ingenious new approaches—Jerrett's use of kriging, for example.

Thus, roughly one decade after the process of setting the old standards for fine particles started in the mid-1990s, a vast amount of new information had been accumulated to aid in setting new standards. Still, most of this new evidence links day-to-day variations in outdoor particle concentrations to day-to-day changes in total and cause-specific mortality, and to variations in emergency and unscheduled admissions to hospitals. Another new body of evidence was devoted to understanding how particles could be so toxic—what, exactly, caused the deaths. Perhaps most importantly, the number of long term studies was considerably larger.

WHY IS THE JERRETT STUDY UNIQUE?

1. The study is based on members of the American Cancer Society longitudinal follow-up study who have lived in Los Angeles for about 20 years. Using individual residence data and combining this with ambient monitoring data adjusted by a method that takes account of all the monitors and weighs the average figure according to distance from the monitor ("kriging"), an exposure metric is assigned to each individual in the study group.

2. The study has shown that residences in highly polluted areas substantially increases the risks of both lung cancer and death from heart disease double to triple previous results from the ACS studies using cross-metro areas analysis.

3. The combination of individually calculated exposure data with health information from a 20-year longitudinal study (that is, one that involves observation of the same items over an extended period of time) is unique.

4. The individual risk factor measured was for particles that were 2.5 microns or less. The average annual level of this pollutant in the most contaminated area was only about 24 micrograms per cubic meter ($\mu g/m^3$). (This compares to the U.S. and California standards of 15 and 12 $\mu g/m^3$, respectively.)

5. Confounders, such as smoking and socioeconomic status, can be virtually excluded due to the care with which these were accounted for.

Long-term Studies Scarce

For very practical reasons, long-term studies examining effects of air pollution on mortality are much more scarce than those of day-to-variations. Long term studies take a great deal of time, and many researchers do not care to be tied for years or even decades to such efforts. They also are very expensive, and there are few institutions with both the money and patience to wait for results. Still, the number and quality of long-term studies available today is double perhaps even triple that of the mid-1990s. They include the following—

Six Cities Reanalysis. Using the same data and statistical methods as the original researchers at Harvard, the reanalysis team confirmed the original point estimates. The all-cause increase in death linked to fine particles was 28 percent, compared to the original calculation of 18.6.[5]

ACS Reanalysis. For the ACS Study, the increased risk of all-cause death associated with fine particles was 18 percent in the reanalysis, compared to 17 percent reported by the original investigators.[36]

In addition to the reanalyses, other long-term studies were conducted—

ACS Extended. The author of the 1995 analysis of the American Cancer Society study population, Arden Pope of Brigham Young University, built on not only his original work, but that of the reanalysis. He doubled the follow-up time from 8 to 16 years, which tripled the number of deaths that could be included. He expanded the ambient air pollution data substantially, including two recent years of fine particle data, and added data on gaseous co-pollutants. He also accounted for a number of potential confounders, such as fat consumption, while incorporating improved analytical techniques. He thus linked raised particle levels with increase in all-cause, cardiopulmonary and lung death rate increases of 4, 6 and 8 percent, respectively. The authors concluded that

their findings provided "the strongest evidence to date that long-term exposure to fine particulate air pollution common to many metropolitan areas is an important risk factor for cardiopulmonary mortality."[37]

AHSMOG 1999. The original Adventist Health Study of Smog (AHSMOG) study followed a group of 6,338 nonsmoking California Seventh-day Adventists who, for religious reasons, are nonsmokers, from 1977 to 1987. In 1999, researchers updated the study to follow the group through 1992. In the original analysis, they had been forced to estimate levels of inhalable particles, which are ten microns (PM_{10}). But in the update, data from pollution monitors were available. In men, increased particles were associated with a rise in lung cancer deaths of 138 percent and in both men and women exposure was associated with increased mortality from non-malignant respiratory disease of 12 percent. Because the participants completed extensive questionnaires when enrolled, a large number of potential confounders were accounted for.[38]

AHSMOG 2005. Another team of analysts returned to the AHSMOG group in 2005, examined 3,239 nonsmoking, non-Hispanic white adults who by this time had been followed for 22 years. Importantly, monitoring data was available for not only inhalable particles of 10 microns or less, but also for $PM_{2.5}$. Comparing monthly concentrations to mortality data, they found that as levels of $PM_{2.5}$ rose, the risk of death from cardiopulmonary disease increased 42 percent.[39, d]

ACS 2005. A team of eight researchers returned to the American Cancer Society to update it to include deaths to the year 2000. Not surprisingly, they confirmed previous findings. The increased risk of all cause and cardiopulmonary and lung cancer death rose 18 and 30 percent respectively, though that of lung cancer was 2 percent.[40]

These studies and more were reviewed by the U.S. National Academy of Sciences as part of a Congressionally-mandated effort to define research priorities after the industry-incited controversies. The review concluded, in the words of an Academy press release, that it—

- confirms the serious risks from exposure to particle pollution, including the most dangerous risk, premature death;
- cites evidence of new risks including negative effects on cardiac and reproductive health;
- underscores concern for susceptible populations, such as those with preexisting lung and heart disease, and diabetes, children, and older adults; and,
- cites findings from clinical and toxicological studies to explain the sickness and early death from lung and heart disease observed in earlier community health studies.[41]

Cumulatively Compelling Science

Cumulatively, these studies are compelling, and leave little doubt that levels of fine particles commonly encountered in virtually every metropolitan area in the United States are linked to death from lung cancer, heart attack, diabetes and other causes. Still, industry has resisted these conclusions, insisting that the case has not been adequately made.

Its advocates cite, for example, a year 2000 study of 50,000 veterans in which the authors concluded there was "no significant (positive) excess mortality risk for this cohort in any of the models considered."[42] One of the authors of this paper was previously manager of air quality at an electric utility company.[43] Another is Technical Executive of the Air Quality, Health, and Risk Environmental Group of the Electric Power Research Institute (EPRI), the research arm of power companies, many of which run particle-emitting coal fired electricity generating plants.[44]

CAUSES OF DEATH IN THE UNITED STATES, 2003

Heart disease	685,089
Cancer	556,902
Stroke (cerebrovascular diseases)	157,689
Chronic lower respiratory diseases	126,382
Accidents (unintentional injuries)	109,277
Diabetes	74,219
Influenza/Pneumonia	65,163
Alzheimer's disease	63,457
Fine Particles	**48,868**
Kidney disease	42,453
Septicemia	34,069
Suicide	31,484
Chronic liver disease	27,503
Renal disease	21,940
Parkinson's disease	17,997
Homicide	17,732
Total number of deaths	***2,448,288***

Source: National Center for Health Statistics, http://www.cdc.gov/nchs/data/hestat/finaldeaths03_tables.pdf#2

Strengths of the Jerrett Study

To the extent that doubts persisted, however, the work by Jerrett and that team ends them. It is worth reviewing a few of the study's many strengths.

- Other long-term studies compared changes in air pollution levels and death rates between cities. Jerrett compared these within a single metropolitan area, southern California.
- In the city-to-city studies the air pollution level for a metropolitan area would sometimes be an average, calculated from a small number of monitors. Jerrett had the advantage of being able to use the network of 23 fine particle and 42 ozone monitors in

[d] The AHSMOG analyses are, in some respects, a challenge to interpret. For example, in this examination, the risk of fatal coronary heart disease (CHD) increased 42 percent for all females for a 10 microgram per cubic meter increase in $PM_{2.5}$, but not males, whereas in 1999 males appeared to be at disproportionate risk. Increases in risk were also found, again in females, as concentrations of $PM_{10\text{-}2.5}$ and PM_{10} rose. Thus, a positive association with fatal CHD was found in the 2005 AHSMOG with all three PM fractions in females, but not in males.

southern California, which is arguably the world's best.

- Because the number of monitors in most city-to-city comparisons is small, researchers have no mechanism with which to calculate missing data. Jerrett, who was originally trained in geography, was familiar enough with kriging to employ it and thus further improve the monitoring data.[45]
- Some of the long-term studies—Six Cities and AHSMOG, for example—have relatively small population study groups. The American Cancer Society cohort, however, was 1.2 million at the outset, and the subset in southern California was 22,905, compared to 8,111 in the Six Cities study[46] and 9,785 in AHSMOG.[47]
- Although all epidemiological studies attempt to account for potential confounders, the American Cancer Society was able to do so in an unusually comprehensive way, in part because it relied on the Society's cadre of well educated and dedicated volunteers. ACS volunteers throughout the nation enrolled roughly 1.2 million friends, neighbors and acquaintances. Enrollees had to be age 30 or older and live in a household with at least one person aged 45 or older. Participants completed a confidential questionnaire that included information on age, sex, weight, height, smoking history, alcohol use, occupation exposures, diet, education, marital status and other characteristics. It was principally these data that allowed for analysis of possible confounders.
- To the extent that metropolitan areas could be further subdivided in the city-to-city studies, the smaller segments nevertheless remained quite large. Jerrett, in contrast, was able to sort data according to 267 zip codes.

What emerges from all this is a study of extraordinary precision and compelling persuasiveness, showing that for an increase in the level of fine particle pollution by 10 micrograms per cubic meter (10 µg/m^3), or one millionth of a gram, deaths of many sorts rose in lockstep. Total, or all-cause, mortality rose 11 percent, while death due to ischemic heart disease, or blockage of the arteries, rose by 25 percent.

It would seem sensible that if death and illness increase with air pollution levels, they would decline as control measures are adopted. Studies bear this out.

Intervention Studies

One way of determining the impact that reductions can have in human terms is through an "intervention" study, which seeks to determine whether declines in air pollution are linked to improvements in health outcomes. While unusual, intervention studies are extraordinarily valuable because they can demonstrate that reducing air pollution saves lives and avoids illness. One such study has been conducted by Francine Laden, of the Brigham and Women's Hospital at Harvard Medical School in Boston who extracted data from the Six Cities Study.[48]

DIABETICS AT RISK

One of the most remarkable findings in the Jerrett study was the link between fine particles and death from either diabetes,[a] which rose 82 percent, or endocrine disorders, which jumped 149 percent. Two other studies have also found that the risk posed by air pollution to diabetics is substantially higher than that for non-diabetics. Indeed, the acute risk for cardiovascular events in patients with diabetes mellitus may be two-fold higher than for non-diabetics.[b]

The explanation for this severe impact on diabetics may be provided by a study of the impacts of fine particle sulfate (which comes mainly from coal-burning power plants) and black carbon soot particles (which are generated primarily by diesel- and gasoline-powered vehicles) on 270 Boston-area residents.[c]

The subjects were divided into two groups, one with a positive diagnosis of type I or type II diabetes, the other of subjects who were not diabetic, but with a family history of diabetes or blood sugar levels slightly higher than normal. Blood to an arm's main artery was cut off using a pressure cuff, then released and the flow monitored by ultrasound. When sulfate and black carbon levels were higher, the blood flow, or vascular reactivity, fell 11 and 13 percent, respectively.

Whatever the cause, the increased susceptibility of diabetics is of special concern because rates of the disease are rising sharply: between 1991 and 2002, its incidence jumped 61 percent, afflicting rough 7 percent of the population.[d]

[a] Diabetes is a metabolic disorder in which blood sugar levels are elevated because levels of insulin are too low. Insulin is the hormone needed to process sugars and starches into energy. Diabetes is widely recognized as one of the leading causes of death and disability in the United States, affecting some 13.3 million Americans.

[b] Zanobetti A, Schwarts J. Are diabetics more susceptible to the health effects of airborne particles? Am J Respir Crit Care Med. 2001; 164: 831–833. and Goldberg MS, Burnett R, Bailar JC, et al. The association between daily mortality and ambient air particle pollution in Montreal, Quebec: 2: cause-specific mortality. Environ Res. 2001; 86:26–36.

[c] National Institutes of Health, "People with Diabetes More Sensitive to Cardiovascular Effects from Air Pollution," May 31, 2005, http://www.nih.gov/news/pr/may2005/niehs-31a.htm

[d] Centers for Disease Control and Prevention, "New State Data Show Obesity and Diabetes Still On the Rise," http://www.cdc.gov/od/oc/media/pressrel/r021231.htm.

An increase in the level of fine particle pollution by 10 micrograms per cubic meter, or one millionth of a gram, deaths of many sorts rose in lockstep. Total mortality rose 11%, while death due to ischemic heart disease, or blockage of the arteries, rose by 25%.

In "Association of Fine Particulate Matter from Different Sources with Daily Mortality in Six U.S. Cities," Laden and her colleagues provide direct, specific evidence that reducing fine particle pollution below the current legal limit of 15 µg/m^3 was linked to a decrease in mortality.[49] It is this limit that the Bush Administration plans to leave unchanged.[50]

Specifically, this study, published in January 2006, shows that decreases in $PM_{2.5}$ exposure from levels at or below 15 µg/m^3 in two of the six cities were associated with a decrease in mortality. Another study, this one in Dublin, Ireland, produced comparable results. There, residential coal burning was a dominant source of fine particles. After coal sales were banned on September 1, 1990, there was an "immediate and permanent" reduction in soot levels of about 70 percent. When researchers compared mortality rates before and after the ban, they found a decline in all cause, respiratory and cardiovascular death rates of 5.7, 15.5 and 10.3 percent respectively.[51]

Implications of the Laden Work

The Laden study is provocative for another reason as well, and extremely relevant to EPA's proposed retention of an annual average of 15 µg/m^3.

The two cleanest cities in the Six Cities study in 1979 were Portage, Wisc. and Topeka, Kan., followed by Watertown, Mass. By 1998, Portage was still the cleanest, while Watertown was very slightly less polluted than Topeka.

In 1979, the average $PM_{2.5}$ level in Portage was about 12.5 µg/m^3 in Portage; very slightly below 15 in Topeka; and, about 17.5 in Watertown. By 1999, levels fell to about 8 µg/m^3 in Portage; and, about 13 in Watertown and Topeka. In other words, Portage started with $PM_{2.5}$ levels below the current annual average, Topeka almost was exactly on it and Watertown somewhat above it. Portage is now roughly one-half the current annual standard, while Watertown and Topeka are about 1.5 µg below it.

For the 1974–89 period, the relative risk (RR) for mortality in Portage was 1.00, and 1.06 for Topeka and Watertown. The RRs for the 1990–98 period were 1.00 for Portage, 0.82 for Watertown and 1.01 for Topeka. Thus, in Topeka which started with an annual average below the standard, there was a decline in mortality. Similarly, by 1990, Watertown's ambient levels had dropped below 15 µg/m^3, and there was a decline in mortality there from a 1974–89 RR of 1.06 to a 1990–99 RR of 0.67.

In other words, it appears that in Watertown, a reduction in ambient levels of $PM_{2.5}$ from about 15 µg/m^3 to about 13, or about 2 µg/m^3, resulted in about a 22 percent decrease in the relative risk of death. Laden's work is very suggestive of a death effect below 12 µg/m^3.

Unlike 1996–1997 when most toxicologists were at a loss to explain exactly how fine particles might be sending people to hospitals and morgues, the findings of Jerrett and Laden come when studies on the toxicology of fine particles have begun to unravel the mechanisms. There is remarkable coherence between these and the epidemiological studies.

Whatever their effects, particles must first enter the body through our lungs, or more accurately, the respiratory tract, which serves two purposes: to transfer oxygen to red blood cells, and remove from them the waste gases, principally carbon dioxide. It is shaped like an upside down tree, stout at the trunk—the trachea—dividing into progressively smaller branches (the bronchus and bronchioles, which have cartilage, thus providing the lung with some stiffness and shape). Finally, there are the leaves or, in the case of the lung, alveoli, so small that between 274 and 700 million of them are in a human lung.[52] This is where the actual gas transfer occurs.

At the Air-Blood Barrier

Only one cell thick and in very close contact with each other, the cells lining the alveoli and the surrounding capillaries average about 1 micron in size. Oxygen passes through this air-blood barrier quickly and into the blood in the capillaries. So, too, do particles, or at least the smallest of them, traveling with the oxygen-rich blood to the left side of the heart, where it is quickly pumped throughout the body.[53]

Exactly what happens next is unclear. It is certain that particles from combustion and other human sources possess toxic properties. Exposure to non-crustal $PM_{2.5}$ is followed by increased heart rate[54] and blood viscosity,[55] as well as a wide range of other responses. Some of these are immediate, while others occur over time. While not benign, crustal particles do not approach the toxicity of those from diesel engines, coal-fired power plants and other combustion sources.[56]

Explaining this toxicity is a challenge, but a vast difference between the current standard-setting process and that in the mid-1990s is that today there are several plausible biological explanations. Ten years ago, scientists were at a loss to demonstrate how things so small might possess such a lethal effect. Of the plausi-

ble explanations for how particles kill and sicken, two of the most important are—

- Restructuring of the respiratory and circulatory systems.
- Inflammation-induced changes in heart function and blood composition.

Inflammation is a complex, major response of the immune system to tissue damage and infection. Chronic inflammation can result in remodeling of the artery wall in atherosclerosis; the bronchial wall in asthma and chronic bronchitis, and the debilitating destruction of the joints associated with rheumatoid arthritis, an inflammatory disease.[57] Thus, long-term inflammation can cause permanent, irreversible change in the body. White blood cells, for example, whose numbers increase in response to fine particles, release cytokine proteins that attack viruses. But cytokines can also attack the body as well: one, for example—tumor necrosis factor—will kill cancer cells, but also can cause rheumatoid arthritis.[58] Several cytokines can also affect the hypothalamus, which acts like the body's thermostat. When these cytokines bind to receptors in the hypothalamus, body temperature goes up, and the entire body labors under the burden of inflammation.[59]

Particles Trigger Cytokines

It is quite clear that fine particles trigger lung production of cytokines that "contribute to the local and systemic inflammatory response," in the words of one group of researchers.[60] Data from the Third National Health and Nutrition Examination Survey (NHANES III),[61] which collects information on the health and nutritional status of Americans, found that PM_{10} was associated with elevated levels of fibrinogen, platelet and white blood cells, which are markers of cardiovascular risk.[62] Volunteers breathing diesel soot in the laboratory displayed "well-defined and marked systemic and pulmonary inflammatory response," in the words of the researchers.[63] Other studies have found increased indicators of inflammation—fibrinogen levels,[64] platelet and white blood cell counts[65]—for example, as well as pulmonary injury and neutrophilic inflammation.[66, 67]

People become vulnerable to short-term spikes in fine particles not because they are young or old, diabetics or emphysmatics, but merely because they breathe.

One of the most troubling possibilities is that long term exposure to fine particles—or perhaps to repeated surges over a shorter period—turns an otherwise healthy person into one who is in a "sensitive" group. If so, people become vulnerable to short-term spikes in fine particles not because they are young or old, diabetics or emphysmatics, but merely because they breathe. Those with coronary heart disease are particularly vulnerable to rises in fine particle levels.[68] So are people with chronic obstructive pulmonary disease (COPD),[69] in which the lungs are so damaged, usually from smoking, that inhaling and exhaling is difficult.[70] A more difficult question, however, is whether air pollution in general, and fine particles in particular, actually cause heart and lung diseases. The evidence suggests that the answer to this question may be yes.

Do Particles "Create" Sensitive Groups?

Consider, for example, the changes in arteries that occur in those exposed to fine particles over long periods. Blood flows from the heart to the brain through the carotid arteries, which are in the neck. With age—and due to some factors, such as smoking—the carotid arteries narrow, increasing the chance of heart attack and ischemic stroke, the most common form.[71] Narrowing of the carotids can be measured by thickness of its intima-media wall (IMT). The measurement is simple and painless, using ultrasound.

IMT is an early marker of atherosclerosis, a general term for the thickening and hardening of arteries, caused when fat, cholesterol, cellular waste products, and other substances accumulate in an artery.[72] Not surprisingly, increased IMT is, in the words of one team of researchers, "directly associated with an increased risk of myocardial infarction and stroke in older adults without a history of cardiovascular disease."[73]

Between 1996 and 2003, scientists measured IMT in 445 men and 356 women aged 40–89 with an average age of 59 years. Individually assigned $PM_{2.5}$ exposures varied from 5.2 to 26.90 µg/m^3 with a mean of 20.3 µg/m^3—again, below the 24-standard proposed by the Environmental Protection Agency. After correction for all known factors, there was a strong association between $PM_{2.5}$ exposure and the degree of IMT.[74] In another study, scientists analyzed data from 798 participants in two clinical trials. After excluding those with diabetes, elevated blood pressure, thyroid disease, life threatening diseases, high alcohol intake and some other conditions, they found that as levels of fine particles rose 10 µg/m^3, IMT increased between 3.9 and 4.3 percent.[75]

Particles Linked to COPD

The evidence in support of the notion that fine particles actually cause COPD, the nation's fourth leading cause of death,[76] is less compelling, but it nevertheless exists. Occupational exposure to fine particles can cause COPD.[77, 78] So, too, can indoor air pollution.[79] Animals exposed in the laboratory to mineral particles developed airway wall fibrosis, a process that can lead to COPD.[80,81]

When 4,379 people who had lived for at least 11 years in a high photochemical pollution area were compared to 2,287 residents of lower pollution regions, the risk of "definite" COPD increased 15 percent in the area with dirtier air after adjusting for sex, age, race, education, occupational exposure, and past smoking history.[82] Researchers in Germany examined the health history of 4,757 women who lived in the industrial Rhine-Ruhr Basin. As the five-year average of PM_{10} rose by 7 $\mu g/m^3$, COPD increased 33 percent. Among those living within 100 meters of a busy road COPD was 1.79 times more likely than for those living farther away.[83]

Taken together with the city-to-city studies, and the time series analyses that compare air pollution changes on daily or weekly bases with death and illness, together with the toxicology studies, the result is a body of evidence that satisfies the nine cardinal requirements expressed by Sir Austin Bradford Hill for establishing causality: strength, consistency, specificity, temporality, dose-response, plausibility, coherence, experiment, and analogy.[84] In short, any remaining doubt that fine particles cause death and illness—and are not merely associated with these outcomes—is a scintilla.

Administrator Rejects Advice of Staff and Science Panel

In the face of this body of evidence, the Administrator of the U.S. Environmental Protection Agency is not only rejecting the advice of his own staff and that of the Clean Air Scientific Advisory Committee by refusing to tighten the annual standard, but proposing to weaken the requirements in several respects.

This is all the more remarkable because over 60 percent of the U.S. population currently lives in an area with fine particle pollution higher than what the law allows. That is unlikely to change. When EPA estimated the levels of $PM_{2.5}$ that would prevail in the year 2020 if emissions limits on diesels, a major source of fine particles, were tightened, it concluded that approximately 56 million people (42 percent of the total U.S. population) will live in areas in 2020 where long term ambient fine particulate matter levels are predicted to be at or above 16 $\mu g/m^3$ after taking emission reductions from the rule into account.[85]

The toxicological evidence fits very nicely with the Jerrett and Laden studies. Fine particles may have short-term impacts that, over time, result in permanent damage, ultimately leading to death. Uncertainties remain, but they have become fewer and fewer.

For those seeking to avoid a tightening of the standards for fine particles, these findings and especially those of Jerrett, Laden and their colleagues, arrive at an inconvenient time. The Clean Air Act, however, was not written for the convenience of polluters, but for the health of Americans. As Sen. Edmund S. Muskie (D.Me.), the law's principal drafter, explained during Senate debate in 1970—

> *The first responsibility of Congress is not the making of technological or economic judgments—or even to be limited by what is or appears to be technologically or economically feasible. Our responsibility is to establish what the public interest requires to protect the health of persons.*[e]

That is still the law.

REJECTION OF CASAC RECOMMENDATIONS

On Feb. 10, 2006, Jeff Young of National Public Radio's program Living on Earth, *interviewed the chair of CASAC, Rogene Henderson:*

Young: (M)embers of the EPA's own Clean Air Science Advisory Committee, CASAC, as it's known, recommended a lower level—somewhere between 12 and 14—for long-term particle emissions. Congress appointed the diverse panel of experts to give EPA rigorously researched and unbiased scientific advice. Committee chair Dr. Rogene Henderson says this is the first time an EPA administrator has not followed that advice.

Henderson: I was surprised and disappointed that the administrator did not choose to follow our recommendations. We're in uncharted waters here. This has never happened before here.

Young: EPA's proposal also would not regulate or even monitor coarse particle dust in rural areas. It would exempt from regulation dusty activities like mining and agriculture. Henderson says the proposal makes it sound as if that idea came from her committee.

Henderson: The CASAC committee did not say that. We recommended monitoring in both urban and rural areas and at no time did we ever mention the mining industry.

Source: Living on Earth, http://www.loe.org/shows/segments.htm?programID=06-P13-00006&segmentID=1

[e] U.S. Senate Committee on Public Works, *Legislative History of the Clean Air Act Amendments of 1970*, 93d Cong., 2nd Sess., 1974, Committee Print (Washington, D.C., U.S. Government Printing Office, 1974) 358.

by David V. Bates, CM, MD, FRCP, FRCPC, FACP, FRSC

Some time ago I commented that every so often an article hits the desk, and you realize that the world has turned. This happened in early November, 2005 when the journal, *Epidemiology*, published a mortality analysis from Los Angeles. The study is concerned with the impact of $PM_{2.5}$.

Michael Jerrett of the University of Southern California had been interested to see how one might combine residential data with the geographic location for ambient air pollution monitors. He used a "kriging" technique exploited by Zidek, to compute the probable air pollution exposure for any specific residential location. He had previously applied this method to a study of regional residential locations in the city of Hamilton in Ontario. [Those interested in the universality of science (nature is indivisible) might note that this method had been developed in South Africa to locate probable ore concentrations in a total region from geographically dispersed drill locations.]

Jerrett and his colleagues then analyzed the overall $PM_{2.5}$ exposure which one would expect from the residential location of the individual who had been enrolled in the study and subsequently died of lung or heart disease. Specifically, they also noted the mortality from lung cancer. They reported that for an increase in fine particle pollution by 10 $\mu g/m^3$ (or one millionth of a gram), all cause mortality rose by 11 percent, deaths due to ischemic heart disease rose by 25 percent, and lung cancer deaths rose 20 percent. They confirmed previous observations that people with diabetes were at higher risk, which is not surprising since higher rates of blood pressure and an earlier incidence of vascular disease are both known to occur in this condition.

(The effect on diabetics gives rise to special concern, because it is believed that the incidence of diabetes in the United States has jumped 61 percent between 1991 and 2002. It now involves 7 percent of the population, who would clearly qualify as susceptible under the Clean Air Act.)

The Jerrett study has shown, beyond question (except by interested parties), that living in a city where the $PM_{2.5}$ levels from vehicle emissions have an annual value of 24 $\mu g/m^3$, is accompanied by an unacceptable increase of risk from dying of heart disease or lung cancer. The $PM_{2.5}$ value of 24 $\mu g/m^3$ is exceeded in most, if not all, cities around the world.

The findings from this study have arrived at a time when the Bush Administration is refusing to tighten the annual limit of $PM_{2.5}$ on the grounds that there is disagreement as to how stringent these levels should be. In a "first" in the fog of air pollution control, the EPA administrator has refused to listen to the advice of the Clean Air Scientific Committee of EPA, which was established by Congress to ensure that sufficient attention was paid to the flood of information coming from the scientific side of the constituency.

There is now a mass of confirmatory data, both in relation to mechanisms and in relation to adverse effects short of direct mortality. Work at the Harvard School of Public Health five years ago indicated clearly that it was the particles from combustion sources in $PM_{2.5}$ that were most closely associated with the advanced mortality that had been documented from the Harvard Six City longitudinal study.

That the exposure to $PM_{2.5}$ is followed by responses short of mortality has been demonstrated in a number of studies. In one study from North Carolina, the patrol cars of nine state troopers working the 3 p.m. to midnight shift were fitted with continuous air pollution monitors. The patrolmen were hooked up to electrocardiograms, with recordings kept throughout the shift and the following morning. Blood samples were drawn 14 hours after the shift ended. It was found that the C-reactive protein in the blood in these samples rose as the level of $PM_{2.5}$ which had been recorded, went up. In addition, the heart beat cycles were affected and the number of ectopic beats increased. The $PM_{2.5}$ averaged 24 $\mu g/m^3$ and ranged from 7.1 to 38.7. The subjects were middle-aged, symptom-free males.

An effect of $PM_{2.5}$ on heart rate variability has been shown in a number of studies, including one of 34 elderly residents of Mexico City, and of 88 elderly nonsmoking residents of Utah, in the USA, where higher levels of $PM_{2.5}$ not only affected heart

Worth Noting

Infant Mortality

Although most attention in the debates over the death effects of air pollution tends to focus on adults, the body of evidence that children are at special risk continues to grow. One of the latest additions to the literature found that as concentrations of $PM_{2.5}$ rose by 10 micrograms per cubic meter, a relatively minor variation, postneonatal deaths rose as well. (Postneonatal mortality is defined as those deaths that occur after the first 28 days of life, but before the child reaches age one.) The increase in all cause, or total, deaths was 7 percent, while the increase in mortality for respiratory causes was 128 percent.[86]

This is by no means the first study to link infant death with fine particles. The first such study, which examined death and pollution data in the Czech Republic, was published in 1999.[87] A study of Seoul, South Korea residents produced similar results, causing the team to conclude that their "results agree with the hypothesis that infants are most susceptible to PM_{10} in terms of mortality, particularly respiratory mortality."[88]

Yet another examination, this one of 23 U.S. metropolitan areas, found that the increases in neonatal all cause and respiratory mortality were 6 and 24 percent, respectively. The authors noted that about approximately 75 percent of deaths were in areas where the fine particles levels were at or below the then-new $PM_{2.5}$ standard of 15 micrograms per cubic meter, and concluded that "Even if all counties would comply to the new $PM_{2.5}$ standard, the majority of the estimated burden would remain."[89]

rate variability but also caused an increase in blood levels of C-reactive protein, believed to be indicative of a higher risk of heart attacks and stroke. A direct effect of $PM_{2.5}$ on increasing blood pressure was found in Boston in 42 men and women with heart disease.

Another type of observation suggests that exposure to $PM_{2.5}$ has something to do with an accelerated rate of formation of thickening of the walls of arteries. The carotid arteries, which are in the neck, are affected by this process, and it is known that cigarette smoking, as well as age, cause the arteries to be narrowed. It is believed that when this occurs, so does the risk of a heart attack, and of course of a cerebral thrombosis or stroke. A new technique has permitted the direct measurement of the thickness of the intima wall of the carotid vessels (IMT). Using ultrasound, this is both simple and painless, and free of risk. In one retrospective study, it was shown that IMT increases with both ageing and smoking. In measurements of IMT in 445 men and 356 women aged 40–89 and averaging 59 years of age, it was possible to assign average $PM_{2.5}$ exposures from 5.2 to 26.9 $\mu g/m^3$, with a mean of 20.3. After correction for all known factors there was found to be a significant association between the average level of $PM_{2.5}$ exposure and the advancement of IMT, such that as levels of $PM_{2.5}$ rose 10 $\mu g/m^3$, IMT increased between 3.9 and 4.3 percent.

It would be fair to conclude that the issue of current $PM_{2.5}$ exposure was pretty well settled, and fully justified the conclusion of a 2004 Review by the National Academy of Sciences:

> *It is becoming more evident from clinical and toxicological studies that ambient fine PM induces respiratory and cardiovascular events that in susceptible, compromised people can explain the morbidity and mortality observed in epidemiological studies. Research has documented that components of hypothesized mechanistic sequences do actually take place, supplying a biological basis for explaining some effects of PM observed in susceptible subpopulations.*

The matter of particulate pollution is currently under review by the World Health Organisation, poised to issue its recommended Guidelines of Air Pollution on the basis of health effects. Its conclusions are eagerly awaited, and may do something to dissipate the current fog on the other side of the Atlantic.

Worth Noting

continued from previous page

The most recent study is significant, in part, however, because it was in California, where the composition of fine particles differs from much of the rest of the United States. In California, fine particles are dominated by localized vehicle and agricultural emissions, while in most of the rest of the nation, the pollutant mix is regional and contains large quantities of pollution, especially sulfate, from coal burning.

Heat Waves and Deaths from Smog and Soot

The formation of ozone, or smog, is directly linked to temperature. As heat increases, so too does the formation of smog (assuming the precursor pollutants like oxides of nitrogen and unburnt gasoline are in the air). There is a similar relationship between fine particles and temperature, although perhaps not quite as pronounced. Of course, both pollutants kill people.

As global warming has begun to tighten its grip on the world, temperatures have risen and, not surprisingly, so have heat waves. When people die in stifling heat, what kills them? Smog and soot, or heat?

Some of Europe's leading researchers attempted to answer this question by studying the heat wave in the summer of 2003 in which deaths were as many as 1,000–1,400 people above average in The Netherlands alone.

When Paul H. Fischer and his colleagues examined the air pollution concentrations they found that levels of both fine particles and ozone had been driven up by the heat: average daily 8- hour ozone concentrations in June–August 2003 were 87 micrograms per cubic meter, compared to 71 (43.5, 35.5 and 30.5 ppb, respectively) in 2002 and 61 in 2000 (considered by the Dutch Royal Meteorological Institute (KNMI) as the most recent year with an 'average' summer). Similarly, the average weekly levels of PM_{10} were 35 micrograms per cubic meter in 2003, compared to 33 in 2002 and 31 in 2000.

After carefully disentangling the effects of pollution from those of heat—a truly formidable challenge for biostatisticians—the group concluded that 400 to 600 of the 1,000 to 1,400, or roughly 4 of every 10 deaths—were caused by smog and soot.[90]

1100 Eleventh Street, Suite 311
Sacramento, CA 95814

HEALTH & CLEAN AIR newsletter