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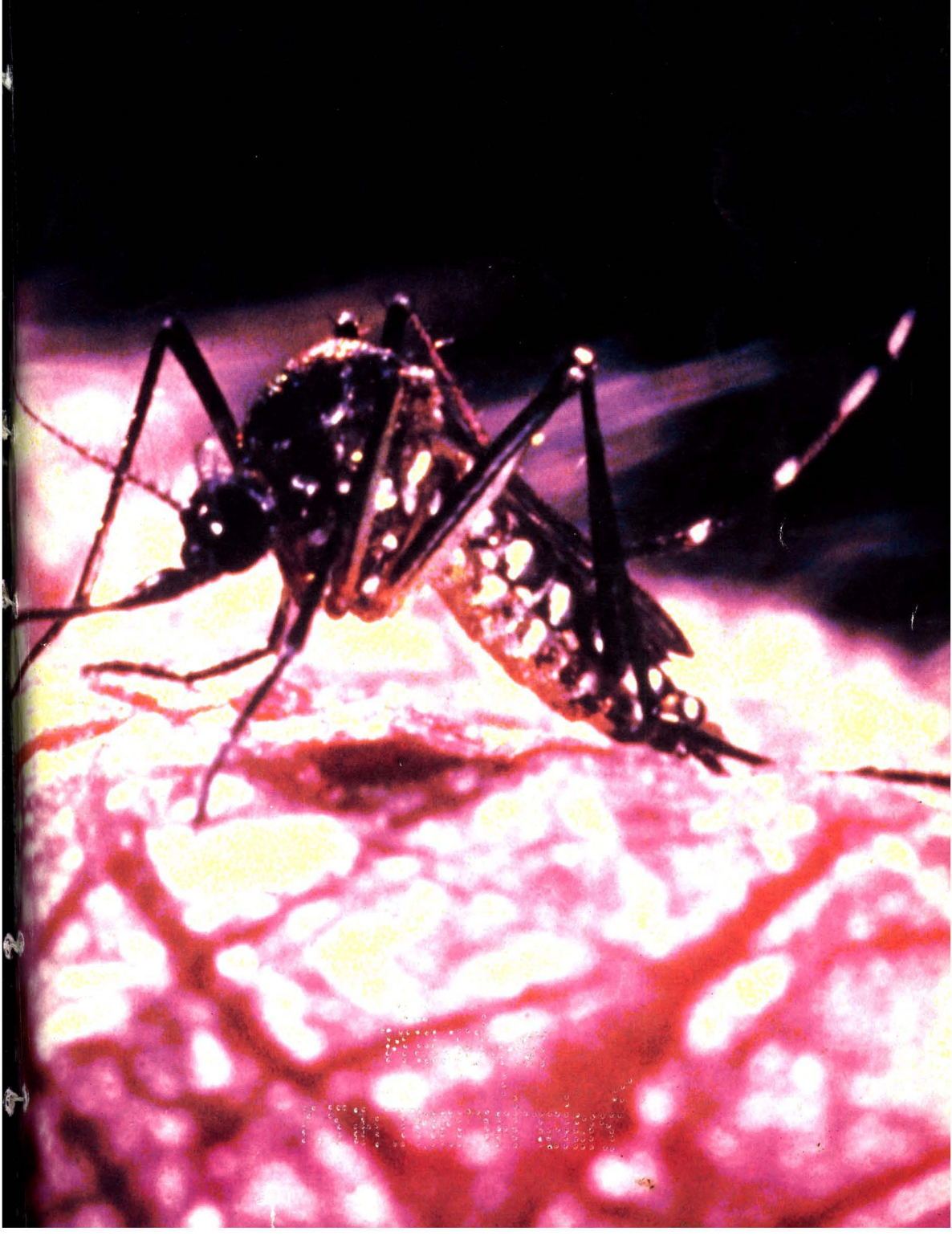

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Contents

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On The Cover:
Global warming may increase the abundance of *Anopheles* mosquitoes, which carry malaria. See Martens et al., p. 458.

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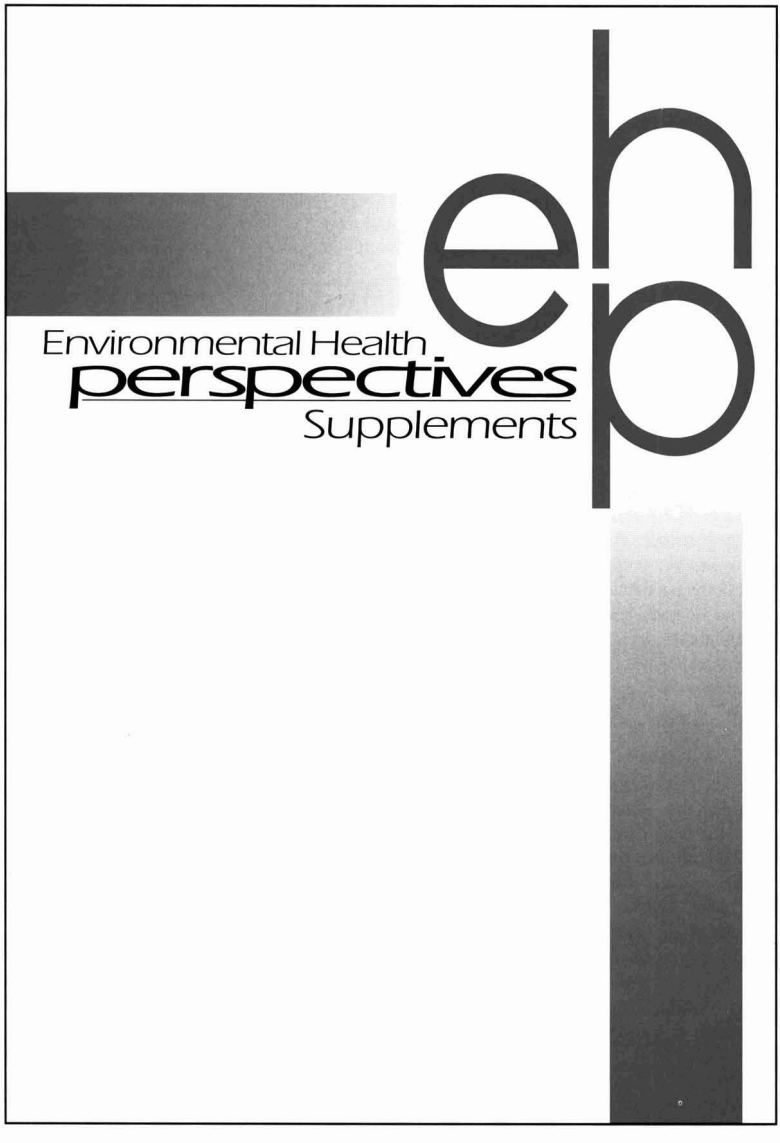

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In This Issue

Environmental Reform in Japan and Western Europe

The pendulum swung cruelly in post-war Japan as living conditions were first improved and then inevitably worsened by unchecked industrialization. The first **Focus** (p. 436) chronicles astounding technological developments closely followed by kogaibyo, diseases caused by pollution. Driven by public health issues, the Japanese have made great strides in reversing pollution in their country of 124 million people. Their environmental plan seeks domestic peace of mind for future generations and international leadership in the environment.

The threats of pollution in Western Europe began in the industrial revolution and now affect the air, soil, and water (p. 442). In addition, there are the modern threats of hazardous waste disposal and radioactivity. The European Union formulates strategies for environmental reforms, controls, and maintenance. However, the proximity of nations means that the problems of acid rain and waterborne pollutants are shared across national boundaries. Reduction of migratory pollutants cannot be accomplished without international laws of environmental protection.

World Bank Woes

For almost 50 years, the World Bank has funded economic development throughout the world. But critics say the benefits of bank projects may exact a high price on the environment and cause economic and social problems for the people they are meant to help. The **Spheres of Influence** (p. 446) examines the controversy surrounding the World Bank, reviews the bank's record on the environment, and takes a look at efforts to reform its lending practices in an effort to reduce the environmental impact of its projects.

One Cancer Cell in 10 Million

Flow cytometry coupled with cell-specific antibody binding and cell-specific dyes now enables scientists to distinguish one cancer cell in 10 million normal cells (p. 450). This detection system is 20 times more sensitive than previous methods. The improved detection system can be used for diagnostic purposes, to prevent reoccurrence of cancer in autologous bone marrow transplants, and for therapeutic dosage selection.

Sustaining Urban Ecology

Restoration of urban habitat is necessary for the sustenance of native populations of flora and fauna. A major concern is reduction in water quality caused by urban stormwater runoff. Cairns and Palmer (p. 452) state that urban improvements are a first step toward sustainability. The authors emphasize that individual education is vital to ensure the creation and maintenance of ecologically sustainable communities.

Estimates of Soil Ingestion

Calabrese and Stanek (p. 454) present data suggesting that aluminum, silicon, and yttrium are the most reliable tracers for estimates of soil ingestion in children. Their previous model relied on different elemental tracers that were more susceptible to error and underestimated the extent of soil ingestion in children. Their revised model for soil ingestion identifies sources of variation and susbstantially corrects for such errors, yielding improved estimates of soil ingestion rates for children.

Mosquitoes Follow Global Warming

Malarial parasites and their vectors could vary in distribution and abundance in proportion to climatic changes, especially those of temperature and precipitation. Martens et al. (p. 458) used a General Circulation Model and generated climate scenarios with the Integrated Model to Assess the Greenhouse Effect to predict malaria epidemic potential into the year 2100. The model suggested the potential for widespread increase of risk due to expansion of areas suitable for malarial transmission. The authors emphasize that the model would be influenced by changes in local environmental conditions, socioeconomic development, or establishment of effective malarial control programs.

Monitoring Populations near Uranium Mines

Au et al. (p. 466) monitored genotoxic responses in populations residing near uranium mines to determine potential adverse health effects. Endpoints included the frequency of chromosome abnormalities and capability of DNA repair. The data indicated there were no discernable effects of uranium exposure on populations residing near the uranium mining operations.

Does Air Pollution Impair Health?

Three articles in this issue address the health effects of air pollution. In the first, Pope et al. review recent epidemiologic studies that evaluated health effects of particulate air pollution (p. 472). They conclude that repirable air particulates contribute to increases in respiratory symptoms, decreases in lung function, increases in hospital admissions, increases in respiratory morbidity characterized by work or school absenteeism, and increases in cardiopulmonary disease mortality. The adverse health effects were observed at levels of particulate air pollution common to many U.S. cities.

Brauer et al. (p. 482) measured acid aerosol particulates in Germany and the Czech Republic for an 18-month period. High-sulfur coal was the major source of pollution during the wintertime, and it was associated with increased mortality or adverse health effects. The data suggested that particulate acidity was not the primary component defining fine particulate air pollution toxicity.

Finally, Styer et al. (p. 490) address the hypothesis that air particulates have caused significant mortality. They conclude that some of the reported effects of air particulates on mortality are unconfirmed. Styer and colleagues analyzed data from Illinois and Utah and reported no evidence that outdoor particulate matter with an aerodynamic diameter less than or equal to a nominal 10 μm (PM_{10}) contributed to excess mortality in Salt Lake City, Utah. There was a positive effect of PM_{10} in spring and autumn in Cook County, Illinois, but not in winter and summer.

PCBs in Fish and Fetal Toxicity

Because PCBs have been associated with spontaneous fetal death in several mammalian species, Mendola et al. (p. 498) examined the relationship between consumption of PCB-contaminated fish from Lake Ontario and spontaneous fetal death in 1,820 women from the 1990–1991 New York state angler cohort study. Prior pregnancies, smoking, and maternal age were taken into consideration in the analyses. Increases in risk of fetal death were not observed based on lifetime estimates of PCB exposure, years of fish consumed, or kilograms of fish eaten between 1990 and 1991, or over a lifetime. The data suggested that eating fish contaminated with PCBs was not associated with an increased risk of recognized spontaneous fetal death.

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Toxicology and Terrorism

Recently, a new chapter was started in the handbook of terror involving the application of nerve gas technology to the killing of civilians. On March 19, a terrorist attack in a Tokyo subway resulted in the loss of 10 lives and injury to over 5,000 others. In view of the lethality of the suspected agent, sarin, the fatalities were surprisingly few. Terrorist attacks on civilians are not new, but what was unique about this particular attack was the use of a nerve agent instead of the customary conventional weapons. The possibility that nerve agents can be used against a vulnerable civilian population is alarming. A new era has begun, and we would be remiss if we did not learn from this one attack and take steps to prepare for the next. There is no doubt that those involved in the use of terror will learn from their mistakes and become more effective in their deployment of these horrific weapons.

From a public perspective there are several questions that must be urgently addressed. What can we do to prevent such attacks and how do we respond if such an attack should occur? Can we prevent terrorist organizations from making nerve agents? How do we prevent them from delivering these agents to their targets? Is there anything that we as a society can do to protect ourselves in the event of a gas attack? How do we minimize our vulnerability? How do we respond to an attack? All of these questions are very difficult to answer.

Agents like GB (sarin), GA (tabun), and VX are easily synthesized; however, handling, storage, and delivery of these agents is not quite so simple. Knowledge for performing these tasks is commonplace, and I suspect that any third-year chemistry student could design and build a facility for their production. Clearly, we cannot restrict access to information. *Chemical & Engineering News* responded to the March 19 attack by showing the reader how easy it is to synthesize sarin from dimethylmethylphosphonate (*1*). The information is in the textbooks, and like most technical information, the methodology for the production of nerve gases is not controllable, even if one wanted to.

Nerve gases are highly toxic organophosphate esters chemically similar to the organophosphate pesticides but with substantially higher acute toxicities. For example, the LD_{50} (mg/kg) for rats via dermal exposures is only 0.1 for VX, 2.5 for GB (sarin), but 6.8 for the pesticide parathion, 4,000 for sevin, and 4,400 for malathion (*2*). In comparison, for humans the estimated dermal LD_{50} values for VX, GB, and GA are about 0.09, 24, and 18 mg/kg, respectively (*2*).

Could the raw materials involved in the manufacture of organophosphates be regulated and controlled as a means of preventing terrorist organizations from synthesizing nerve agents? Unfortunately, the starting materials are very common and easily obtained. As pointed out in *Nature* (*3*), legitimate chemical manufacturers are reluctant to disclose their use of raw materials, and the idea that pyrophosphate or phosphoric acid could be taken off the free market is quite unrealistic.

Delivery of weapons onto passenger aircraft has been, to a large degree, prevented by use of scanning equipment. Judging from the reduction in the number of highjackings in recent years, this monitoring program has been highly successful. Perhaps we could establish a similar program for screening all subway passengers or for screening all people who attend large, indoor functions. Imagine the New York subway at rush hour as passengers passed through checkpoints. The sheer number of people involved suggests that a screening program would be extremely difficult to establish. Such security would be needed not only in the underground itself but also in all outlying stations and in the maintenance facilities. It would certainly be an immense, although not impossible, task, and if terrorist attacks on commuter facilities become commonplace there might come a time when such a system has to be instituted. Deployment of nerve gases against civilian populations might be minimized by using appropriate detection devices in conjunction with appropriately trained security forces. Perhaps dogs might be trained to detect nerve gases which to humans seem odorless. The problems are similar to those encountered in preventing the deployment of terrorist bombs.

There are several reasonably effective antidotes to nerve gases. GB, GA, and VX are all organophosphates that, like their less toxic pesticide cousins, inhibit acetylcholinesterase, resulting in the accumulation of acetylcholine at the nerve synapses. Accumulation of acetylcholine results in the overstimulation of parts of the nervous system that control smooth muscle, cardiac muscle, and exocrine glandular function. In general, death results from respiratory failure. Several agents can antagonize the accumulation of acetylcholine. Atropine when used in conjunction with oximes such as pralidoxime, obidoxime, or trimedoxime (*4*) may prevent and reverse, to a degree, the central nervous system effects of the nerve gases. The problem is that atropine and the oximes are themselves highly toxic and they should be administered to a victim of a gas attack only by trained personnel (*4*). It would not be possible for the general population to carry such toxic agents and to self-administer them in the event of a gas attack. In addition, nerve gas exposure could result in mental confusion, dizziness, nausea, and vomiting, and self-administration under such circumstances would be highly risky.

It is unlikely that, in the event of a terrorist attack on a civilian population, emergency personnel could respond with appropriate equipment and antidotes in less than 30 minutes, even if antidotes and other materials were available in the quantities projected. With agents that can kill in seconds, 30 minutes after the gas is in the air is too late. In view of the complexities involved, it seems unlikely that an attack on civilian lives in a crowded public place could be prevented. However, we can act to minimize casualties which are to a degree determined by the nature of our responses and the speed with which they are put in place. Emergency and medical personnel, especially those in cities where large numbers of people congregate at certain times, should be trained to deal with terrorist attacks involving nerve agents. Such personnel should have on hand substances that might limit the toxicity of nerve and/or blistering agents in sufficient quantities to treat thousands of people. Equipment and protective clothing for emergency and medical personnel should also be available.

One approach that might help reduce the number of casualties in the event of gas attacks in crowded public buildings involves the use of sprinkler systems. GB, GA, and VX are all miscible with water (*2*), and washing with weakly alkaline solutions is part of the protocol established by the military for the decontamination of personnel exposed to nerve gases (*4*). Most public buildings in the United States have sprinkler systems installed in the event of fire. Perhaps sprinklers could be deployed almost immediately as a means of confining the released gas and reducing its concentration. In the absence of decontamination kits, washing with copious amounts of water or weak alkaline solutions could remove the nerve agent or at least reduce its concentration in the air.

Suppose that a room containing 1,000 people were exposed to an air concentration of nerve gas sufficiently high to transfer a dose of agent to each of the occupants equal to the LD_{50}, then 500 of

those people would die. However, if the concentration of agent in the air could be reduced by 50%, assuming a linear dose response, then fatalities would be reduced to 250, a saving of 250 lives. It is unlikely that a sprinkler system could remove nerve gas from the air with 100% efficiency, but many lives might be saved even with only partial removal of the gas. Experiments could easily be designed to test the hypothesis and with appropriate modifications to sprinkler systems, perhaps involving flow rates and droplet sizes, rendered optimally effective in removing toxic agents from the air. In addition, sprinkler systems could be coupled with nerve gas detectors such as the time-of-flight mass spectrometers currently under development at Johns Hopkins or the surface acoustic wave sensors currently being developed by the U.S. Naval Research Laboratory and thereby reduce the response time possibly to within seconds of the initial gas release.

It seems reasonable to suppose that if nerve gas attacks in crowded, enclosed spaces could be blunted through use of sprinkler systems coupled with specific detection devices, then the presence of such a system might, itself, be a major deterrent. After all, there would be little point in carrying out an attack if its chances of success were substantially reduced.

Gary E. R. Hook
Co-Editor-in-Chief

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Misunderstood MTBE

Your recent article panning methyl-*tert*-butyl ether use (*EHP* 102:913) was extremely misleading and focused on unpublished, and therefore not critically reviewed data, which is inconsistent with standards of scientific journals. Given the confusion caused by the article, you should provide more accurate information to your readers on why methyl-*tert*-butyl ether (MTBE) is in gasoline and how it is being managed in a manner protective of public health.

In 1990, Congress passed the Clean Air Act Amendments, which contained a requirement to include oxygen in fuel to reduce carbon monoxide (CO) emissions from motor vehicles. Once oxygenates were required by law, the industry began the process of tooling up for the production of oxygenated fuels. Either alcohols or ethers can be added to provide oxygen and both have been used previously. During the 1979 fuel crisis, alcohols had been added to gasoline to form gasohol. MTBE was added to gasoline as an octane enhancer after the lead phase-out. MTBE had also been used in a three-year pilot CO reduction program in the Southwest beginning in the winter of 1989–1990.

There was a considerable body of toxicological data on MTBE, including neurotoxicity studies, genetic toxicity studies, and reproduction and developmental studies. In addition, preliminary results were available from chronic bioassays in rats and mice prior to the onset of the winter fuels program. These results did not suggest MTBE would be hazardous, particularly at the low concentrations likely to be encountered in fuel use. Thus, required by law to add an oxygenate, industry legitimately made MTBE its principal choice. Ethanol, however, is also widely used, and other compounds such as ethyl-*tert*-butyl ether, *tert*-amyl methyl ether, and *tert*-butyl alcohol are being considered. Oxygenates have been added to winter fuel in 39 cities since November 1992 for CO reduction and are now in reformulated gasoline, which has been required to be sold in approximately 35 geographic areas to reduce ozone since January 1, 1995.

How has the oxygenate program fared? From the standpoint of CO reduction, it has been successful. EPA estimates that "a reduction of over 2 billion pounds of carbon monoxide annually is associated with the winter program." There have been a few complaints from users about reactions to the new product, something not surprising given MTBE's very distinctive ether odor. In 1989, there were a few complaints in the Southwest, but they disappeared in 1990 and 1991. With the initiation of the winter fuel program in 1992, there were scattered complaints in New York, Montana, and more frequent complaints in Alaska and New Jersey. Industry responded by collaborating with EPA to conduct several studies to assess exposure during normal activities and attempting to duplicate exposures to assess health effects in human volunteers in controlled laboratory situations.

The results of these studies were reassuring. Exposures during refueling and commuting were consistently low, averaging 0.3–0.5 ppm during refueling. Acute symptoms described in the complaints could not be replicated in clinical chamber studies (*1*). Finally, in a study comparing healthy garage workers exposed to high and low MTBE concentrations, no differences in self-reported symptoms could be demonstrated that were attributable to MTBE exposure (*2*).

We still hear reference to complaints in New Jersey, although principally from representatives of groups, not from individuals. We find these complaints perplexing since New Jersey law minimizes exposures by requiring stage II vapor recovery systems throughout the state and by not allowing self-service fueling stations. It is also interesting to note that oxygenated fuels are widely used in various parts of the United States, yet the complaints appear to be focused in New Jersey.

In summary, the government mandated the use of oxygenates in fuels, and the industry is complying with that mandate. There is a large body of toxicologic data about MTBE, which makes up the largest fraction of oxygenates currently in use. That data do not suggest untoward health effects from the very limited exposures encountered during normal use of gasoline. Both government and industry have managed introduction of MTBE and responded to legitimate complaints in an appropriate manner. The article you published was incorrect and misleading and not representative of the quality of articles that should appear in your publication.

Robert T. Drew
American Petroleum Institute
Washington, DC

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Clarification

The November 1994 issue of *EHP* contained a forum article on methyl-*tert*-butyl ether that referred to the North Carolina scientific Advistory Board's review of the carcinogenicity data for MTBE. The conclusion of the article stated that "The Board concluded that the state should consider requesting that the EPA remove MTBE from gasoline because of the uncertainties surrounding it." This statement is incorrect. We did not make such a recommnedation. The following summary represents our report to the North Carolina Department of Environment, Health and Natural Resources.

George Lucier, chair
Mary Beth Genter
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North Carolina Scientific Advisory Board
on Toxic Air Pollutants

Summary of the Carcinogenicity Assessment of MTBE conducted by the Secretary's Scientific Advisory Board on Toxic Air Pollutants

Abstract. The Secretary's Scientific Advisory Board on Toxic Air Pollutants (SAB) examined the scientific evidence pertaining to MTBE carcinogenicity and came to a consensus agreement that, according to the National Toxicology Program (NTP) classification of carcinogenic activity, there is "some evidence" for carcinogenicity of MTBE in animals. The SAB agreed "some evidence" approximately corresponds to the "C" classification by the EPA. In an exception to the SAB policy of not quantifying risk for group C carcinogens, a range of exposures that could be associated with a potential

risk of 1 in 100,000 (1×10^{-5}) was calculated. This range is 0.04 mg/m^3 to 0.64 mg/m^3. The annual concentration estimated by the EPA that maximally exposed people would be subjected to in areas with a 4-month oxyfuel season ranges between 0.03 and 0.05 mg/m^3. SAB and EPA estimations indicate that the range of potential risk of maximally exposed people in North Carolina may be between 1×10^{-5} and zero at current exposure levels.

Data assessment. The merits and deficiencies of the scientific information relevant to MTBE carcinogenicity were considered carefully and are summarized below.

Two chronic inhalation studies have been performed, one on F344 rats, the other on CD-1 mice; exposures were 400, 3,000, and 8,000 ppm MTBE, 6 hours per day, 5 days per week (*1,2*). Problems with the studies include MTBE-induced toxicity (other than induction of neoplasms), decreased survival of high-dose animals, and substantially shorter than lifetime exposures. These problems impart considerable uncertainity to application of the resulting data to carcinogenicity hazard characterization.

An increase in kidney tumor incidence (combined adenomas and carcinomas) in male rats exposed to 3,000 ppm MTBE via inhalation was considered to contribute to the weight of evidence of carcinogenicity. There was no significant increase in tumor formation in male rats exposed to 8,000 ppm MTBE in the same study. The dose–response effect required to attribute the tumors to MTBE exposure unequivocally may not have been detected because the 8,000 ppm dose group was sacrificed 15 weeks before the 3,000 ppm group due to excess mortality among subjects. Had the high dose group lived longer, they may have developed tumors. The SAB considered the possibility that tumor formation was due to induction of α-2_u-globulin, a protein specific to male rats and not relevant to other animals or humans. The kidney tumors could not be attributed solely to induction of the α-2_u protein mechanism because an overabundance of α-2_u was not detected in histological sections of treated rats, though a pattern of pathology similar to that associated with α-2_u was observed. The SAB considered the possibility that kidney tumors observed in this study were secondary to toxicological damage resulting from exceedance of the maximum tolerated dose. Though kidney damage preceded tumors, a chronic study conducted by the NTP on a major metabolite of MTBE, *tert*-butyl alcohol (TBA), produced evidence of kidney tumors at a dose not exceeding the maximum tolerated dose when TBA was administered in drinking water. The male rat kidney tumors may not be attributed fully to the toxic effect of MTBE on the kidney, or to induction of α-2_u globulin, but may be due to a TBA-mediated mechanism. There are no data available to use for a quantitative comparison of rodent and human MTBE metabolism.

Increased interstitial cell adenoma tumor incidence observed in the testes of male rats in the inhalation study mentioned above was considered to contribute to the weight of evidence of carcinogenicity. A significant dose response in tumor incidence was seen from 64% in concurrent controls to 94% among the high-dose rats. The historical incidence of testicular adenomas in these rats ranges from 86 to 91%, but concurrent controls are generally considered the most appropriate controls for comparison. The high spontaneous background rate of testicular tumors in this strain of rat makes interpretation of the significance of the data difficult, but the clear dose–response effect compels the SAB to include these benign tumors in the weight of evidence of carcinogenicity.

Female CD-1 mice exposed to 8,000 ppm MTBE exhibited a significant increase in liver adenoma tumor incidence, which was considered part of the weight of evidence for carcinogenicity. No increase in tumor incidence was observed at the lower two doses. Body weight gain in mice exposed to 8,000 ppm was decreased 24% compared to controls, which may indicate the maximum tolerated dose was exceeded.

Male mice exposed to 8,000 ppm MTBE exhibited an increase in liver carcinoma incidence, which was considered part of the weight of evidence for carcinogenicity. Body weight gain in male mice exposed to 8,000 ppm was reduced by 15%, and the mortality rate of males was increased at this dose. These factors indicate the 8,000 ppm exposure may have exceeded the maximum tolerated dose in male mice.

A chronic study in which MTBE was administered to Sprague-Dawley rats by gavage in an olive oil vehicle reportedly has been conducted in Italy by Maltoni. A representative of Maltoni's laboratory, Dr. Myton Mehlman, reported "dose-related" increases in combined lymphoma and leukemias, hematoreticular tumors, uterine sarcomas, and testicular Leydig cell tumors in MTBE-treated rats. The experimental design and results of this study have not been sufficiently reported or reviewed to allow the information to be used in a weight-of-the-evidence evaluation of carcinogenicity.

The SAB concludes there is "some evidence" for carcinogenicity of MTBE in animals according to NTP guidelines for peer-reviewed data characterizing carcinogenic activity of chemicals. The board recognizes "some evidence" in the NTP classification system approximately corresponds to a "C" carcinogen in the EPA classification system. The board's policy as recommended in 1986 by the North Carolina Academy of Sciences is not to assess carcinogenicity risks for compounds the EPA has designated group C carcinogens. The SAB was asked specifically to review carcinogenicity of MTBE because its use as an oxygenate in gasoline could result in exposure of a large number of people to MTBE. In an exception to the policy of not quantifying risk for group C carcinogens, the board estimated a range of exposure levels that could be as high as 10^{-5} risk.

Assuming MTBE is a carcinogen in humans, the data from animal studies were used by the SAB to calculate an estimate of human risk due to exposure. The calculations were based on the kidney tumor incidence in male rats chronically exposed to 3,000 ppm of MTBE. Human unit risks were calculated using four different equations to estimate a range of ambient concentrations of MTBE which would pose an acceptable risk to a person exposed continuously for 70 years. An acceptable risk level of 10^{-5} was used, as suggested in the North Carolina Academy of Sciences Report and Recommendations to the Air Toxics Panel (*3*), for animal carcinogens (known human carcinogens are set at 10^{-6} risk). The range of concentrations at a risk of 10^{-5} calculated by the SAB was 0.04 mg/m^3 to 0.64 mg/m^3. A concentration range rather than a single concentration is submitted by the board to the Department of Environment, Health and Natural Resources because uncertainty inherent in the data makes one estimation no more realistic than another. The lower concentration is clearly the most conservative.

The EPA summary of health effects of MTBE contains exposure estimates for the general public based on limited sampling conducted at gas stations, at the property lines of gas stations, and inside commuting cars (*4*). These concentrations are purported to be reasonable worst-case estimates applicable to working adults who live near gas stations or major roadways. The annual MTBE concentration estimated by the EPA for maximally exposed people in areas with a four-month oxyfuel season ranges between 0.03 and 0.05 mg/m^3.

Conclusion. The SAB determined there is some evidence for carcinogenicity of MTBE in animals. The SAB estimated a human risk of cancer due to MTBE exposure by extrapolating from the animal data to estimate a risk to humans. The risk calculations were used to estimate concentrations of MTBE which would pose minimal risk to humans exposed continuously for 70 years. The range of concentrations calculated by the SAB expected to pose a 10^{-5} risk was 0.04 mg/m^3 to 0.64 mg/m^3. The EPA estimated that an adult commuter who lives next to a gas station could be exposed to 0.03 to 0.05 mg/m^3 of MTBE annually in a locale which has a four-month oxyfuel season. The SAB and EPA estimations indicate that the range of potential risk of maximally exposed people in North Carolina may be betweeen 1×10^{-5} and zero at current exposure levels.

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If you think you're too small to have an effect, you've never been in bed with a mosquito.
Bette Peele

Forum

Starving Tumors

Research conducted by a team of California scientists points the way to what ultimately may become a promising cancer treatment: a technique that triggers tumor regression through the injection of one of two different proteins. After injecting a single dose of either a monoclonal antibody or a synthetic protein into the vasculature surrounding tumor fragments grafted onto chick embryos, the scientists observed an astounding result: the tumors not only stopped growing, but they actually began to decrease in size.

The experiments, led by cell biologists Peter C. Brooks and David A. Cheresh at San Diego's Scripps Institute, fall into an area of cancer research called tumor angiogenesis—the process by which a tumor produces substances that support the development of new blood vessels necessary for tumor growth.

Their findings appear promising. According to the study, published in the 30 December 1994 issue of *Cell*, the proteins not only destroyed newly sprouting blood vessels that nourished the growing tumor but were also nontoxic to the surrounding healthy tissue. While the researchers don't claim to have found a cure for cancer, they remain hopeful that their research will have a positive impact on human cancer treatment.

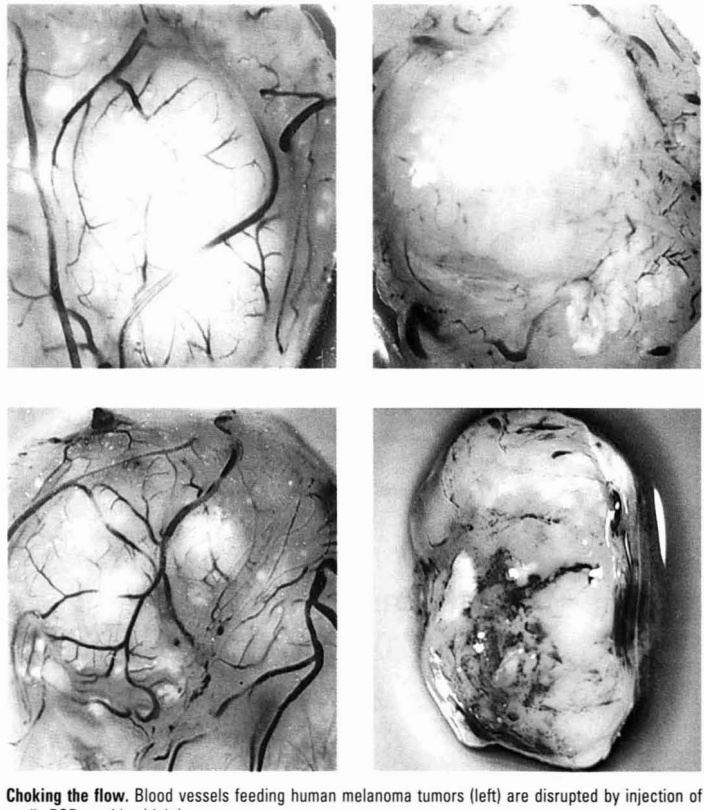
According to Brooks, research began after his team made the initial observation that a cell surface molecule, or integrin, known as $\alpha_v\beta_3$, was highly expressed in the proliferating blood vessels around the tumor, but not in the tumor itself. "In order for a tumor to grow beyond one to two millimeters, they required a blood supply," Brooks explains. "Instead of targeting the therapy to the tumor, we targeted it to the vasculature around it." It's a novel approach, since the other eight compounds known to inhibit tumor angiogenesis—now in clinical trials at research institutions in the United States and Europe—are targeted to affect the tumors themselves.

In their attempts to halt tumor growth, the researchers targeted the $\alpha_v\beta_3$ integrin, which allows the cells lining the blood vessels to attach to and interact with the extracellular matrix. The genetically engineered monoclonal antibody developed at the Scripps Institute and a synthetic peptide developed by E. Merck of Germany both disrupt $\alpha_v\beta_3$ function. The monoclonal antibody is licensed to Ixsys Inc., a San Diego biotechnology company which, according to Brooks, is planning to begin clinical trials with the antibody (known as LM609) on humans in 12–18 months.

In their study, Brooks and Cheresh describe how the human body selectively allows the development and destruction of vascular cells. The $\alpha_v\beta_3$ integrin sends out a survival signal that normally would allow maturation into a blood vessel. "The antibody and the peptide both block the transmission of survival signals to the endothelial cells, leading to apoptosis, or programmed cell death," Brooks explains. "The tumor also dies," he adds.

To observe the impact of the proteins on tumor growth and survival, the scientists planted tumor fragments onto 10-day-old chick embryos, employing a classical model for studying angiogenesis that was pioneered by Judah Folkman, a veteran angiogenesis researcher at the Harvard Medical School. After several hours, new blood vessels had begun to form in the tumor fragments.

At the 24-hour mark, the scientists introduced either of the two proteins to some embryos, and allowed others to grow without the proteins as a control. The researchers observed a dramatically



Brooks et. al./*Cell*

Choking the flow. Blood vessels feeding human melanoma tumors (left) are disrupted by injection of cyclic RGD peptides (right).

reduced number of blood vessels feeding the tumors in the embryos injected with the proteins. The tumors actually regressed and the embryos developed normally. In the control embryos, the blood vessels proliferated in their usual pattern, promoting the growth of the tumors.

"The research is very promising and has great potential," says James Pluda, an angiogenesis expert at the National Cancer Institute in Bethesda, Maryland. The experiment designed by the Scripps researchers "approaches disrupting the angiogenic pathway at a point that is different than other [studies have shown]," says Pluda.

"We're excited about having it progress," says Pluda, who oversees the development of anti-angiogenic drugs at NCI. "It's very interesting; it's also very preliminary," he cautions. The proteins could lead to unwanted side effects in other tissue, which could inhibit wound healing, for example, or possibly lead to fetal damage in pregnant women.

At this stage of research, scientists at Ixsys are completing toxicology studies to determine the extent, if any, of adverse effects of the LM609 antibody. They will also perform tests to rule out any biological properties that would discourage the use of the antibody in humans.

According to Brooks, the Scripps research team duplicated their chick-embryo test results in experiments on small sections of human skin grafted onto mice and observed a twofold reduction in tumor size. Their laboratory findings held true for a broad range of solid-tumor human cancers, including malignant melanomas and cancers of the lung, breast, pancreas, brain, and larynx.

According to Brooks, the team collaborated with another Scripps researcher, ophthalmologist Martin Friedlander, and discovered that the protein therapy may be useful in treating several eye disorders as well, including diabetic retinopathy and macular degeneration.

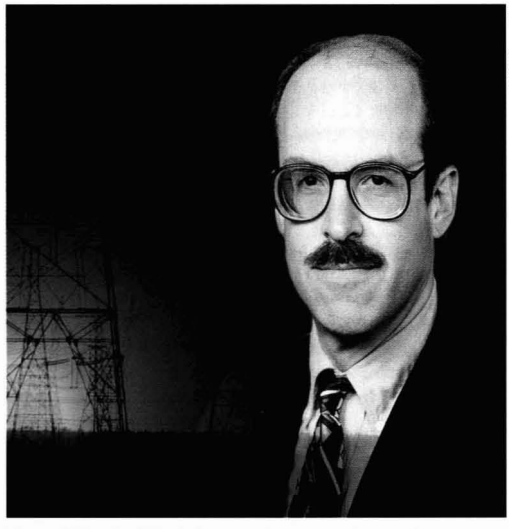
Elusive EMFs

Do electric and magnetic fields (EMFs) cause cancer? Researchers still don't know for sure, since the latest epidemiological look at EMF health effects contradicts some previous findings.

The new study, conducted by epidemiologist David A. Savitz of the University of North Carolina-Chapel Hill School of Public Health, underscores the need to identify biological mechanisms associated with EMF health effects, NIEHS officials say.

Savitz, whose work in 1988 helped spark intense public and scientific debate over the safety of EMFs, now concedes that future investigations must identify "biologically relevant exposure metrics." If properly defined, he adds, epidemiological studies may still shed light on EMF effects.

"I hate to give up on epidemiology outright, but I think that it needs to evolve," says Savitz. "We need either more innovative epidemiological studies or biological studies."



UNC-Chapel Hill

Power thinker. David Savitz is among those researchers moving to mechanistic studies of EMFs.

In his newly published review of 138,905 male utility workers, men exposed to high-level 60-Hertz magnetic fields were about twice as likely to develop brain cancer, although they developed only about 70% as many brain tumors as expected. Nonetheless, men subjected to extremely high-level fields experienced 2.6 times greater risk than the average American, Savitz reported with coauthor Dana Loomis in the *American Journal of Epidemiology* (vol. 141, no. 2).

Yet, Savitz found no link between magnetic fields and leukemia, except among electricians. This finding is puzzling when compared with other recent studies.

A 1993 report by J.D. Sahl and colleagues failed to identify any statistically significant link between magnetic fields and brain cancer or leukemia among 36,000 workers at the Southern California Edison Company. Another study of 223,292 Canadian and French utility workers, published in 1994 by Gilles Theriault and associates, offered no convincing evidence of an increased brain-cancer risk among highly exposed groups. Unlike Savitz, however, Theriault reported that exposed individuals were up to three times more likely to develop certain leukemias.

Savitz was instrumental in launching numerous epidemiological studies of EMF effects. In 1988, he published a case–control study of 356 childhood cancer cases whose findings seemed to confirm a 1979 study by epidemiologist Nancy Wertheimer and physicist Ed Leeper. Among 344 Denver-area children, they reported, those dwelling within 49 to 131 feet of high-power electricity lines were two to three times more likely to die of cancers.

Despite 16 years of subsequent research, however, the debate over EMFs continues. In his latest study, Savitz carefully ruled out the effects of two other workplace carcinogens: polychlorinated biphenyls (PCBs) and solvents. But he could not account for many other variables such as cigarette smoking among test subjects or magnetic fields within homes.

Researcher Philip Cole of the University of Alabama at Birmingham questions Savitz's interpretation of the EMF data. Among 138,905 workers, brain cancer and nervous system cancers claimed the lives of 151 men: 8 fewer deaths than expected. In an unpublished evaluation of the Savitz study, Cole says this finding is in fact "negative, or at most weakly positive." But Savitz says utility workers tend to be healthier than the average American. "It's a pretty well-established phenomenon that working populations have lower mortalities from a whole range of causes," he says.

Future studies must account for more complex variables, says Wertheimer. Many researchers believe that EMFs may work cooperatively with other carcinogens to promote tumor development, she notes. Overall, the body of epidemiological research thus far suggests a relatively small increase in cancer risks (1.5 to 2.5 times greater) for those exposed to high-level magnetic fields, according to Savitz. "Savitz has done the best job possible," Wertheimer continues. "But we still don't know if [his test subjects] used electric blankets or lived in high-exposure neighborhoods. We still have a very blunt tool."

Attempts to hone that tool are being made using toxicological and basic biological studies as the focus of an EMF health effects research program directed by the NIEHS and administered by the U.S. Department of Energy.

"It didn't make sense for us to fund

additional epidemiological research," says Dan VanderMeer, NIEHS director of the Office of Program Planning and Evaluation. "We decided to focus on those health conditions that have been identified in epidemiological studies."

Dubbed EMF RAPID, for Electric and Magnetic Fields Research and Public Information Dissemination, the program was authorized by Congress in October 1992. Over a five-year period, Congress authorized up to $65 million to support research and public information. The law also calls for matching private funds.

Using animal models, EMF RAPID grant recipients are testing epidemiological findings related to leukemia, breast cancer, brain tumors, and other diseases, VanderMeer reports. In addition, molecular and cellular studies are addressing possible biological mechanisms, including immune-system suppression, direct or indirect DNA changes, disruption of cellular communications, and impacts on melatonin, a hormone that blocks tumor formation *in vitro*.

EMF RAPID funds were also used to expand an existing NIEHS animal study conducted as part of the National Toxicology Program. At the IIT Research Institute (IITRI), a 21,000-square-foot laboratory makes it possible to expose 2,400 animals to magnetic fields under highly controlled conditions, says Gary Boorman, chief of the Pathology Branch in the NIEHS Environmental Toxicology Program. Principal investigator David L. McCormick of IITRI exposes rats and mice to magnetic fields to assess reproductive, immunological, and carcinogenic effects, as well as melatonin levels.

In all studies, researchers are trying to replicate robust effects, says Michael Galvin, a general physiologist at NIEHS. "An effect that appears only once and is not robust enough to be replicated consistently or demonstrates a so-called Cheshire cat effect would be difficult to assess," Galvin notes.

Wertheimer worries that NIEHS researchers may fail to identify a health hazard because they are focusing on whether EMFs initiate tumors. In fact, she says, EMFs may promote cancer development only when tumors are initiated by some other agent. "The idea of direct DNA damage is still foremost in their minds," Wertheimer says of NIEHS officials. "I don't think that's what we're dealing with here." However, according to VanderMeer, NIEHS is also supporting mechanistic studies of possible EMF effects on cell signaling, cell membrane function, tissue and organ systems, and free radicals. "These mechanisms," says VanderMeer, "are important irrespective of whether EMFs may act as direct or indirect carcinogens."

The NIEHS decided to emphasize tumor initiation because research groups in Canada, Sweden, and Germany were already investigating co-promotion effects, Boorman says. But, he adds, EMF RAPID funds will support two co-promotion studies at IITRI. Using genetically engineered rodents with a known cancer susceptibility, McCormick's team will assess whether EMFs speed tumor development among animals exposed to carcinogens such as diethylnitrosamine. Plans for additional promotion studies using a rat breast cancer model are also being developed at NIEHS.

Chemical Weapons: Safe until 2004?

In a December 1994 report, the General Accounting Office questioned an Army assessment that the U.S. chemical weapons stockpile can be safely stored until 2004. This is Congress's latest deadline for the Department of Defense to destroy stockpiled unitary chemical weapons—those that contain a single lethal agent.

Of concern are 478,000 M55 rockets stored at sites in five states and on Johnston Atoll in the Pacific Ocean. According to GAO and technical consultant Sandia National Laboratories in Albuquerque, New Mexico, these stockpiled M55 rockets are unstable as stored and inadequately monitored by the Army, the Department of Defense's lead service in chemical matters.

Initially, Congress directed the Department of Defense to destroy M55s and the rest of the stockpile by 30 September 1994. When the Army fell behind in

Chemical Stockpile Munitions and Locations

Storage site	Weapons	Agents stored
Aberdeen Proving Ground, Maryland	Ton container	H
Anniston Army Depot, Alabama	Projectiles and cartridges	H, GB, VX
	M23 mine	VX
	Ton container	H, GB
	M55 rocket	GB, VX
Blue Grass Army Depot, Kentucky	Projectiles and cartridges	H, VX
	Ton container	H, GB
	M55 rocket	GB, VX
Johnston Atoll	Projectiles and cartridges	H, GB, VX
	M23 mine	VX
	Ton container	H, GB, VX
	M55 rocket	GB
	Bomb	GB
Newport Ammunition Plant, Indiana	Ton container	VX
Pine Bluff Arsenal, Arizona	M23 mine	VX
	Ton container	H
	M55 rocket	GB, VX
Pueblo Army Depot, Colorado	Projectiles and cartridges	H
	Ton container	H
Tooele Army Depot, Utah	Projectiles and cartridges	H, GB, VX
	M23 mine	VX
	Bomb	GB
	Spray tank	VX
	Ton container	H, GB, VX
	M55 rocket	GB, VX
Umatilla Depot Activity, Oregon	Projectiles and cartridges	GB, VX
	M23 mine	VX
	Bomb	GB
	Spray tank	VX
	Ton container	H, GB, VX
	M55 rocket	GB, VX

The chemical munitions stockpile is located at eight sites in the continental United States and on Johnston Atoll in the Pacific Ocean. Aberdeen Proving Ground and Newport Army Ammunition Plant store only bulk agent. SOURCE: Chemical Weapons, Stability of the U.S. Stockpile, GAO, December 1994.

implementing its $8.5 billion on-site incineration program, Congress extended the deadline to 2004 and asked the Army to evaluate the stockpile's physical and chemical integrity. The Army's July 1993 report—based on inspection and laboratory data and old stockpile assessment reports—said the stockpile was safe for now but uncertain beyond 2004. Congress asked GAO to review the Army's estimate and contingency plans if something goes wrong.

Responding to the GAO report and recommendations made in 1994 by the National Research Council, the Army Chemical Demilitarization and Remediation Activity, based at Aberdeen Proving Ground, Maryland, released a statement February 16 that said work would begin in fiscal year 1995 to determine the storage life of leaking and nonleaking M55 rockets.

Each M55 rocket consists of a warhead that carries 10 pounds of nerve agent (GB) and an explosive charge, and a solid-rocket motor with a nitroglycerin-based propellant and a stabilizer that keeps heat from building up as the propellant decomposes. If the decomposing propellant gets too hot or acidic, the M55 could autoignite.

All stockpiled weapons contain a mustard/blister agent (H) or one of two nerve agents (VX or GB). M55s carry GB, and, the Army report adds, nerve agents, especially GB, become acidic over time and can corrode metal warheads of rockets, mortars, and projectiles.

"The propellant is unstable and so is the chemical agent," says Donna Heivilin, GAO's director of Defense Management and NASA section and author of the 1994 report to Congress, "and the M55 design makes it hard to physically separate the propellant from the GB. If the propellant blows up, the chemical agent would disperse. This is what makes the M55 more dangerous [than other stockpile weapons]."

Threats to stockpile storage include earthquakes, plane crashes, tornadoes, accidents during handling and maintenance, autoignition of the propellant, and chemical leaks from the warhead. And the potential danger to human life is immense, even if one rocket ignited, because, according to the Army's 1994 report, *M55 Rocket Storage Life Evaluation*, "the resulting explosion and fire in a storage igloo could involve many of the 4,000 rockets that typically are stored together."

"The congressional mandate is that the Army dispose of these [unitary chemical weapons] in the safest, most environmentally sound fashion," says Craig Williams, national spokesperson for the Chemical Weapons Working Group, an international coalition of environmental and ecological groups. "But the Army's focus is on the comparative risk of continued storage versus incineration. We've been trying for years to broaden the scope of that analysis to include comparisons among continued storage, reconfiguration, reconfiguration with partial neutralization, and incineration."

Reconfiguration, Williams says, "involves moving the M55s to a munitions detonation-containment building, using robots to disassemble the munitions, separating chemical agents from other components, and partially neutralizing the byproducts. Then we'd have hazardous waste, which isn't great. But what we have now are rockets and mortars ready to launch and send nerve agents randomly into communities. We'd have reduced the risk of exposing chemical warfare agents to facility workers and the community to zero."

At the Army Chemical Demilitarization and Remediation Activity at Aberdeen Proving Ground, Mark Evans, special assistant to the program manager, says this is easier than it sounds. To neutralize the M55s, he says, "we'd have to build 90 percent of the demilitarization [high temperature incinerator] facility we plan to build anyway. We are updating cost estimates for rocket separation, but there are no good neutralization techniques for VX and GB, and we'd produce a lot of waste. The Army believes that if the risk assessments show the rockets can be stored through 2013, our incineration program is the safest method."

The neutralization proposal seems to indicate that construction of the demilitarization facilities could be sped up, but that's not true, according to Evans. A facility at Tooele Army Depot in Utah is built and is in testing, Johnston Atoll's facility is operational, and there are contracts to

Deadly Sarin

The death of 10 people and the injury of 5,000 more in the terrorist attack on the Tokyo subway system March 19 serves as a tragic reminder of the lethal potential of nerve agents.

The organophosphate sarin (isopropyl methyl phosphonofluoridate), also known as GB, has been identified as a component of the gas used in the attack. Sarin was first developed in Nazi Germany. At lethal doses, it can cause death within seconds when inhaled. At more moderate doses, it can cause nausea, diarrhea, and interfere with mental ability.

Sarin primarily affects the respiratory and nervous systems (see Munro et al., *EHP* 102:18–38). Subtle changes in EEG patterns and increases in rapid eye movement during sleep were observed in a group of workers one to six years after accidental exposure. Brain damage has resulted at concentrations of sarin high enough to induce convulsions. Respiratory effects include bronchoconstriction, wheezing, and increased airway secretions.

Like other organophosphorus compounds, sarin works by inhibiting acetylcholinesterase, an enzyme that breaks down the neurotransmitter acetylcholine, thus overstimulating the nervous system. Once sarin enters the blood, it can penetrate the blood–brain barrier. In the case of sarin, death is caused by depression of the brain's respiratory center.

Pupil constriction, or miosis, has been observed up to 60 days after exposure to sarin. Eye pain and dim vision may also occur. Transient, prolonged changes in psychological function, manifested as depression, nightmares, confusion, and deficits in motor skills and intellectual ability have been observed in individuals exposed to organophosphate insecticides, which are similar in structure to sarin.

However, unlike some organophosphate insecticides, long-term effects have not been documented for sarin. "Sarin itself should not cause any long-term health effects," said Nancy Munro of the Oak Ridge National Laboratory in Oak Ridge, Tennessee. "[It is] highly unlikely to cause carcinogenicity."

Indeed, studies have shown that sarin is neither carcinogenic, genotoxic, or teratogenic. Delayed effects such as organophosphorus-induced delayed neuropathy (OPIDN) may be more of a concern. Although OPIDN has not been associated with sarin exposure, it has been documented in people exposed to organophosphate insecticides. OPIDN usually occurs within 5–30 days of exposure, beginning with weakness, tingling, and muscle twitching, and progressing to paralysis of the toes, hands, and thighs. Recovery is slow and incomplete. The problem, according to Michael Ellis of the University of Texas Medical Branch Poison Center in Galveston, is that organophosphorus compounds accumulate in lipid tissues such as fat and nerves.

But, like Munro, Ellis emphasizes that long-term effects are not the concern with sarin: "This stuff was made to kill people," he says. The ease of concocting deadly agents such as sarin has stimulated questions about public safety worldwide.

build and operate facilities at Anniston Army Depot in Alabama (to be completed in 1999), Umatilla Depot Activity in Oregon, and Pine Bluff Arsenal in Arizona (both to be completed in 2000). The Blue Grass Army Depot facility in Kentucky would be operational by 2002.

Over the next year, the Army will examine two approaches for determining the storage life of nonleaking M55s. The Army's approach combines relatively new data on propellant chemistry with a probabilistic method for evaluating storage life. According to this method, the chances of autoignition are less than one in a million before 2013. A second method derived by Hercules Corporation, the propellant manufacturer, estimates the chances of autoignition are less than one in a million before 2043.

There are no estimates on autoignition for leaking M55s, which have been found at all six munitions storage sites. Such leaks, caused by corrosion that eats small holes in the metal warheads, let chemicals or vapors escape inside or outside the weapon. External leaks can be quickly detected by monitoring. Internal leaks can't be detected without disassembling the weapon, and a 1985 Army assessment of M55 rockets estimated that 1–3% had internal leaks.

But no one knows the extent of the hazard these leaks pose; the GAO report says the Army has never sampled the leaking munitions because it considers them too dangerous. The Army says there is insufficient evidence to determine, as the GAO report concluded, that leaking rockets have a shorter storage life than nonleaking rockets.

"It is not known if leaking M55 rockets could autoignite during handling if agent were to come in contact with energetic material found in the burster and fuse," the Army statement says. "Previous assessments of the stockpile stability have raised the possibility, but there is insufficient data to reach a conclusive determination. The Army will determine what effects, if any, the agent has on energetic material."

Responding to GAO's call for a contingency plan for emergency disposal of the M55, the Army says it will develop a plan that outlines the steps it will take if the rockets' deterioration accelerates.

Sandia further recommended that the Army immediately expand its stockpile monitoring to include propellant samples from nonleaking and leaking munitions at each storage location. But the Army, whose safe-storage-life projections of nonleaking M55s are based on measuring master samples of rocket propellant stored at Picatinny Arsenal in New Jersey, says it will continue using master samples for periodic assessments after it verifies the master samples still represent propellant stored in the field.

Master samples are used, Evans says, because "we have to think about putting workers at risk who extract propellant sample from fully loaded chemical munitions. We use machines to cut the rounds apart in a room with 28-inch-thick walls because of the potential for problems."

The Army tests will include taking field samples from Tooele, where some rockets were partially dissassembled years ago, and from Johnston Atoll, where some of the rockets have leaked.

"If we do all those tests," says Evans, "and the propellant is different from the master samples, we'll need to initiate a much more extensive field-sampling program, and that will cost a lot of money. If we believe it's different and worse, you may see us try to expedite activities at rocket sites." GAO agrees samples should be taken from all sites, but says expanded monitoring won't answer all questions about stockpile stability.

"We have reason to believe that propellant and agent affect each other, but we don't know if it changes anything," Evans adds. "Only one data point indicates that it may. We need to move from 'it may' to 'it does' or 'it doesn't.'"

Spying on the Environment

Since the end of the Cold War, the CIA, which is facing budget cuts, has been searching for new ways to use its spying equipment, which is no longer being used to its full capacity. In October 1992, the CIA selected a team of 70 civilian environmental scientists to work with officials to examine whether the CIA's spy equipment could be used to provide information on the environment. The idea was presented by Vice President Al Gore, who had long believed that the CIA's records contained valuable information on climate, land use, oceans, and atmospheric conditions.

The task force was given access to the satellite system run by the National Reconnaissance Office (NRO), whose name was classified until last year, to determine if the equipment could be applied to environmental science. The CIA conducted a series of 13 experiments to determine whether the systems could be used to measure environmental changes such as greenhouse gases, ocean temperatures, polar ice thickness, and forest and desert boundaries.

The satellites contain devices that are able to take very detailed photographs at close range through telescopes in all types of weather and light conditions. An example of how this equipment could be used for environmental purposes lies in the former Soviet Union. Dozens of launch clusters and about 1600 missile silos are located along a trans-Siberian railway. The CIA satellites have been photographing this area daily for decades. As a result, the CIA has years of data on the snow melt in that area, which is an indicator of climate change.

The CIA also has years of ocean data as a result of submarines in the Arctic collecting sea ice measurements daily for decades. Sea ice is also an important factor in climate change measurements.

The task force completed its initial report last December, and it was circulated throughout the intelligence community on a classified basis. The scientists found that, indeed, the CIA's archives and collection devices could provide invaluable information on climate change. The report is not a policy document; it merely discusses the possibilities.

Among the possibilities that the task force discussed is the satellite tracking of changes in vegetative and desert boundaries, which may indicate global climate change. Also, the report says that underwater listening systems could monitor fluctuations in ocean temperature by measuring changes in ocean sound speed over long distances.

The report also addressed forests and biodiversity. Currently, scientists have access to civilian satellite photographs of the world's forests taken by LANDSAT, which produces infrared color images of land areas and oceans. But the LANDSAT photos are not nearly as precise as the CIA's satellite photographs. LANDSAT can only achieve resolution of 10 meters, while the NRO can reach up to 10 inches. While LANDSAT can only take broad pictures of forests, the NRO satellites can zoom in to count the number of trees in an area and determine what species they are. The task force report says that scientists could combine LANDSAT data with NRO data to obtain detailed information on forests.

The report also discusses the use of a spy device that uses infrared technology to analyze the chemical composition of plumes of missiles as they streak across the sky and other heat patterns, such as factory emissions. The device could be used to analyze the reflection of sunlight off a forest canopy to determine the chemical composition of forests. This would provide information on whether forests contain certain chemicals that are necessary for healthy vegetation.

The report says that the CIA also has the ability to scan for forest fires. The Defense Support Program early-warning satellites, which are designed to detect missiles emerging from silos, could be used to detect forest fires.

The CIA could also use its Global

Positioning System to track ice floes and ocean buoys to provide further information about ocean temperature, salinity, and current. U.S. Navy undersea listening devices that monitor the ocean for submarines could be used to track whale migration and listen for storms, undersea volcanoes, and earthquakes.

Although the possibilities sound promising, the plan may not materialize due to several problems. For example, the CIA could decide that the risks of revealing too much about the intelligence structure outweigh the potential benefits to environmental scientists. Even if the CIA produces environmental data, the agency plans to disguise the origin of the data so that scientists may not be able to determine where the information comes from. Some scientists are bothered by the idea of secrecy surrounding the CIA information.

"The cultural antagonism here is that the fundamental tenet in science is that you tell everyone everything, and the fundamental tenet in intelligence is that you don't tell anyone anything," John Pike of the Federation of American Scientists told *E Magazine.*

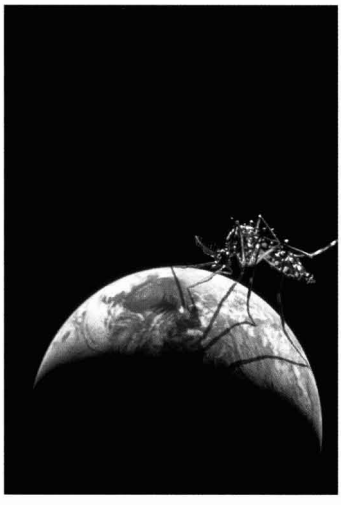
Scientists also worry that some of the results the CIA presents will not be reproducible because civilian scientists do not have access to the same type of equipment that the CIA does. Another problem scientists foresee is that the process of gathering environmental information may be too expensive, especially in a time of massive federal budget cuts.

Finally, the new Republican-dominated Congress, which is largely against increased spending for the environment and for increased defense spending, may believe that the proper role of the CIA does not include collecting scientific data or any data other than that of national security.

Climate's Impact on Malaria

Hoping to provide a tool that could aid scientists and world health authorities in stemming the spread of malaria throughout the world, a team of four scientists from The Netherlands has created a mathematical model that could predict the impact of global climate changes on malaria risk worldwide. Findings from their recent research published this month in *EHP* (pp. 458–464) suggest a widespread increase in risk due to the geographical expansion of areas suitable for malaria transmission.

According to the study by Willem J.M. Martens and colleagues, climate changes expected during the next century could potentially alter both the distribution and incidence of malaria—a disease believed to afflict more than 300 million people and kill more than 1.5 million each year.



WHO/TDR/LSTM/Joseph Tart

The mighty mosquito. A combination of factors, including climate change, could increase the epidemic potential of malaria-carrying mosquitoes.

Malaria parasites, plasmodium, develop inside mosquitoes and enter the human bloodstream through mosquito bites. The parasites develop through many growth stages and ultimately cause host red blood cells to erupt, resulting in flulike symptoms. The parasite's life cycle depends on transmission between mosquito and humans. Malaria incidence depends on several factors—the abundance of the anopheline mosquito species, human behavior, and the presence of malaria parasites. Anthropogenic climate change may impact the incidence of the disease as well, by affecting the behavior and geographic distribution of the mosquitoes, as well as the life cycle of the parasite. Climate change could also influence factors such as vegetation and the availability of breeding sites.

To predict and assess such changes, the scientists employed an integrated mathematical model to estimate the possible spatial shift in areas prone to malaria transmission, considering possible changes in the worldwide burden of malaria due to changes in climate. The model incorporates three interrelated modules, or systems: the climate system, the malaria system, and the impact system. These systems are linked together in a straightforward manner, with output from one system serving as input for the next.

To generate climate scenarios, the research team used a climate assessment model known as IMAGE (Integrated Model to Assess the Greenhouse Effect) to simulate greenhouse gas emissions and their effect on global mean temperature. The simulated global mean temperature changes are then converted into regional seasonal temperature and precipitation changes by standardizing the output of a General Circulation Model (GCM).

The mathematical model also incorporates the basic reproduction rate of plasmodium, which researchers defined as the average number of secondary infections produced when one infected individual enters a host population where everyone is susceptible. The basic reproduction rate is used to calculate the critical density threshold necessary to maintain parasite transmission. Researchers also defined the epidemic potential of malaria as the reciprocal of the vector population's critical density and used this as a comparative index for estimating how changes in temperature and precipitation patterns may affect malaria risk. Scientists worked other submodels into their research as well, including a standard population model and an epidemiological model for infectious diseases.

According to Martens, this study, part of an ongoing project begun in 1992 at the Dutch National Institute of Public Health and Environmental Protection, goes a step beyond previous research in this area: "Most other studies focused only on climate change effects on mosquito populations. We modeled the climate system, mosquito system, and human system in order to arrive at [a] better understanding of the complex interactions between [them]," Martens said.

Martens said he and his colleagues pursued this project because little attention had been given in the past to assessing possible adverse health effects of global environmental disturbances through environmental modeling systems. "Most of the studies focus on just one aspect and do not pay attention to the possible synergistic health effects," he explains. "We try to fill this gap in scientific research."

This model shows further promise because it attempts to identify regions and populations vulnerable to the disease. In their study, Martens and his colleagues show that climate changes will expand the boundaries of geographic regions susceptible to malaria transmission, and thus bring about a widespread increase in potential malaria risk. According to the study, a global mean temperature increase of several degrees in the year 2100 increases the epidemic potential of the mosquito population in tropical regions twofold, and more than 100-fold in temperate climates. And, the study concludes, there is a risk of reintroducing malaria into nonmalarial areas.

"It is an excellent study," said Robert Mendelsohn, an economist and professor of forest policy at the Yale School of Forestry and Environmental Studies, who studies the economic impact of climate change in the United States. "It is exactly the kind of thing that needs to be done."

EHPnet

In the aftermath of tax season, some people may be looking for examples of federal money being put to good use. One such example can be found on the Internet. The federal government has an extensive World Wide Web (WWW) server that is a tremendous information resource and is available free of charge to anyone who can log on. Within this single Web server, located at the URL http://www.fie.com/www/us_gov.htm, is a wealth of information on all branches of the federal government: executive, legislative, and judicial.

Sites under the executive branch include information on all of the cabinet level agencies under the control and direction of the president and the departments within this branch including, for example, Defense, Education, Energy, and Health and Human Services. Each department listing has subheadings (hyperlinks) that may be located by clicking on them. In addition, access to the White House Server allows users to tour the White House, become acquainted with the presidential family (Socks included), and keep up to date on the president's latest statements. Users may also read a copy of the vice president's National Performance Review.

Under the legislative branch of the Web server, users can access the House of Representatives home page and obtain information on legislative schedules, membership of House committees, and how to contact their representative. As of March, the only information located under the hyperlink to the Senate is provided by Senator Edward Kennedy (D-Massachusetts). As of yet there are no hyperlinks set up under the judicial branch site. These areas may be under construction, as they are listed in the federal budget for 1995.

By far the bulk of information on the federal government Internet site is located in the executive branch department hyperlinks. These resources allow researchers to obtain information about possible research opportunities and find information on grants and contracts from a particular federally funded institute: at some sites, grant applications may be obtained simply by downloading them. Examples of some of the hyperlinks available include the Army's Environmental Technology Office, the National Marine Fisheries Service, the Department of Energy's Office of Environment, Safety and Health, the National Institutes of Health, Lawrence Livermore National Laboratory's Biology and Biotechnology Research Program, the National Biological Survey, the National Academy of Sciences, and the National Science Foundation.

Mendelsohn said the study is valid in that it considers not only ecological factors, but predicts where malaria could and should appear, and how climate could affect these areas. However, Mendelsohn says, the study fails to adequately address artificial intervention by humans and how that might affect malaria risk due to climate changes. "I was hoping they would address what could happen if man were involved," he says. While the model promises to serve as a useful tool for scientists and public health policy-makers, the research team cautions that any increase in malaria risk must be interpreted along with "the change in malaria transmission associated with the socioeconomic development, population growth, and the effectiveness of control measures."

Climatologist Laurence Kalkstein of the University of Delaware's Center for Climatic Research, who worked on a model to assess the spread of dengue, another tropical disease spread by the mosquito, praised the Martens study. "I believe it's a good attempt to bring together factors to slow the spread and emergence of malaria," he said. "We're working with [the researchers] to provide a more sophisticated climatological component for the model."

While preventive and protective measures including vector control are available to individuals, families, and communities at risk for contracting malaria, scientists and health officials worldwide continue in their search for a viable malaria vaccine. At this point, the greatest hope appears to rest with a vaccine known as SPf66, formulated by Colombian physician and chemist Manuel Elkin Patarroyo. The first malaria vaccine, SPf66 targets the later, more complex blood stages of the malaria parasite and functions to prevent disease rather than to prevent infection.

"The Patarroyo vaccine is a major breakthrough in the scientific efforts to elicit protective immunity in humans by artificial immunization," says Renato Gusmao, director of the Pan American Health Organization's division of communicable diseases and prevention control in Washington, DC. One advantage of SPf66, according to Gusmao, is that it is a synthetic peptide free of biological impurities. Clinical trials have shown it to be nonimmunogenic, safe for human use, and partially effective (31–67%) in reducing symptoms of malaria disease caused by the *P. falciparum* mosquito.

While recent clinical trials have shown promise, some within the international scientific community evince skepticism toward SPf66 as an effective antidote in widespread use. Gusmao says that one problem lies in production methods. Because the vaccine has been produced by an experimental laboratory, potential production volume is limited and lot-by-lot production is subject to variations, according to Gusmao.

"The next step is the construction of a GMP [Good Manufacturing Practices]-level production plant," Gusmao says. Standard, high-volume production will allow increased coverage for the massive clinical trials needed to overcome the statistical weakness of the trials published to date. Such a facility would also give scientists a chance to tinker with the vaccine's formulation—improving the standard peptide by remodeling it, improving or changing the vaccine's adjuvant, and altering the drug's dosage or route of administration.

According to Gusmao, a GMP plant is expected to begin production in 1997. "Hopefully, the continuous efforts of Dr. Patarroyo's group to improve the basic SPf66 will [make it] available for GMP production at that time," he says.

Meanwhile, research efforts are underway to develop two different vaccines: one to block transmission and one to block infection. However, Gusmao says, "both developments have failed to show significant levels of protective immunity thus far."

While the quest for a useful, widely available vaccine continues, government and public health officials around the world will continue their struggle to counteract the devastating effects of the disease on the populations most at risk. Early diagnosis and immediate and adequate treatment, along with established preventive and protective measures, remain the chief weapons in the battle against malaria. Tools such as the Martens model for predicting the incidence of malaria may yield valuable information on the subtle interplay between environmental, biological, and climatological factors and malaria risk.

First Pan American Conference on Food Safety

May 14–19, 1995
Mexico City, Mexico

An important conference on Pan American food safety will explore current issues, new concepts, and future directions for food safety and quality in the Americas. Many food quality and safety issues arise from the increasingly complex marcketplace within the region combined with rapid advances in food technology and the impact of the North American Free Trade Agreement (NAFTA), and other similar treaties, on trade and distribution. The presentations and discussions that will take place during the conference are aimed at advancing the harmonization of food safety regulations throughout the Pan American region and beyond.

A distinguished group of international experts will cover a wide spectrum of subjects related to food safety and quality including:

- Sanitary verification of foods, sanitary food packaging, controls in food preparation, HACCP, and street foods.
- Chemicals in foods and water, microbiology, mycotoxins, food biotechnology, and food irradiation
- Legislation and the consumer, total quality control, quality control administration, and controls and challenges.

This very exciting program will provide participants an opportunity to share perspectives and gain practical insights into this diverse issue through plenary presentations, poster sessions, technical exhibits, and informal gatherings.

The conference is sponsored by the International Life Sciences Institute (ILSI) and ILSI Mexico in collaboration with numerous other international and national agencies and organizations.

Target audience: Those interested and concerned with food safety and quality, including national and regional health policy planners and managers, scientists and technologists from industry, government, and academia, as well as food processors, food and health enforcement personnel, and consumers will benefit from attending the conference.

Call for posters: A poster session will complement the plenary sessions, which will feature invited speakers. Interested investigators are encouraged to submit abstracts for consideration for poster presentation.

Further information: A meeting announcement, which includes registration information and poster submission information, is available from:

Lili Merritt
Telephone: 202-659-0074
Fax: 202-659-3859
Internet: meetings@dc.ilsi.org

Protecting the People Who Feed Us

Editor's note: This article on the University of California-Davis Center for Environmental Health Sciences is the sixth in a series that appears intermittently in NIEHS News. The series highlights the activities of Environmental Health Sciences and Marine and Freshwater Biomedical Sciences Centers.

The University of California-Davis, located in California's lush central valley, began in 1905 as Berkeley's "farm" where students came to study agriculture. Since that time, UC-Davis has become a full-service campus. The UC-Davis Center for Environmental Health Sciences was established in 1992 and currently consists of 10 departments. Under the direction of Fumio Matsumura, a professor of environmental toxicology, the center takes an interdisciplinary approach to research in the fields of epidemiology, organ toxicity, biomarkers of exposure, and mechanistic toxicology.

Studies of the occupational health of agricultural workers and the specific hazards associated with their work, such as dermal exposure to pesticides and inhalation of agricultural dusts, are conducted in collaboration with National Institute of Occupational Safety and Health and the State of California. Center investigators collect biomonitoring data in farmworker communities using blood and urine tests, chest radiograms, spirometry, and health and work questionnaires. In addition, soil is tested and air is monitored using portable air sampling pumps.

At the Institute of Toxicology and Environmental Health (ITEH), reproductive biologists Bill Lasley and James Overstreet focus on the reproductive health of farmworkers. Their goal is to develop assays for urinary hormone metabolites that can be used to detect reproductive toxicity in female or male workers. Tests are being developed that can detect infertility in women and men and menstrual dysfunction in women, as well as spontaneous abortion and abnormal pregnancy. Many of these assays have already been used by epidemiologists in studies of exposed workers.

Miller of the Department of Environmental Toxicology conducts research on male reproductive toxicity. She is investigating cellular mechanisms that make the testis uniquely vulnerable to adverse effects after exposure to environmental chemicals such as nitroaromatic compounds, many of which are used as agricultural chemicals, the fungicides benomyl and carbendazim, and the rice herbicide molinate. Miller studies the role of metabolic activation in testicular toxicity, testicular tubulin as a target for toxicant action, and immunocytochemical probes for assessing testicular damage. Her group has found that carbendazim, a metabolite of benomyl, inhibits testicular ß-tubulin assembly at a much lower concentration than that which affects the brain tubulins. The microtubules in the testis may have a role in these differential effects. Another study is focusing on the development of markers of toxic exposure in sperm. The study uses biophysical (motility, morphology), cellular, and biochemical approaches to develop markers for site-specific effects on spermatogenesis and/or sperm maturation.

Investigators in the animal/inhalation core are using cross-species studies to define possible effects of inhaling dust on farmworkers. Epidemiologic studies of California citrus and grape harvesters have shown an increased prevalence of signs of restrictive lung function compared to citrus orchard workers. Jerold Last and Hanspeter Witschi treated rats with single or repeated instillations of dust samples collected in the field. Responses of the lung were evaluated by analyzing lung lavage fluid, lung collagen content, histopathology, and cell kinetics. Dusts collected in vineyards have fibrogenic potential, whereas dusts collected in citrus groves are biologically less active. The animal/inhalation core will conduct more tests to confirm the effects of grape dust, assess the mechanistic basis of its ability to cause fibrotic lung changes, and identify the causative constituents.

There has been debate in recent years about the impact of rice straw on public health in the Sacramento Valley, the major rice-growing area of California. Much of the discussion has focused on amorphous silica fiberlike particles released by burning rice straw. There have been reports of unexplained cases of mesothelioma possibly associated with amorphous silica fiber exposure from sugar cane farming. Currently, the health effects of exposure to amorphous silica fibers are not known.

The ITEH has been working on a study of pulmonary pathology and mineral content of lung tissue from California farmworkers. Previous studies have suggested that California farmworkers have pneumoconiosis with inflammation and fibrosis associated with silica or silicate exposure and that restrictive pulmonary function may be associated with this population. The ITEH developed a protocol to evaluate subclinical histologic lesions and dust exposure. Histopathology of autopsy samples provides a method of systematically analyzing lung tissue for early, subclinical pneumoconioses in this population. Microdissection allows reproducible analysis of the lungs for histologic changes and morphometry.

Center investigators Dennis Hsieh and Daniel Jones are trying to determine the mutagenicity of fractions of combustion products of toxic wastes and diesel fuels. Mutagenicity of vehicular diesel exhausts, by-products from the incineration of plastics, and fumes of cooking meat were tested. About equal mutagenicity was found in the particulate and the vapor phases of the diesel exhausts. A toxic polyaromatic hydrocarbon from incineration of plastics was not mutagenic, and mutagenic heterocyclic amines were found in the aerosols of the cooking fumes but not in the vapor phase. Further studies will be performed to identify the major mutagenic components in vehicular diesel exhausts and the products of plastic incineration.

Jones is also characterizing the organic constituents of agricultural dusts using analytical techniques such as gas chromotography–mass spectrometry and liquid chromatography–mass spectrometry. Similar methods have been developed to detect pesticide metabolites excreted in urine such as mercapturic acids and dialkylphosphates. Electrospray ionization mass spectrometry has been used to determine the catalytic mechanism of epoxide hydrolase. Another class of important detoxifying enzymes, glutathione-*S*-transferases, consists of numerous individual isozymes whose distribution in tissues depends on gender. Mass spectrometry and enzyme assays are being used to investigate the mechanisms by which these enzymes become inactivated by exposure to reactive toxins.

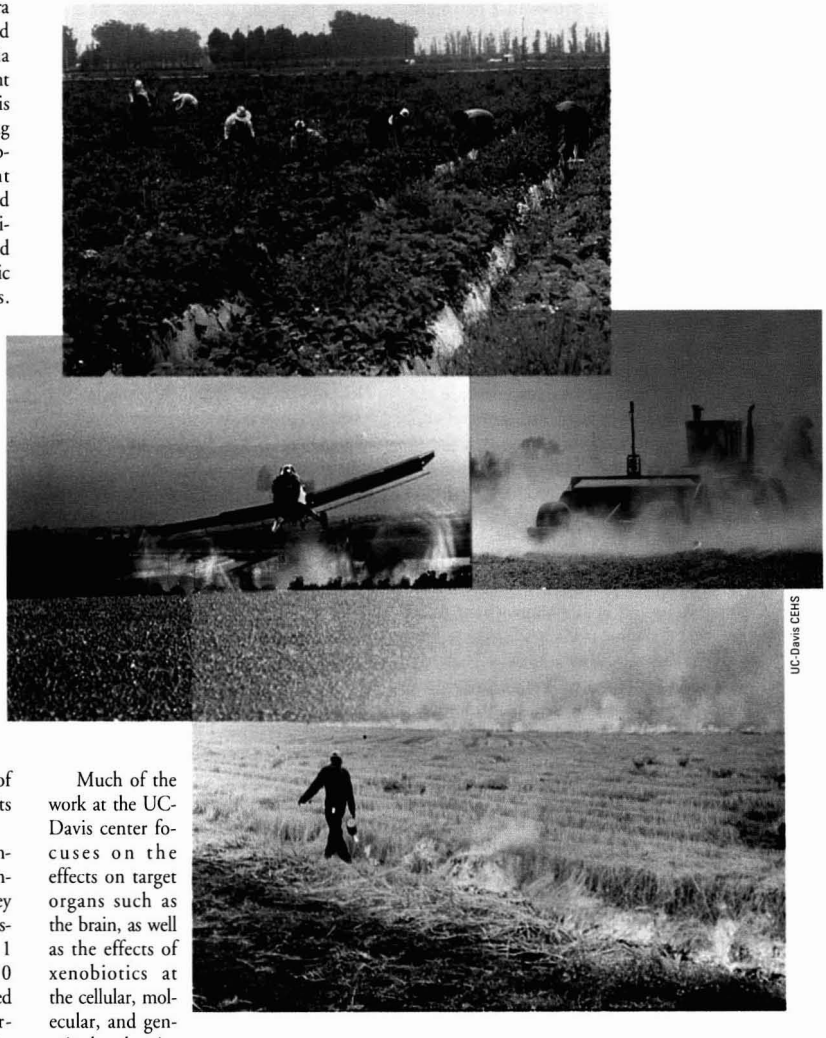
A study led by Alan Buckpitt is looking at the metabolism and toxicity of a pesticide,

ethylene dibromide (EDB), in isolated Clara cells and in airway segments from mice and rhesus macaques. EDB is metabolized via cytochrome P450 monooxygenase-dependent pathways to bromoacetaldehyde (which is thought to be the reactive metabolite binding to protein). Earlier studies demonstrated substantial differences in P450-dependent metabolism at different airway levels and between species. The toxicity and tumorigenic effects of EDB may be site selective and this will depend on the balance of metabolic enzymes present in different airways. Although animal studies with EDB were quite conclusive, earlier epidemiology studies of lung diseases among workers exposed at relatively high levels were inconclusive. Center studies are intended to provide fundamental data on carefully defined subsections of the lung, leading to a better understanding of the metabolism of compounds like EDB.

The laboratory of Robert Rice in the Department of Environmental Toxicology studies the responses of human keratinocytes in culture as a model for epidermal toxicity. One focus is the growth inhibition and genotoxicity of mycotoxins and heterocyclic amines, which are greatly potentiated by inducers of cytochrome P450 activity such as TCDD. Rice and coworkers also study arsenic perturbation of differentiation that may contribute to its carcinogenicity.

Matsumura and Essam Enan have examined the effect of TCDD and other dioxin-type chemicals on glucose transport. They showed that TCDD reduced glucose-transport activity in normal keratinocytes in 1 hour at concentrations as low as 10 nanomolar. By contrast, TCDD stimulated glucose transport in immortalized keratinocytes. Further studies will address the molecular mechanism by which TCDD and its congeners alter glucose-transport activity, with emphasis on species and sex differences.

Some organophosphate esters cause long-term damage to the nervous system known as organophosphate-induced delayed neuropathy (OPIDN). The mechanism of toxicity underlying OPIDN is not known, but inhibition of an enzyme known as neuropathy target esterase (NTE) may be involved. Center investigators use highly differentiated nerve cultures, species sensitive to OPIDN such as the chicken, and protein isolation to study OPIDN and the role of NTE. Recent work showed specific effects of OPIDN-causing chemicals such as diisopropyl fluorophosphate excluded kinesin protein phosphorylation as a mechanism for OPIDN and demonstrated that phospholipase A_2 effectively solubilizes NTE in its active form. This work forms the basis for development of monoclonal antibodies to NTE.



UC-Davis CEHS

Agricultural workers are exposed to pesticides by a number of scenarios including foliar contact, dust from field preparation, aerial spraying, and burning.

Much of the work at the UC-Davis center focuses on the effects on target organs such as the brain, as well as the effects of xenobiotics at the cellular, molecular, and genetic levels. An example of a multilevel study is the research on epoxide hydrolase (EH). EH is found in most organs in the body and is believed to play a key role in the detoxification of oxides and epoxides. Such epoxides are, in many cases, the actual carcinogenic and mutagenic substances formed as the by-products of metabolism of environmental pollutants such as pesticides and polycyclic aromatic hydrocarbons. Charles Plopper has developed a method to locate distribution of EH in the kidney cells of the rat. Future studies will focus on EH in the lung and liver using light microscopy and ultimately electron microscopy to locate distribution of EH at the subcellular and suborganelle levels. David Grant and Bruce Hammock have also been working on several different EH projects including mapping of the soluble EH gene. Their goal is to determine how and to what extent EH affects differential susceptibility to toxic exposures.

Carboxylesterases are important in the metabolism of xenobiotics as targets of the action of several classes of toxins. In support of work on NTE, surrogate spectral substrates have been made that will be valuable in the purification of NTE. Spectral substrates for butyrylcholinesterase have been produced that are 10 times more sensitive than standard substrates. Similarly, new substrates for hepatic carboxylesterase assays have resulted in a 10–50 times increase in sensitivity.

Wilson is collaborating with Isaac Pessah on research into the maturation of acetylcholinesterase (AChE) forms in cultured quail myotubes. Ryanodine is a potent, naturally occurring plant toxin and insecticide.

Their studies have shown that persistent block of the sarcoplasmic reticulum calcium ion channel with ryanodine induces a transition from embryonic to mature forms of the enzyme. This is the first time maturation of AChE has been demonstrated in embryonic myotubes in culture, and it demonstrates an important role of calcium channels in the process. Center investigators are now researching ryanodine receptors in cultured human cells to study the effect of pesticides.

Pessah is also examining key calcium regulatory proteins within the microsomal membrane of muscle and nerve cells which appear to be the target of site-selective oxidation by various quinone structures. Quinonoid structures are ubiquitous in the environment, having both natural and anthropogenic sources. Human exposure to quinones can occur clinically (e.g., the antineoplastic anthraquinones) and by environmental exposure to diesel exhaust, cigarette smoke, and industrial particulate matter. Quinones are of significant concern to human health because their intrinsic electrophilicity can induce various patterns of acute and chronic oxidative damage to biological tissues. Quinone toxicity is closely associated with changes in cellular calcium regulation in a number of cell types. Ryanodine-sensitive calcium channels are uniquely sensitive to quinone-mediated oxidative insult. Recently, the center studies have shown that the microsomal membrane possesses a small number of highly nucleophilic thiols and that these thiols are located on the ryanodine receptor and its associated modulatory proteins. Inter- and intramolecular redox reactions between reactive sulfhydryls on the ryanodine receptor complex regulate calcium ion channel function and calcium transport across the microsomal membrane, which may be an important molecular basis for quinone-mediated toxicity. Pessah's laboratory is now determining the exact role that these altered macromolecules play in cellular dysfunction and organ-selective toxicity.

New Clues to Infant Mortality

Newborn babies in at least 20 countries have a better chance of surviving than those born in the United States. A paper in the March 1 issue of *The Journal of the American Medical Association* suggests that high rates of preterm delivery in the United States may be part of the problem.

For many years, researchers in the United States have focused on birth weight as a crucial component in infant mortality. Babies in Norway and other Scandinavian countries are heavier, and this was thought to be why more of them survived. "Our results suggest that birth weight itself is not the problem," said Allen Wilcox, the NIEHS epidemiologist who directed the study, conducted by an international team of researchers. Research comparing babies born in the United States and Norway showed that if the United States could lower its rates of preterm delivery to Norway's level, one of the lowest in the world, U.S. infant mortality might be decreased to Norway's level as well.

"The most surprising thing," said Wilcox, "is that even if we could reduce our preterm deliveries in the U.S. and lower our mortality, our birth weights would still be lighter than Norway's."

Wilcox points out that the study's findings are consistent with international trends. Japan and Singapore have surpassed the Scandinavian countries in achieving the lowest infant mortality rates in the world, despite the fact that babies weigh less in the Asian nations than in Scandinavia or the United States.

"We still don't know why the U.S. has more preterm deliveries than other countries," said Wilcox. "We don't even understand what causes labor to begin. But we do think these are the right questions to be asking. If we could aim more of our research towards figuring out how to prevent preterm deliveries, we might be able to make some real headway in lowering infant mortality."

The study was conducted as a collaboration among scientists at the National Institute of Environmental Health Sciences, the National Center for Health Statistics, the University of Bergen in Norway, and the Free University of Brussels in Belgium.

NIEHS/NTP Events

The Fourth International Congress on Toxic Combustion By-products will be held June 5–7, at the University of Utah's Foothill Housing Complex in Salt Lake City.

One of the most significant challenges facing industry today is the control of potentially toxic emissions from all types of combustion sources. The goal of the Congress is to provide an international forum for researchers and practitioners to share information, present recent developments, and discuss future steps in the formation and control of combustion by-products and the subsequent effects of exposure on human and ecological health.

The Congress will have invited lectures in the morning sessions and parallel technical sessions in the afternoon. A poster session and reception will be held on Monday afternoon, June 5. Topics will include the formation and fate of gas-phase by-products, particulate aerosols and soot; halogenated and other organics and metals; advanced diagnostics and control in combustion systems; the fate and transport of by-products when released into the environment; and the relationship between the by-products and their subsequent exposures and health effects.

NIEHS is a co-sponsor of the Congress with the School of Public Health, University of California, Berkeley; Sandia National Laboratory, Livermore, California; U.S. EPA; Coalition for Responsible Waste Incineration; and Advanced Combustion Engineering Research Center, Salt Lake City, Utah.

For more information contact Cathy Koshland, (510) 642-8769.

International ATSDR Congress on Hazardous Waste: Impact on Human and Ecological Health will be held June 5–8 in Atlanta, Georgia.

The purpose of the Congress is to promote exchange of findings and recommendations related to human and ecological effects of hazardous waste. The meeting, co-sponsored by the NIEHS, will bring together a variety of environmental health scientists, environmental engineers, clinical and public health physicians, health educators, public health administrators, industry health and safety managers, environmentalists, and the general public.

For more information contact John S. Andrews, (404) 639-0708.

NTP Review of Technical Reports on Two-year Animal Studies will be conducted by the National Toxicology Program's Board of Scientific Counselors Technical Report Review Subcommittee on June 20 and 21, at the conference center, building 101, NIEHS, in Research Triangle Park, North Carolina.

The meeting will be open to the public and registration is required. Technical reports to be reviewed at the June meeting are: codein, butyl benzyl phthalate, *t*-butylhydroquinone, salicylazosulfapyridine, scopolamine, hydrobromide trihydrate, and 1,2-dihydro-2,2,4-trimethylquinoline.

The reports on butyl benzyl phthalate, *t*-butylhydroquinone; salicylazosulfapyridine, and scopolamine will, in addition to the traditional two-year study results, report findings with groups of animals tested under mild dietary restrictions. A separate report will deal with the effects of dietary restriction on the results of these collected studies and draw some conclusions about the usefulness of this approach for performing toxicity and carcinogenicity studies. Also to be reviewed at this meeting is a short-term toxicity report on 1,4-butanediol, and presentations are planned concerning the toxicological findings of a series of prechronic inhalation studies on carbon disulfide.

The next scheduled review, also open to the public, will be December 5 and 6, at NIEHS, when the subcommittee will review reports on the toxicity and carcinogenicity studies of nitromethane, tetrafluoroethylene, molybdenum trioxide, D&C Yellow no. 11, sodium xylene sulfonate, and phenolphthalein.

For further information contact L. G. Hart, (919) 541-3971, FAX (919) 541-0719.

Risk Assessment of PAHs in the Environment will be held on June 26–28, at the Hyatt Regency Airport in San Francisco.

This conference on state-of-the-art data on health risk assessment of complex mixtures of polycyclic aromatic hydrocarbons (PAHs) will consider both cancer and noncancer risk assessment. The focus will be on new data relevant to hazard identification and dose–response assessment and issues relating to bioavailability of PAH mixtures in the environment.

The conference will bring together government, academic, and industry scientists involved in research and regulatory areas. The meeting is sponsored by the U.S. EPA and co-sponsored by the NIEHS, the U.S. Department of Energy, the ATSDR, the American Petroleum Institute, the National Center for Toxciological Research, the Electric Power Research Institute, the Society for Occupational and Environmental Health, and the Gas Research Institute.

For further information contact Alex Taylor, (215) 643-5466, FAX (215) 643-2772.

Update of Review of the Criteria for Inclusion of Substances in the Biennial Report on Carcinogens will be held June 29 and 30, at the NIEHS in Research Triangle Park, North Carolina.

This review is mandated by the Public Health Services Act (Section 301). The NTP Board of Scientific Counselors will meet to receive and review the report of the ad hoc working group, receive public comment on the report, and develop the board's recommendation concerning selection criteria. The meeting includes a public session for which registration is required.

The ad hoc working group of the National Toxicology Program Board of Scientific Counselors was established to receive public comments on criteria for inclusion of substances in the report and to review and make recommendations on the criteria. This ad hoc group met in April in Washington, DC, to receive public comments and review and make recommendations on the criteria. Issues addressed were the adequacy of existing criteria for future reports and the incorporation of mechanisitic data as part of the criteria.

A draft discussion and background document may be obtained from the contact listed below. Written comments must be received by June 16 to be considered at the review. Oral comments during the public session will be limited to five minutes to permit maximum participation. Written comments accompanying oral statements are encouraged.

For further information and to register, contact L. G. Hart, (919) 541-3971, FAX (919) 541-0719.

Rays of Hope in the Land of the Rising Sun

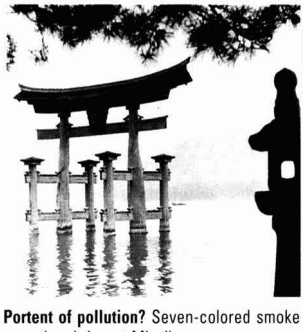
Joseph Tart

In 1970, French author Robert Guillain viewed with dismay "a dark ring of tall, smoking chimneys" creeping toward the shoreline across from one of the most famous sites in Japan: Miyajima, a sacred island bearing a shrine that at high tide seems to float on the sea. At the time, however, smokestack emissions were considered no threat. Quite the opposite: seven-colored smoke was viewed as an omen of prosperity. Now the third largest economy in the world, this ancient nation paid the same price as nearly every other industrialized country for its hasty entry into the era of manufacturing and consumerism. For a time, the air of its cities was choked with smog. A heavy aerial suspension of sulfur dioxide led to increased death rates from asthma and bronchitis. Water pollutants poisoned thousands. Japanese officials and official histories blame not only hasty development, but the structure and population of the country for environmental degradation and health problems. Eighty percent of Japan's population of 124 million people lives on 25% of the land area of this mountainous archipelago, where they must share the space with industry. Unchecked, this density of population, traffic, and economic activity has quickly overwhelmed this small country. Japan is finding that human health and industrial prosperity can co-exist, but the price is eternal vigilance and continual engineering.

Now the nation has some of the strictest pollution controls in the world. The worst of the air pollution has cleared, and the water is largely safe. Yet, prosperity continues to create new problems. More and more cars clog the roadways, overwhelming the pollution measures instituted in the 1970s. The water is safe for drinking and agricultural use, but the ecology of Japan's waterways is not always in the proper balance to support indigenous wildlife. Factories continue to emit greenhouse gases that contribute to global warming.

With this in mind, the nation's unique government–industry leadership is tailoring new plans to deal with emerging problems. Previously isolationist, Japan is now participating more in global pollution control efforts; always commercially minded, it wishes to supply the world not only with Walkmans, but with air pollution control technology.

Although Japan and the West seem to be largely on a common course now in environmental efforts, the origins of the Japanese environmental movement are unique. Unlike the United States, where the environmental movement was largely linked to the preservation and protection of nature, in Japan the movement was health driven.



Reuters/Bettman

Portent of pollution? Seven-colored smoke near the shrine at Miyajima was once considered an omen of prosperity.

Class Action

Industry exploded during the post-World War II recovery with the goal of transforming Japan from a feudal, agrarian society into a modern, middle-class export power. The Environment Agency reminisced in its official history, " . . . almost every kind of environmental pollution and destruction of nature could be observed in this small country, Japan. Deterioration of environmental conditions and destruction of the environment was considered to be inevitable, or even regarded as some sort of necessary evil consequent upon expansion of production."

The extent to which production would cause harm was not anticipated, however. The Japanese, said Miwako Kurosaka, senior associate at the World Resources Institute in Tokyo, had "introduced Western technology without deep consideration of what that meant. Technology is like a knife; if you don't know how to use it, it can be destructive."

Unwilling to pay the price, angry fishermen in 1958 broke into a paper factory in Tokyo that had polluted fisheries, inaugurating an era of social protest that would last into the early 1970s. As a result of the fishermen's actions, two laws designed to limit industrial water pollution and conserve water quality were instituted. These laws, however, covered only limited areas and substances and were not adequately followed, according to Hideshi Kurasaka, former chief of the Environment Agency's Planning Section and now a researcher at the University of Maryland.

In the 1960s, citizens began to show symptoms of exposure to air pollution and heavy metal contamination. Coughing, watery eyes, and a worsening of respiratory diseases were observed. A small number of men were seen by physicians near the city of Minamata exhibiting stupor, confusion, difficulty writing or using chopsticks, and other symptoms. These men were found to have brain damage from eating methylmercury-contaminated fish, and their particular syndrome became known as Minamata disease. Some citizens visited the industries which had dumped mercury into the local waters to seek redress, and were "completely ignored," said Miranda Schreurs, an environment specialist and assistant professor in the University of Maryland Department of Government and Politics. The syndrome eventually affected between 2,000 and 3,000 people and included effects such as birth defects and even deaths.

In 1967, 12 asthma victims living in Yokkaichi sued companies in the area's petrochemical complex for health effects allegedly caused by sulfur dioxide emis-

sions. A court ruled that the companies had been negligent in siting and operating the complex and for failing to use the best available technology to control emissions. Three other suits were filed by victims of Minamata disease, caused by mercury-contaminated water, and victims of itai-itai, a disease caused by waterborne cadmium that resulted in symptoms such as nausea, vomiting, diarrhea, and in some cases, kidney dysfunction. Together, the afflictions were called kogai-byo—diseases caused by pollution—and the legal actions became known as the Four Big Kogai Lawsuits. The industries whose emissions had caused the new diseases were heavily fined.

Families of the victims of Minamata disease also brought lawsuits against the factory manager and president of the company responsible, according to Shigeyuki Okajima, an environmental journalist and deputy director of the commentary department at *Yomiuri Shimbun*, a prominent Japanese newspaper. Victims also sought redress from the government for failing to stop the dumping, but were unsuccessful.

During this era and into the 1970s, the United States passed national pollution control laws and established the Environmental Protection Agency. Japan, taking its cues from the West, began its own internal reforms. The Pollution-related Health Damage Compensation Law was enacted, establishing a polluter-financed, nationwide compensation fund for victims of designated air and water pollution-related diseases, such as Minamata disease, itai-itai, chronic bronchitis, and asthma. Victims who lived for a specified amount of time in a designated pollution area became eligible for health and welfare compensation under the law.

In 1967, the Basic Law for Environmental Pollution Control was established to regulate air, water, and soil pollution. Japan established its Environment Agency in 1971, which quickly became responsible for formulating and setting emission standards. The National Institute for Environmental Studies was established in 1972 in the newly created Tsukuba City Science Park. In 1980, the cabinet issued an order requiring environmental impact statements to be filed for large public projects. The edict on impact statements is meant to serve as a guideline only, said Schreurs, and environmental quality standards are considered to be goals rather than requirements.

Yet, these goals are usually met through a combination of negotiation and the top-down style of the nation's government–industry partnership. The emission standards, for instance, spurred the Ministry of International Trade and Industry (MITI) to research and develop desulfurization technology and prompted a switch from high-sulfur to low-sulfur fuels. As a result, Japan became a world leader in manufacture of desulfurization and denitrification filters for industrial smokestack emissions, Schreurs said. With the Arab oil embargo, Japan began to rely more on nuclear power. Now, some 30% of the nation's electricity is supplied by nuclear power plants.

World Resources Institute-Tokyo

Miwako Kurosaka—Technology can be destructive if misused.

According to Mitsusune Yamaguchi, secretary of the Global Environmental Conservation Promotion Committee of the Tokyo Marine and Fire Insurance Company, Ltd., who spoke at the U.S.–Japan environmental conference sponsored by the University of Maryland in December, MITI met with each of the 87 business groups in its charge and showed them a plan to help make their activities more environment friendly. Each group was told to "voluntarily" (Yamaguchi's quotes) submit its own plan for compliance.

Many cities have instituted regulations that are stricter than national standards, Schreurs said. Lacking the international clout of MITI, local governments and citizens find they are able to enforce compliance the old-fashioned way: they may threaten a product boycott or suggest a certain permit be withheld unless standards are met, Schreurs said.

Difficulties in achieving goals in some areas remain. The Kyodo News Service reported last year that a central government survey found that many local governments had failed to identify soil and groundwater polluters in their areas. The localities blamed the failure on a lack of funds for enforcement. Although the Japanese business–government partnership is famous, companies have been known to conduct behind-the-scenes business arrangements to seek leeway in ambitious pollution-reduction timetables, according to Pat Murdo, Washington, DC spokesperson for the Japan Federation of Economic Organizations, known as the "Keidanren," which represents 1,000 leading Japanese businesses. "It's a normal situation," Murdo said. "They're not angels on either side."

With environmental safeguarding now a fact of life, the cost of compliance with regulations is built in when new construction begins. Japan ranks among the Organization for Economic Cooperation and Development (OECD) member countries that invest the most in pollution abatement and control, about 1.6% of gross domestic product. "In Japan, when a new factory is constructed at a cost of 100 billion [yen], anti-pollution devices account for some 30 billion," said Shigeyuki Okajima, vice chief of the commentary section for *Yomiuri Shimbun*.

Air Pollution

Japan faced unprecedented air pollution in the early 1970s. News photos sometimes showed Tokyo traffic police wearing

Reuters/Bettman

Minamata's legacy. Victims of mercury poisoning protested in front of the Environment Agency in 1992 when a district court cleared the agency of responsibility for the disease 40 years after it was first detected.

breathing masks, and small epidemics of chest discomfort, muscle spasms, and eye irritation among schoolchildren were reported. Around the same time, deaths from asthma and chronic bronchitis increased, according to a retrospective study from Mie University in Tsu.

Japan's establishment of sulfur oxide and nitrogen oxide emission standards, considered among the strictest in the world, led to dissipation of the famous "Tokyo smog," along with the air pollution in other cities. Through the introduction of low-sulfur fuel, development and use of desulfurization processes and installation of technology to filter smokestack gases, sulfur and nitrogen oxide emissions have been drastically reduced.

Reuters/Bettman

Fine kettle of fish? Past contamination of Japan's fishing and agricultural water continues to cause health problems.

"Japanese pollution problems peaked in 1972 and began to abate after 1980," Syouzou Azuma of Japan's House of Representatives reported during the Second U.S.–Japan Seminar on the Global Environment, sponsored by the Johns Hopkins Foreign Policy Institute and the Japan Institute of International Affairs in 1993. Now, Japan produces less air pollution than any other industrialized nation, according to Curtis Moore and Alan Miller, authors of *Green Gold: Japan, Germany, and the United States and the Race for Environmental Technology.*

Researchers continue to study the effects of sulfur dioxide inhalation. A study at Mie University found that although mortality from asthma and bronchitis increased during peak pollution years, it decreased as anti-emission measures reduced sulfur dioxide content of air.

Sulfur dioxide in Japan's air decreased by 82% over the past two decades, according to OECD. As of 1989, Japanese utilities emit only one-eighteenth the sulfer dioxide per kilowatt/hour of the average of the United States, Germany, France and Canada, according to the Tokyo Electric Power Company. Japan's sulfur dioxide emissions from mobile sources was about 20% of those in the United States, according to OECD figures from 1989.

Nitrogen oxides are another story. The nitrogen oxide burden in air dropped by only 21% over 20 years of emission controls, and while the OECD found this the best among its members, Japan still considers it a problem. "This is primarily due to a rapid increase in motorization," said Kurasaka. "The number of automobiles owned in 1990 is three times that in 1971. We can't stop the traffic, so we have to solve the problem by other methods," he said.

One such method is the 1992 law on special measures concerning reducing total nitrogen oxide emissions from vehicles within special designated zones. Under this law, residents in a designated zone are not permitted to use a vehicle that does not meet the standard on nitrogen oxide emissions. Another solution may be to create bus routes, or even covering main roads and scrubbing emissions clean of noxious gases. When engineers get together, they describe this approach as the "tunnel scrubber," Kurasaka said.

The health effects of nitrogen oxides have been difficult to sort out; however, one study speculated the gases may change the structure of lung proteins. "At high concentrations, it causes more coughing, more phlegm," Kurasaka said. "This is not sickness, but it is not healthy." What is uncomfortable irritation for most people may be a factor that can worsen asthma.

Another problem is continued emission of industrial carbon dioxide, a major greenhouse gas that contributes to suspected global warming. Japan emits 4% of the world's total industrially produced carbon dioxide and one-fifth of that of the United States, but aims to lower that figure even further. Reported schemes include bubbling the gas from industrial processes through beds of algae, which would consume the gas and convert it to carbohydrate.

A pledge to hold carbon dioxide emissions to 1990 levels by 2000 received much publicity in recent years, but there is still discussion about what it means. According to Murdo, industry wanted a much longer time line but then settled for the insertion of the term "per capita" in the reduction clause. Regulating emissions on a per capita basis would still permit an increase, Murdo said. The reduction is on construction of new nuclear power plants, as well as promotion of energy conservation and wider use of renewable energy.

Water Pollution

Industrial discharge of heavy metals into fishing and agricultural water—such as that used to irrigate rice paddies—has largely ceased, but research into past contamination and its ongoing effects continues.

Studies conducted by Nagasaki University School of Medicine and Kanazawa Medical University found that dietary cadmium causes progressive and irreversible kidney damage and that mortality rates from this damage increase in proportion to exposure to cadmium, compared to the general population. Renal dysfunction may even progress after exposure to cadmium has ended, another study at Kanazawa Medical University showed. Meanwhile, researchers at Argonne National Laboratory in Illinois said their research supported Japanese studies that suggest cadmium exposure enhances bone loss in post-menopausal women.

Japan now has two standards for water quality enforcement. One set governs emissions that might affect human health, the other deals with ecological issues crucial to the support of wildlife and the natural environment. Standards "on pollutants toxic to human health have been achieved," Kurasaka said. These standards regulate emission into water of 22 substances including cadmium, cyanide, lead and other heavy metals, and PCBs.

"For water quality associated with the living environment, however, the rate of achieving standards has been low, especially in enclosed water areas, such as lakes and reservoirs, bays, and inland seas," Kurasaka said. Recently, for instance, runoff of fertilizers and untreated residential water into lakes caused an overgrowth of algae, which cut off oxygen to fish and caused their death.

Acid Rain

Reports of acid rain were becoming common in the news during the early 1970s. After two days of precipitation during the summer of 1974, 4,000 Tokyo residents reported teariness and eye irritation—injuries apparently related to exposure to acid rain—to the Tokyo Hygiene Bureau.

The incident and other similar reports made the news, but these stories disappeared from the press in 1975, said Schreurs. Around this time, factory emission controls began to reduce the release of pollutants that contributed to acid rain in Japan. Mysteriously, however, the problem continued.

It was not until the 1980s, with Europe's concern over trans-border acid rain, that Japan began to worry that the same thing might be happening on its mountainous islands. Minor damage to trees and lakes led to fears of worse effects. Although Japan's soil is highly alkaline and therefore has managed to neutralize many of the effects of acid rain, there are doubts about how long this effect can last.

Japan is pointing the finger of blame at China, one of the biggest coal-burners in the world, and at South Korea. According to a six-year study sponsored by Japan's power companies, South Korea is responsible for 15% of the acid rain in Japan and China is responsible for one-half. Japan is trying to export sulfur scrubbers to China, while working with the United States to coax China to adopt more efficient energy technologies.

Cancer Rates

As in many industrialized countries, there is concern about the relationship between cancer rates and environmental factors. In Japan, cancer has been the number one cause of death since the mid-1980s, replacing stroke, which led the list for the three previous decades, according to Seiya Yamaguchi, president of the Environmental and Occupational Health Institute, a private consulting organization.

Stomach cancer is still the most frequent cause of cancer death among Japanese living in Japan, but its incidence is declining. Although the traditional diet containing pickled and highly salted foods is considered to be a factor, the role of genetics and *Heliobacter pylori* bacteria is also under investigation. Some studies have shown a link between higher rates of gastric cancer and the presence of *H. pylori*-related chronic gastritis.

The incidence of lung cancer is increasing, and polluting substances in the air are suspected of playing a role, but the Japanese also have a tobacco habit. Results of a recent study by Yamaguchi which broke down smoking by occupation showed that 48% of all Japanese office workers were smokers and 51.5% of agricultural workers smoke. The Centers for Disease Control in the United States estimates that 25% of U.S. adults smoke. Smoking has also become more popular among young Japanese women. In 1970, 9.8% of women aged 20–29 smoked; in 1990, the figure had risen to 20.2%.

Whereas breast cancer is the second leading cause of cancer mortality in the United States behind lung cancer, breast cancer rates are relatively low in Japan. The reasons are under investigation, but may include diet. The Japanese diet is high in phytoestrogens, substances found in food that animal studies and epidemiological studies suggest have an anticancer effect. Tofu, green tea, and other staples of the Japanese daily menu contain substantial levels of phytoestrogens.

U. of Maryland

Miranda Schreurs—Public access to environmental information is limited in Japan, but this may be changing.

Workers exposed to arsenic in copper and gold smelting factories, as well as people living close to these operations, have increased rates of lung and skin cancer, said Yamaguchi, but a causal relationship has not been established.

"Occupational and work-related diseases have been found in 1991 to be around three percent of total workers in Japan," Yamaguchi said. "However, the incidence of disease has gradually changed from substance-related poisoning and/or injuries to psychological disorders caused by several kinds of stress and social, familial anxiety." The Ministry of Labor has instituted preventive measures, such as the Total Health Promotion Plan, which makes it an employer's responsiblity to provide stress-reduction opportunities such as sports facilities.

International Cooperation

Since the 1970s, Japan has entered into a number of agreements with the United States to provide for cooperation in scientific research and policy development, many of which address issues of environmental health.

Two of the main policies shared by these two governments are the Agreement on Cooperation in Environmental Protection and Development Related to Innovative Environmental Technology. In addition, under the U.S.–Japan Cooperative Medical Sciences Program, a panel of U.S. and Japanese scientists meet annually to address the issue of environmental carcinogens. Nine other panels meet under this program to discuss other areas of health such as infectious disease. David Strother, Japan program manager with the U.S. EPA's Department of International Activities, says that programs such as these provide impetus for research and policy development. Said Strother, "Once a year, people have got to wake up and say 'What have I done? What do I need to do?'"

Many Japanese scientists conduct pre- and post-doctoral training in the United States under programs administered by the National Insititutes of Health's Fogarty International Center.

Risk Assessment

A realization of Japan's scientific establishment has been that Japan so far lacks a mechanism by which to measure the dangers that polluting substances pose to both population and nature. Rather than conducting risk assessment science, government and industry simply responded to health concerns. Now, he said, the nation's

WHO/UN PHOTO

The people press. Japan's rapid population growth exacerbates existing environmental problems.

Reuters/Bettman

New voices. Japanese environmental activists protest against the arrival of 1.7 tons of plutonium to the Tokai nuclear power plant northeast of Tokyo.

leadership would like to branch out, and it is beginning to rely on research conducted in the West, including the United States, to assess Japan's risk from substances such as dioxin and airborne mercury. "We want to broaden and cover more substances," Kurasaka said.

The media has kept the public informed of environmental risks since the 1960s, but now the government produces a steady stream of reports and position papers that receive attention even outside Japan. Although Japanese officials may seem open about some of the remaining pollution problems in their country, researchers point out that the government decides how much scientific information will be released to the public about any given risk. "Japan is a far more closed society than the United States when it comes to information," Schreurs says. "There is no Freedom of Information Act, so right there the public's access to information is limited." The public, Schreurs said, is largely acquiescent in this arrangement, but there are signs this is changing. A survey conducted by the Japan Center for a Sustainable Environment and Society following the 1993 Earth Summit in Brazil indicated that environmental awareness among Japanese was increasing. Environmental education ranked at the top of a list of priorities presented to survey respondents.

The Future

For the next century, Japan has two main environmental goals: domestic peace of mind for future generations and leadership in the international sphere, said Prime Minister Tomiichi Murayama upon acceptance of an environmental plan.

Based on passage of the basic environmental law in 1993, the Japanese cabinet in December adopted a plan that "incorporates the concepts of recycling, co-existing with nature and the participation of all groups in the nation to protect the environment," the Kyodo News Service and others reported. Under the law, governors of severely polluted prefectures are developing environmental projects to be approved by the prime minister. At least 150 programs for 39 areas had been approved by mid-winter, Kurasaka said.

Industry, through the Research Institute for the Earth, a government–industry organization sponsored by MITI, is searching for technologies to remove or recycle contaminants such as carbon dioxide, while MITI itself is pushing for investment in ways to boost energy efficiency.

Also under discussion are ways to clean up land contaminated by runoff from toxic disposal areas. The government instituted measures to govern dumping and protect farmland, but hasn't come to any conclusions about past toxic waste that may be trickling into residential areas. "This hasn't caused any problems yet, but it may have the potential one day to cause problems the way Love Canal did in the United States" unless new regulations are instituted, Kurasaka said.

U. of Maryland

Hideshi Kurasaka—Japan has achieved much of its goals for human health standards.

Under discussion is a Superfund-like measure. Last fall, the government also announced a fresh set of directives to prevent trichloroethylene—widely used by dry cleaners and semiconductor makers—and other widely dumped, cancer-causing agents from further seeping into soil and groundwater. A 1988 survey of 10,000 wells found that trichloroethylene contamination exceeded acceptable limits in 222 wells. The chemical is regulated under the 1989 water pollution control law, but seepage continues in some areas.

Japan's participation in global activism is increasing. In April 1990, MITI announced its plans for New Earth 21: Action Program for the 21st Century, which calls for international cooperation in establishing a 100-year plan for environmental clean-up after 200 years of pollution caused by the industrial revolution. Prior to meeting with U.S. EPA Administrator Carol Browner in November 1994, Sohei Miyashita, Japan's Environment Agency director general, said the United States and Japan "are in a position to lead the world's environment policy."

Japan's nongovernmental organizations, which tend toward nature appreciation, tend to be smaller and quieter than U.S. environmental groups. A few, however, are activist such as the Nature Conservation Society of Japan, which opposes construction of an airport that would endanger wildlife on Anajima Island and, in cooperation with the World Wildlife Fund, composed the "Red Data Book" leading to passage of laws to protect endangered species. "A matter of great urgency is promoting an increase of membership of nongovernmental organizations to support our activities," said Takuko Hasegawa, an NACS research officer.

Ironically, the industry that Japan exports—its factories in developing nations, particularly Asia—do not follow the sterling example of their homeland. *The New York Times*, *The Economist*, and others have assiduously reported incidents of heavy-metal poisoning among residents of communities around Jakarta Bay, Indonesia, site of many Japanese-operated factories, and severe air and water pollution near a copper smelter owned by a Japanese consortium. "We remain naïve when building factories in developing countries. It shames me to say that some Asian people remind us, 'Please do not make me another victim of Minamata,'" said Okajima.

Big companies are beginning to behave more responsibly, one reason being they can afford to. Smaller companies may take a while longer. Among all companies, however, awareness is growing. "Business people are more concerned about such criticisms," said Kurosaka. "Japanese business is realizing it cannot contribute to those things any more." Kurosaka continued, "All Japanese economic activities depend on resources of other countries. It means our image is more important than before. But it's more than image; it's survival. Japan must maintain good relations with these countries for survival."

Jan Ziegler

Jan Ziegler is a freelance journalist in Washington, DC.

Third Congress of Toxicology in Developing Countries
Cairo, Egypt
November 19-23, 1995
Together for Human and Environmental Welfare

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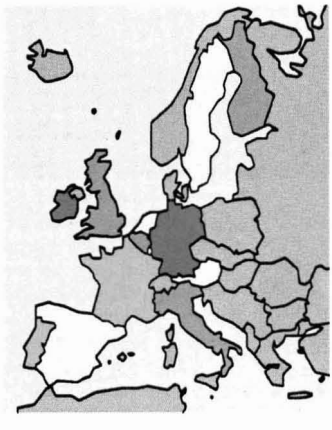
All's Not Quiet on the Western Front: Europe's Continuing Environmental Battle

From the cool northern climates of Scandinavia to the warmer regions along the Mediterranean, the countries of Western Europe face chronic environmental health problems that have evolved since the Industrial Revolution more than a century ago. Today, Western Europeans continue to struggle with the environmental legacy of their economic development, including extensive urban air pollution, accumulated pesticides and other chemicals in the soil, groundwater, and drinking water, acid rain, and the complicated disposal of hazardous and radioactive waste. Like other developed nations, they also face a variety of competing interests: how to reduce pollution levels while maintaining economic and industrial strength.

"Many of Western Europe's pollution problems and environmental laws are similar to ours here in the United States," says Michael Waters, senior scientist and associate laboratory director for international programs at the U.S. EPA. "Much of their environmental research is also analogous, including, for example, studies of automobile emissions in Italy and air pollution in Scandinavia."

Tied to climate, culture, human activity, and political and social commitment, each country has developed its own set of environmental issues to be addressed and strategies to deal with them. At the same time, national solutions have been both enhanced and complicated by the strengthening of the European Union (EU). Formerly known as the European Community, the EU shapes continent-wide environmental policies for its 15 member states: Britain, France, Germany, Italy, Spain, Belgium, Denmark, Greece, Ireland, Luxembourg, the Netherlands, Portugal, Austria, Sweden, and Finland.



In addition, numerous international agencies and organizations have developed departments that are also proposing solutions for Western Europe's environmental problems, including the Organization for Economic Cooperation and Development (OECD) and the United Nations Environment Programme (UNEP).

In recent years, the EU has passed a number of "very strict laws, very strict regulations, that had never been seen before in Europe," says Dinko Kello, director of the Environmental and Health Policies Unit for the World Health Organization in Copenhagen and secretariat to the European Environmental and Health Committee. "During the 1970s, when the United States was developing some of its most important environmental laws, Western Europe was, quite frankly, back in the Stone Age. In the 1970s, Europe was just starting to realize there was an environment."

"But today we can see a very major reduction of sulfur emissions throughout Western Europe, for example, because the legislation that had been discussed for years is now coming into force," says Kello. "One of the major achievements is the closing of 32 main coal mines in the United Kingdom. But one of the questions that still persists, since the Union [EU] is made up of sovereign governments, of course, is how to compensate those countries for their economic sacrifices. We have a five percent tax on all purchases throughout Europe which is partially used for that reason, to compensate countries in such conditions."

Last June, Kello organized a conference of 100 environmental and health ministers and other representatives from the various countries to address some of these issues. At the meeting in Helsinki, Kello says, the group was trying "to sort out some of the confusion and overlapping work that goes on. A lot of organizations are dealing with bits and pieces of the whole picture. You've also got the OECD, UNEP, the European Commission, the Council of Europe, and then many supporting organizations, including the World Bank."

Delegates to the European Parliament, the legislative arm of the EU, meet regularly in Brussels to set minimum environmental standards their countries must meet. The European Commission is the executive branch of the EU and also has the power to initiate, administer, and enforce legislation. In 1991, the EU issued 280 directives and regulations on environmental matters, including 120 on industry, trade, and pollution. In May 1993, 200 pieces of environmental legislation were passed. Kello says that Western Europe's "green parties" were often in the majority in the European Parliament during the 1980s and that their efforts were critical in developing and passing tough legislation in the parliament.

"Experience has taught us that the industries do not take the measures by themselves," says Ritt Bjerregaard, the EU's newly appointed Environment Commissioner, in the January–March issue of *Tomorrow* magazine. "That is why common [European] Union rules are clearly required for what emissions, effluents, and dangerous substances should be permitted and how they should be handled. . . . As a Dane, I have a spontaneous sympathy for and attachment to the environmental movements, but I must be aware of the strong and opposite interests in this area and try to handle them all. We must have public debate before decisions are made."

Shared Problems

Western European governments are often at odds over environmental issues, especially those without boundaries, such as acid rain and river-borne pollutants. Because the winds of Western Europe travel in a northeasterly direction, countries in Scandinavia and

northern Europe are hardest hit by acid rain generated farther south. For example, more than 60% of Holland's severe acid rain problems originate beyond its territory—a level it can reduce only with the cooperation of its neighbors. A 1993 international conference in Geneva failed to produce an agreement on decreasing acid rain in Western Europe; the United Kingdom was among those countries that refused to promise to reduce its sulfur emissions (one of the ingredients in acid rain) by the proposed 60%. Although the UK still relies heavily on the burning of coal, the chief source of sulfur dioxide, a 1991 report by the British Medical Association claims the country has reduced such emissions by 40% since 1970.

Despite a low overall infant mortality rate, infant respiratory-disease mortality in Western Europe remains three times higher than in North America, in part because of high levels of air particulates and sulfur dioxide, according to a 1993 report by Physicians for Social Responsibility. Air particulates and sulfur dioxide vapors can increase airway resistance when inhaled, especially in asthmatics. A 1987 World Health Organization report estimated that 5% of Western Europeans suffer from asthma.

In addition, countries bordering Eastern Europe, such as Finland, Germany, and Austria, must contend with ongoing migratory pollutants and other environmental threats from the former Soviet bloc. For example, Finland and its Scandinavian neighbors have been concerned with high pollution levels in the Baltic Sea, in great part a result of rampant industrialization and disregard for the environment in the former Soviet Union. In addition, the Austrian government is currently trying to stop the Czech Republic from building a Soviet-style nuclear reactor.

"Since they suffered from the effects of Chernobyl, the Austrians are concerned about the possibility of another severe accident if the reactor was not built to western standards," says David Schwarzbach, program associate for energy policy at the National Resources Defense Council in Washington, DC. "They're also concerned that wastes might not be properly handled and could migrate along some of their shared rivers."

But at the same time that many governments are seeking solutions to environmental problems, they must also focus on recovering from a nagging recession. This effort to combine environmental and economic concerns was widely discussed at the 1992 Rio Earth Summit, after which the EU issued its Fifth Environmental Action Program, called "Towards Sustainability—A Program of Policy and Action for the Environment and Sustainable Development."

For example, EU attempts to regulate emissions of chlorofluorocarbons (CFCs), implicated in the production of greenhouse gases, have often met resistance, especially from the French. The EU has directed its member states to phase out production of CFCs and other ozone-depleting chemicals, such as methyl chloroform, by the end of 1999, as agreed upon in the Montreal Protocol of 1987 and the Helsinki Meeting in late 1988. But although some countries have banned all production of CFCs before the end of the century, the compounds have a long atmospheric lifetime, and real reductions may not be seen for at least 100 years, according to the 1993 report by the Physicians for Social Responsibility.

WHO

Dinko Kello—Questions remain of how to compensate countries that make economic sacrifices for environmental gains.

EU member states are also required to run environmental impact assessments (EIAs) for major projects and wide-scale policy plans, examining them for potential effects on the environment, including air, soil, water, and public health. In Holland, for example, EIAs focus on energy-supplying industries such as coal, electrical, nuclear, and wind, defense (air bases, naval ports), harbors, artificial islands, and chemical and steel industries, among others.

Because its members are sovereign states with often conflicting agenda, the EU has been seeking ways to "harmonize" its many directives. A first step in this process is to integrate the separate protocols used in the many independent environmental studies conducted by industries, regulators, and international organizations. After the recent passage of an EU Harmonization Directive, the union's largest member states, including the United Kingdom, Germany, France, and Italy, agreed to review a major share of active investigations, resulting in less duplication, according to David Buffin, editor of *Pesticides News*, published by The Pesticides Trust in London. "This way, we can hopefully get more harmonization in the decision-making as well. Although each region has quite a different set of concerns, at least the data will be in agreement."

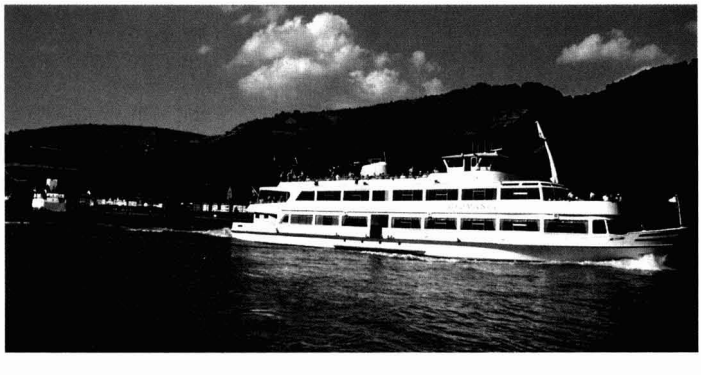
In addition, the OECD and the International Programme on Chemical Safety (IPCS) of WHO met in early March to hammer out a set of mutually acceptable conclusions and recommendations on chemical risk evaluations. While much of the discussion focused on the problems of getting good information to and from developing countries, the delegates recommended that a short-term pilot project be immediately undertaken "to ensure that completed evaluations had undergone examination by an internationally representative group of countries," according to the meeting summary. To make the review process easier, the IPCS and the OECD were "invited to develop a common harmonized format, together with guidelines for the preparation of evaluation documents, including Good Assessment Practice."

The Netherlands

Despite limited natural resources and its vulnerability to flooding, Holland has become a highly successful agricultural and industrial nation thanks to a sophisticated system of dikes, pumping, and draining. However, with half of the country below sea level and a rapidly growing population, Holland is also heavily polluted. One sign of this environmental decline: the otter, whose presence indicates water quality and healthy riparian ecosystems, is now extinct in Holland.

"Holland in particular has the problem of post-war industrial development and pollutants taking decades to percolate through to the groundwater," says Buffin. "This is causing a lot of worries in Holland—sort of like a bomb ticking away. And once you've contaminated the groundwater source, it's almost impossible to clean. Being located on lowlands makes the Dutch rely heavily on groundwater, but it also means the water is even more vulnerable to contamination."

Flowing from eastern Switzerland

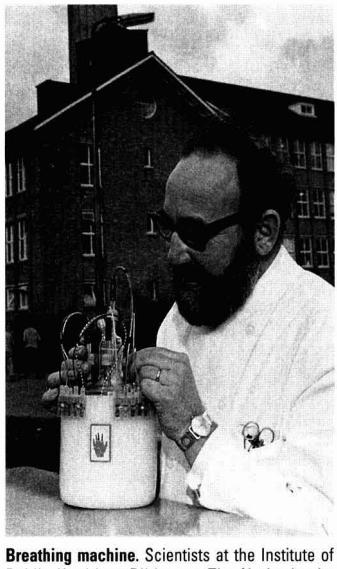


A clear success. Cleanup of the once heavily polluted Rhine River is one sign of progress.

through Germany to its North Sea delta in Holland, the Rhine River deposits industrial pollutants along its banks and into the sea. In recent years the EU has been working to "depollute" the North Sea as one of its many transnational projects. "The Rhine is a fantastic success story," says Kello. "It's a wonderful example of Western European countries coming together to solve a particular environmental problem. And the best news is that fish are now coming back to live in the Rhine."

Nearly half of Holland borders the North Sea, making it an area of particular concern, says Buffin. For example, persistent organochlorines are draining into the North Sea, not just from Holland but from Eastern Europe and the United Kingdom. Studies have shown a buildup of the organochlorine toxaphene in mackerel, dolphins, and porpoises in the North Sea, especially around Ireland and Scotland. But toxaphene has never been used in Europe. It is believed the chemical may have traveled for years from the United States or the Caribbean, where it was once used in cotton production. Toxaphene was banned in the United States in 1982.

In response to environmental degradation, the Dutch have developed a National Environmental Policy Plan (NEPP) that is rapidly attracting international interest. In presenting the plan in 1989, the Dutch government announced that "unless we set a different course quickly and resolutely, we are heading for an environmental catastrophe. . . . Therefore, the NEPP initially deals with environmental hazards caused by traffic, curbing carbon dioxide emissions, taking remedial action in cases of soil contamination, tackling acidification, and gaining better control of the entire waste chain."



WHO by T. Farkas

Breathing machine. Scientists at the Institute of Public Health at Bilthoven, The Netherlands, monitor sulfur dioxide in the air.

For example, the NEPP "seeks a fertilizer balance" to handle problems caused by agriculture and industry, according to a May 1994 article in *Environment* magazine. Under NEPP guidelines, groundwater must meet standards similar to those of drinking water; no more phosphate and nitrate may enter water and soil than can be absorbed through natural processes. The policy also calls for a 50% drop in the use of pesticides by the year 2000, an 80% reduction (relative to 1980) in sulfur dioxide emissions, and a 75% reduction in auto emissions of nitrogen oxides and hydrocarbons.

With its concentration of petrochemical industries, the shipping city of Rotterdam, considered the largest port in the world, is also the most polluted city in Holland, according to Ronald van der Oost, an ecotoxicologist at the OMEGAM Environmental Research Institute in Amsterdam. "Amsterdam is moderately polluted," he says, "in part because of ships traveling through the canals and sediments discharged from several sites. However, it's not very clear what the exact sources of pollution are in the canals. There are also pesticides from agricultural uses, and although the insecticide DDT is banned, there are still traces, along with PCBs from industry, detectable in the environment."

Inland lakes are also subject to pollution which migrates along streams and through underground leaching. The Bodensee, or Lake Constance, covers 207 square miles along the borders of Germany, Austria, and Switzerland. Through strictly enforced legal measures, the Vienna-based International Commission for the Protection of Surface Waters at Lake Constance has had considerable success in getting phosphates reduced in the lake from 87 to 43 milligrams per cubic meter from 1979 to the present.

Southern Continental Europe

In what the July/August 1994 issue of the *Bulletin of Atomic Scientists* referred to as the French "mess nucleaire," author Mary Byrd Davis criticized the French nuclear program for its "near-total secrecy regarding its waste-disposal practices." Davis noted that weapons production has spread contamination in the air, water, and ground. Military sites, she noted, are not regulated like civilian sites, and few environmental laws cover them.

Until such accidents were made public several years ago, a plutonium fire 37 kilometers from Paris in the 1960s was kept secret, as was a "mix-up" in fuel rods in 1974 that seriously contaminated a French plutonium workshop. In 1977, seven tons of uranium hexafluoride were released from a nuclear plant, creating a visible cloud of hydrofluoric acid. Nuclear sites in general, Davis reported, have been targeted as a source of air and water pollution, including suspect effluents released into rivers and ponds. For example, mercury released through sewers and into the air have led to detectable levels in lakes near the Mediterranean.

The Pesticides Trust

David Buffin—Members of the EU are working toward harmonization of research and decision-making.

In a dramatic case of accidental exposure to chlorinated hydrocarbons, a fault in a reactor in a chemical plant released dioxins into the atmosphere at Seveso, Italy, less than 20 miles north of Milan. The 1976 accident contaminated seven square miles around the plant and forced 900 people out of their homes. Though no one died as a result, residents near the plant suffered burns and skin rashes from exposure, followed by the symptoms of chloracne, a disfiguring skin disease caused by the exposure to dioxins and other chlorinated organic compounds. Studies on other effects of exposure are considered unreliable because few baseline data were collected before the accident. However, some records have shown an increase in soft tissue sarcomas, as well as a rise in the malformation rate among live births from 1.03 cases per 1,000 in 1976 to 19 per 1,000 in 1978.

The second largest country in Europe, Spain's urban air pollution levels regularly exceed the average for western Europe. In addition, tourism has damaged beaches in the Catalonia region and along the Mediterranean. Inadequate sewage and water treatment facilities have also contributed to severe pollution in the sea.

Traditionally lagging in environmental awareness, Spain has become more "eco-conscious" in recent years. For example, the Spanish plastics manufacturers established a special foundation to help increase environmental awareness throughout Spain. A September 1992 article in *Business America* asserted that "Spain has achieved remarkable economic growth at the expense of environmental concerns. But increasing pressure to comply with EC standards is now forcing Spain to address those concerns."

As the most polluted country in Europe, Portugal received more than $3 billion in structural funds from the EU in 1994 and 1995. The funds are earmarked to help improve site remediation, industrial effluent, urban water management, and solid waste collection, removal, and disposal. The Portuguese government is also working on improving the supply of potable water to urban areas and the safe removal of waste-

water. One area hard hit by such public sanitation problems is the Algarve province in southern Portugal, world-renowned as a tourist destination. During the high season, the Algarve population doubles to more than 800,000, increasing pressure on an already weak civil infrastructure.

The United Kingdom

In the 19th century, London became notorious for a thick black smog caused in part by incomplete combustion during the widespread burning of coal. Thousands of Londoners died from acute respiratory illnesses. In 1952, more than 4,000 people died as a direct result of air stagnation that caused a concentration of atmospheric pollutants, especially sulfur dioxide and suspended particulates, according to the 1993 Physicians for Social Responsibility report. Chronic bronchitis has been so common in the United Kingdom, that it is often referred to as "the English disease."

After the British government passed its first Clean Air Act in 1956, pollution levels began to drop dramatically. Industries were told to improve their combustion processes, and some workplaces stopped using coal altogether. Over the next 30 years, ambient smoke fell by almost 90% and ambient sulfur dioxide levels by 40%. However, London air pollution levels continue to regularly exceed WHO guidelines. To address this chronic problem, the British Royal Commission on Environmental Pollution plans to recommend stronger enforcement of regulations, as well as an increase in fuel taxes, which by discouraging consumption would help reduce carbon dioxide emissions, according to a July 1994 article in *The Economist.*

WHO by L. Taylor

Stripped sentinels. Acid rain from industrial pollution has decimated entire forests in Europe.

It is believed that food grown in England may be contaminated through the common practice of using sewage sludge, often laden with heavy metals, as a fertilizer for edible crops. Recent soil quality studies have revealed traces of zinc, copper, cadmium, nickel, and chromium on such farmlands. EU sludge regulations for 1996 will restrict the use of sludge as a fertilizer for edible crops, but some observers have suggested that heavy metals should simply be removed from the waste at its source, thereby allowing sewage sludge to be "recycled" for use on land. However, in April 1994, the United Kingdom criticized an EU wastewater treatment directive to remove phosphorus from discharged sewage because of the high cost of compliance for British sewage treatment facilities.

"Another rather big issue in the UK is the very high levels of breast cancer, especially in certain agricultural regions," says Buffin. "We believe this may be associated with organochlorines, especially lindane, whose levels are particularly high in vegetable production." Lindane, an insecticide with a slow rate of biodegradation, has been detected in the blood and fat tissue of the general public in a number of countries, probably as a result of food contamination, according to a 1993 report by Physicians for Social Responsibility.

"If you compare the UK today with five or more years ago, there is now a much greater acceptance that we can potentially cause problems through anthropomorphic activity," says Buffin. "But I think in terms of the European Union as a whole, the UK is seen as a country that keeps questioning everything. Society is still very split on many issues."

WHO/UN Photo by Zafar

Toxic playground? On World Health Day in 1988, children play outside a nuclear facility in France.

Scandinavia

In 1971, Denmark became the first industrialized European country to establish a ministry that focuses exclusively on environmental matters. In 1988, the Danish government established a set of stringent policies to combat the greenhouse effect by lowering carbon dioxide emissions. One highlight of that plan is the Rube Biogas plant, located in the flat marshlands of southwest Denmark, which converts farm fertilizer and slaughterhouse wastes into a clean energy source. The Danes also plan to expand their use of windpower and other alternative energy forms.

With 70% of their land covered by thousands of lakes and thick forests, most Finns live in the southern part of the country. Finland shares much of its eastern border with a heavily polluted region of Russia as well as its shoreline with the Baltic Sea, contaminated in part by industrial development in the former Soviet Baltic republics, Estonia, Latvia, and Lithuania. To help prevent further problems, the Finnish government has developed a program to work with Eastern European countries on environmental protection measures, especially on airborne and waterborne pollutants carried by the Baltic.

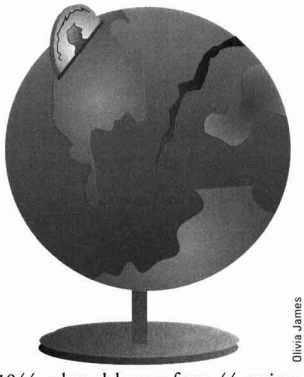
Among the countries of Europe, Sweden is often considered the most environmentally conscious of all. Attempts to remedy problems cross all sectors, according to Buffin. "There's always a lot of agreement from the beginning," he says. "Whenever the Swedes look at a program, everyone agrees on the best thing to do. Sweden's environmental laws are very strong and in fact much stronger than any other country. And now that they have voted to join the Union [in fall 1994], they may try to raise the level of environmental laws in other European countries."

As WHO's Kello points out, Western Europe has now emerged from the "Stone Age" and is well on its way to effectively managing its environmental and health problems. But perhaps the region's greatest asset—its rich patchwork of cultures and histories—may also present its strongest challenge: reconciling the needs of individual nations with the needs of an entire region of nations. In the areas of environment and health, sovereign governments must reach beyond their boundaries to seek solutions compatible to both sets of interests. With more transnational cleanup efforts and stricter regulations concerning air, water, and soil quality, the whole may well become greater than the sum of its parts.

Rebecca Clay

Rebecca Clay is a freelance journalist in Washington, DC.

Breaking the World Bank



Olivia James

In 1944, when delegates from 44 nations met at Bretton Woods, New Hampshire, to create the World Bank, they dreamed of an institution that would rebuild war-ravaged Europe, reduce poverty, and help further peace. In 1946, the World Bank opened for business, but its attention soon shifted from reconstructing Europe to fostering economic development in poor nations. Over nearly 50 years, the World Bank has extended $300 billion in loans worldwide to pay for 6,000 development projects such as roads and dams, mostly in developing nations. By 1993, the bank provided about $23 billion in loans annually. Although one might expect these nations to feel a debt of gratitude to the World Bank, currently 130 international organizations are running a vigorous public campaign against the institution. Using the slogan "50 Years Is Enough," campaign leaders argue that many World Bank loans and policies have done far more more harm than good, fostering environmental destruction, social disruption, and increased poverty.

Help or Hindrance?

World Bank defenders argue that the institution has delivered on much of its initial promise. "In country after country, the World Bank has made a difference," writes Henry Owen, senior consultant to Salomon Brothers and co-chair of the U.S. Bretton Woods Committee, in the September/October 1994 issue of the journal *Foreign Affairs*. "In many regions, the Bank's projects clearly have helped. Per capita income in both rich and poor people has substantially increased in the countries that have received the most Bank aid."

But critics of the World Bank are lobbying for reductions in American financial support of the institution. "We want no more funding for the World Bank until it proves it can be a positive force," says Steve Hellinger, executive director of the Development Group for Alternative Policies, a nonprofit organization based in Washington, DC, which is spearheading the 50 Years Is Enough campaign.

American taxpayers' largest recent contribution to the World Bank was $1.85 billion in 1993. These funds were provided to the International Development Agency (IDA), an arm of the bank that offers inexpensive loans to the poorest nations. Now the Clinton administration is asking Congress to provide another $1.85 billion.

World Bank defenders argue that it is an integral part of building damaged economies. Today, the bank contributes financing to rebuild South Africa's private sector, weakened after international anti-apartheid boycotts. The bank is also helping former communist Eastern Europe, including the Czech Republic, Hungary, Poland, Slovakia, and Slovenia, to embrace market economies and democracy.

Poland, in particular, has benefited from World Bank aid. "Poland was facing a lot of problems" after the communists left power, Owen says. "It had high inflation, runaway wages, but in one year, with financial stabilization by the International Monetary Fund, and funds to build infrastructure from the World Bank, Poland is a success story."

In a sense, the reconstruction of former communist economies returns the bank to its roots, the rebuilding of Europe. The vast majority of the World Bank's greatest accomplishments and biggest failures, however, have occurred in developing nations.

The bank's successes include easing hunger in poor countries during 50 years of explosive population growth and political turmoil. Since the Bank's beginnings, for example, it has contributed financial and technical assistance to the "green revolution" in agriculture, an initiative that began in the late 1940s to develop higher-yielding crops and better irrigation techniques for Third World farmers. Higher-yielding varieties of wheat and rice helped nations such as Pakistan, Turkey, Indonesia, Malaysia, Sri Lanka, and Mexico to build up food supplies.

Another notable success story is the bank's bolstering of India's agriculture to help that nation become agriculturally self-sufficient in the 1960s. The World Bank provided large-scale financial and technical assistance to encourage farmers to plant new crop varieties. As a result, India doubled its wheat crop between 1966 and 1972. The bank also helped India to build an infrastructure for food reserves and distribution. Today, the bank continues to fund and coordinate research and development of new technologies around the globe, especially in agriculture. In June 1994, the bank agreed to spend $100 million over two years to fund projects at the Consultative Group on International Research, a consortium of 18 agriculture research centers around the world studying new strains of crops, such as drought-resistant corn.

But critics question whether the World Bank has been effective in reducing poverty, considering the vast sums it loans. The number of desperately poor worldwide remains high. More than one billion people still live in severe poverty, with per capita incomes of less than a dollar a day, according to World Bank figures.

Furthermore, the World Bank has clearly made mistakes in funding projects that ended up damaging living standards and the environment in some developing countries. In one famous case, the bank loaned Brazil $443.4 million between 1981 and 1983 to build highways into the nation's northwestern rainforests and to establish 39 rural settlement centers to attract settlers. Settlers were supposed to raise tree crops, such as coffee and cocoa for export. But the government failed to help the settlers with promised agricultural extension services and credits, and the settlers, in desperation, began burning down trees to grow annual crops such as beans and maize. A few years later, when the nutrient-poor land was exhausted, the settlers were forced to abandon the ruined sections of forest.

For years, the World Bank failed to pay

enough attention to the environmental and social consequences of its policies, experts say. And too often the bank ignored the voices of local people. When the World Bank has helped to build hundreds of dams, power plants, and other projects in some developing nations, residents have been displaced from their homes without compensation for resettlement and driven into poverty, critics say. For example, coal mining and power plant projects in Singrauli, India, uprooted 200,000 people without compensation.

In the early 1980s, the World Bank began requiring that governments have a resettlement compensation program. Yet governments still fail to provide people with enough money to resettle, experts say. "The problem is that the bank must work with all kinds of governments," says retired World Bank Chief Economist Barend de Vries. In many cases, these governments can be incompetent, repressive, and corrupt.

"I'd be wrong to say that we've been brilliant in the area of resettlement," says Jocelyn Mason, environmental policy analyst at the World Bank. "Resettlement is very difficult; improving resettlement is an urgent priority."

Bank Organization

The United States and other wealthy nations actually support a minor portion of World Bank loans. The bank is a semi-independent arm of the United Nations that supports most of its projects by borrowing on the capital market; that is, the bank reinvests funds. It issues bonds and then loans investors' money to developing countries.

The bank is run jointly by representatives of donor countries and nations that receive the loans. It has 176 member nations, but voting shares are weighed in proportion to a nation's contributions to the bank. The United States is the largest donor and the bank's most influential member, with about 18% voting power.

The World Bank has three components. The largest part is the International Bank for Reconstruction and Development, which provides interest-bearing loans to moderate-income nations such as Brazil. Second, the International Development Agency makes below-market-rate loans to the poorest nations; the IDA generally loses money on these transactions, so they must be supported by the United States and other wealthy nations. Third, the International Finance Corporation's loans promote private-sector development and assist corporations that invest in developing nations.

The bank also works closely with the International Monetary Fund (IMF), another creation of the 1994 Bretton Woods conference, to help stabilize or reconstruct struggling economies. The bank is a powerful attractor of capital. It not only lends billions of dollars to developing countries, but its loans can legitimize projects, helping to draw additional funds from regional development banks, aid agencies, private commercial banks, and national governments.

Economic Policies and Environmental Consequences

In recent years, the World Bank has played a controversial role in pressuring struggling economies to address runaway inflation and growing debt. Bank supporters argue that these economic reforms, called "structural adjustment," eventually provide more jobs and raise living standards. Critics say that structural adjustment often increases poverty and damages environmental and human health.

Under the conditions of structural-adjustment loans, nations may be required to privatize state-held industries, reduce regulations that inhibit commerce, promote exports, restrain wages, and cut state budgets. In addition, nations are usually required to remove inefficient subsidies on crops, energy, water, and other resources.

For most of its history, the World Bank placed no conditions on a nation's economic policy. But in 1980, the bank gave its first structural-adjustment loan to reduce the impacts of an international oil crisis on developing nations. Since then, the World Bank has worked closely with the IMF to encourage governments with inflation and debt-ridden economies to reduce bureaucratic expenditures.

The success stories of structural adjustment include Brazil, Argentina, and Thailand, which experienced hyperinflation, with prices and wages rising astronomically during the 1980s. "The purpose of structural adjustment is to reduce inflation by reducing government deficits," says Owen. "You must follow strict fiscal and monetary policies. It hurts everybody over the short term—the poor, middle-class, and rich. But over the longer term, you see higher living standards and faster rates of economic progress."

However, Bruce Rich, senior attorney with the Environmental Defense Fund and author of the 1994 book *Mortgaging the Earth: the World Bank, Environmental Impoverishment, and the Crisis of Development*, argues that in the 1980s, "the impact of these policies on the poor in many countries was devastating: real wages dropped, and government health and education services were slashed." Today, about one-fourth of bank loans have structural-adjustment conditions, according to Rich.

Steve Hellinger of the Development Group for Alternative Policies says that structural adjustment abruptly opens up economies, leading to rapid extraction of natural resources, just as environmental ministries are being cut. "You see countries not enforcing environmental regulations under structural adjustment." In addition, small farmers abruptly taken off crop subsidies or other subsidies may be forced into poverty.

"In Africa, weak governments facing a lot of internal strife could not make the adjustments" to freer markets, agrees de Vries. He adds that in most countries, the poor, especially in urban areas, were hurt by cutbacks in government expenditures and by increases in food prices when crop and other subsidies disappeared. However, de Vries notes that

Banking on the Environment

The World Bank is not the only institution doling out the dough for environmentally related firms and projects worldwide. In a survey of 177 investment and commercial banks around the world by the United Nations Environment Programme (UNEP) and Salomon, Inc., 31% of respondents said they loan or invest in environmentally related firms today and almost three times that number said they expect to in the next 15 years.

Although these findings may mean good news for the environment, the optimism should be cautious. According to the survey, nearly half of respondents do not monitor or evaluate environmental risks after funding is committed; 46% of respondents do not stay current on environmental policies and practices in other countries; and, with respect to environmental liability, loan contract terms and conditions related to borrowers' performance and activities are not used by 45% of responding banks. However, most respondents did predict that over the next five years they are likely to add environmental criteria to all procurement decisions and become more involved in resource reduction, energy conservation, and recycling.

In announcing the survey results at the United Nations headquarters, UNEP Executive Director Elizabeth Dowdeswell said, "The thousands of investment and loan decisions made each day at financial institutions have a profound effect on our planet's environmental condition. Fostering informed and responsible policies and practices in the financial services sector is essential if we are to ensure that development takes place in an environmentally sustainable manner."

The UNEP will hold an expanded roundtable on commercial banks and the environment in Geneva in October.

governments with stronger bureaucracies, such as those in Latin America, have generally fared better under structural adjustment. Since 1990, the bank has redesigned structural-adjustment loans to lessen the impact on the poor, de Vries adds.

The bank now includes safety nets to the poorest people in structural-adjustment loans, including phasing out subsidies more slowly, according to Mason.

Bank Reform

In 1987, the World Bank initiated a major effort to bring environmental and social concerns into each aspect of its work, according to a 1994 World Bank report, *Making Development Sustainable.* Over the past several years, the bank has sought to reduce environmental damage and social dislocation caused by its policies. In addition, the bank began emphasizing lending for environmental protection, health, and education. In fiscal year 1994, the World Bank lent more than $2.4 billion for environmental programs in developing countries, about 10% of its total loans.

The bank is now working with nongovernmental organizations to reduce the adverse impacts of its projects. "The World Bank has very talented, relatively progressive economists who are really trying to change, to work more closely with local people," says Orrin Kirshner, economist with the Institute for Agriculture and Trade Policy, a nonprofit organization based in Minneapolis, Minnesota.

The World Bank's activities to protect and enhance the environment are based on a four-part agenda, according to the bank's *Making Development Sustainable* report. First, the bank is working to help countries set priorities, build institutions, and implement programs for sound environmental stewardship. "In some developing countries, you can have very limited government capacity," says Mason. "Many countries, for example, don't have environmental monitoring capacities, and the bank helps government agencies develop those."

The bank also advises former communist-block nations, which historically neglected environmental protection. "In Poland and Hungary, just two examples, you have tremendous, varied problems to address, so where do you start?" asks Mason. "A nation in that situation can't afford to address everything right away. So we enourage countries to establish priorities. Then, through technical assistance, we help countries set environmental standards that are clear and scientifically based. We help with data collection. And we help governments create conditions so they can reach the stakeholders who will be affected by regulations."

Second, the bank aims to expand the role of environmental assessments in reducing the environmental impacts from bank-financed projects. Today, nations receiving loans must make environmental assessments on each project, which must be approved before the project can move forward. But those responsible for assessments leave a project once it is underway. Now the bank is examining how to expand the role of the environmental assessment throughout the design and construction of a project, according to Mason.

Third, the bank is helping countries understand the links between reducing poverty and protecting the environment. Today, in many developing nations, poverty creates higher fertility rates, because families believe they must grow larger in order to survive. But as populations grow, they put greater pressure on natural resources and in turn increase poverty. The bank is attempting to break this cycle by reducing poverty through health and nutrition and family-planning programs. In addition, the bank provides accessible credit to the rural poor and improves living conditions with clean water and sanitation.

Fourth, the bank aims to address global environmental challenges through participation in the Global Environmental Facility (GEF). The World Bank administers the GEF in cooperation with the U.N. Development Programme and the U.N. Environment Programme. The GEF is the primary funding mechanism for research and education on climate change, biodiversity loss, and depletion of ozone. Furthermore, the GEF runs environmental programs in international waters, including the Mediterranean Sea and the Baltic Sea.

In 1995, GEF approved $60–80 million in grants for a program that would help phase out ozone-depleting substances in Eastern Europe. Also in 1995, GEF allocated about $220 million to fund research and education on climate change and biodiversity issues.

Still, these new programs and reforms are not coming quickly enough for critics, who say that the bank still makes too many errors and misjudgments. Critics point out that the bank's record in funding well-designed development projects actually worsened after it started on an environmentally friendlier direction in 1987.

Bank reviews, conducted by its own Operations Evaluation Department, found that 30.5% of its development projects—dams, roads, and power plants—were failures in 1989. That is, the projects did not live up to their own goals such as reducing poverty without damaging the environment. Yet by 1991, the percentage of unsatisfactory projects had increased to 37.5%.

But defenders say the World Bank should not be punished for examining its own effectiveness. "You must give the bank credit for looking at its own successes and failures," says de Vries. He adds that many bank loans have failed because the institution has historically taken on innovative projects. "The bank has a healthy degree of risk and is constantly trying new things, and when you take many chances you are likelier to fail."

"It's extremely difficult to do successful development, and the standards by which the bank's Operations Evaluation Department judges projects are quite high," says Mason. "There are a large number of objectives to meet, and if a project is not successful in all of its components, parts of a project can still be a success. Just because the Operations Evaluation Department considers projects unsatisfactory does not mean they are disasters."

Nevertheless, in 1993, the bank announced a policy agenda, *Getting Results,* with the aim of making development projects more effective. In this agenda, World Bank President Lewis T. Preston declared that the bank would more rigorously assess the development impacts of projects before loans are given.

Furthermore, over the past two years, the World Bank has strived to improve its projects by reaching out to local people, acknowledging that affected parties should have a voice in the development process and should be able to receive important bank documents. In January 1994, the bank issued a new policy on disclosure of information. Through a new information office, nongovernmental organizations can now get environmental assessments and other documents on projects likely to have significant environmental impacts.

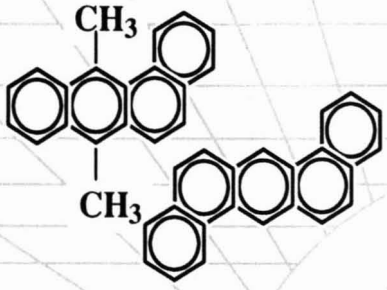
In 1993, the bank also established an independent inspection panel to strengthen the institution's accountability. The panel can investigate claims of people who charge that their interests have been damaged by bank projects and that the bank has not followed its own policies when implementing or appraising projects.

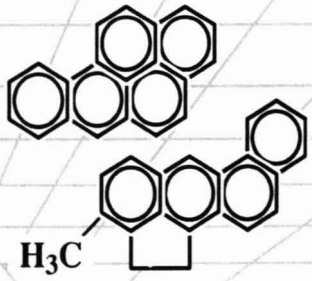
The World Bank has highly skilled economists and other professionals who have proven that they want to learn from their mistakes. With the bank's financial resources and access to information, these professionals will be needed to help developing nations cope with unforseen changes in the environment and the international economy. But the World Bank must continue to work more closely with local people to ensure that they have a voice in deciding which projects will help improve their economies and protect their natural resources.

John Tibbetts

John Tibbetts is a freelance journalist in Charleston, South Carolina.

Meeting Announcement





Risk Assessment of PAHs in the Environment

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This conference will provide state-of-the-science data on health risk assessment of complex mixtures of polycyclic aromatic hydrocarbons (PAHs) in the environment. The conference will focus on new data relevant to hazard identification and dose-response assessment, and will also address issues relating to the occurrence and bioavailability of PAH mixtures in the environment. Both cancer and non-cancer risk assessment will be considered. The conference will target government, academic, and industry scientists involved in research and regulatory areas applicable to PAH risk assessment. The conference will include technical presentations, panel discussions, breakout sessions, and a poster session/reception.

For more information please contact: **Alex Taylor**
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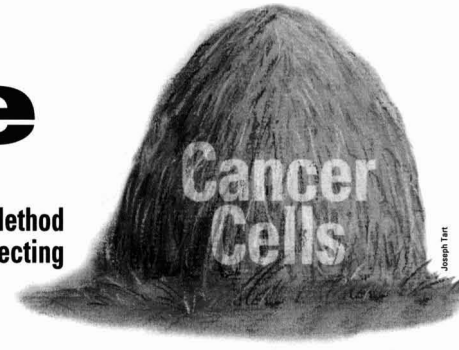
Finding the Needle in a Haystack: New Method for Detecting



Cancer has touched or transformed the lives of millions of people. The American Cancer Society estimates that there are about 1.2 million new cases of cancer per year. Environmental factors, such as chemicals, radiation, and viruses, as well as internal factors such as hormones and inherited mutations, may all contribute to development of various cancers. Successful diagnosis and treatment of cancers relies in part on detecting cancer cells within the body. Recently, a team of researchers led by Hans-Joachim Gross at the M.D. Anderson Cancer Center developed a new technique to detect very low levels of cancer cells in clinical samples of normal cells in blood and bone marrow. This innovative technique uses flow cytometry and allows researchers to find 1 cancer cell in 10 million normal cells, a detection level about 20 times more sensitive than is possible with current methods such as immunocytochemistry and polymerase chain reaction.

Applications

Current techniques for detecting low levels of cancer cells can provide different types of information for researchers and clinicians. For example, a blood sample from a patient that is newly diagnosed with cancer can be tested to determine if the cancer is spreading to other areas. Patient blood samples can also be tested after treatment with chemotherapy to determine if the number of tumor cells has decreased.

Another application of the detection methods is for testing samples of bone marrow that are removed from cancer patients undergoing bone marrow transplants. Bone marrow transplants are currently used to treat a variety of blood cancers including leukemia, lymphomas, and multiple myelomas, many of which may be environmentally mediated. Marrow transplants may also be used as part of a course of therapy for nonhematologic diseases such as solid tumors, immunological dysfunctions, and inherited enzyme deficiencies. Gross's new flow cytometry assay is primarily targeted for application as a cancer treatment. In addition to being a more sensitive cancer cell detection method, the new flow cytometry assay is unique in that it may someday be used to remove cancer cells from a sample of bone marrow. Although some years away from practical use, this process may eventually decrease the likelihood of a cancer recurrence after the bone marrow transplant.

Flow Cytometry

Flow cytometry is based on analysis of light scatter and staining from a continuous sample of cells as they pass a detector. The light source is typically one or more lasers. The detectors capture forward and side scatter of light as each cell flows through the analysis point. This highly sensitive technique allows the characteristics of cells or other particles to be studied in great detail.

Lasers are a good light source because they can provide a bright, narrow, stable beam. However, the color output of laser light is very restricted. This disadvantage restricts the choices of dyes that can be visualized in a flow cytometer. Increasing the number of lasers allows additional colors to be visualized and increases the sensitivity of the analysis. The flow cytometer that Gross uses in the detection step contains three lasers in a complex arrangement that allows analysis of a large number of experimental parameters, thereby increasing the accuracy of the data.

In addition to measuring light scatter, some flow cytometers can sort cells based on the signal they emit. Cells can be stained with antibodies linked to colored dyes. Then, as the sample is run through the sorter, all cells emitting a specific color light signal (e.g., red) will be physically shunted into a collection test tube, while cells with other colors (e.g., green) will be collected in a second tube. In his model system, Gross used a FACS (fluorescence-activated cell sorter) to sort BT-20 breast carcinoma cells. The BT-20 cells were labeled with a UV-excitable blue dye called 7-amino-4-chloromethylcoumarin (CMAC). This dye allowed the detector to count the "blue" cells and deposit either 0, 40, 400, or 4,000 cells into four tubes each containing approximately 1×10^8 peripheral blood stem cells. The purpose was to create experimental samples with a known number of cancer cells. The mock samples were run through a detector, and the number of cancer cells actually detected was matched against the number that should have been detected.

A second flow cytometer with three lasers was used for the detection step. Researchers stained the BT-20 cancer cells to distinguish them from the stem cells. Several different antibodies against each cell type were used to label the cell mixture to ensure the most accurate detection. The rare cancer cells were stained with three antibodies linked to dyes that are yellow and two shades of red. The stem cells were stained with a panel of five antibodies all linked to a green dye called fluorescein isothiocyanate. In his study, published in the January issue of the *Proceedings of the National Academy of Sciences*, Gross said, "The requirement that the rare cancer cell be simultaneously positive for three separate colors and negative for a fourth color [allows] detection of as few as one cancer cell in 10^7."

The signal from the cell samples was then transmitted to a computer which generates a scatter plot of the BT-20 cells. The blue CMAC dye originally used to count the cancer cells was then used as a final test to validate the results from the

selective sorting of cancer and stem cells. After the red and yellow cells were plotted, these cells were examined under a UV light. The presence of blue UV sensitive dye in all of these cells helped confirm that the assay was successful in sorting the cancer cells.

Better Marrow

Bone marrow is usually collected for an autologous transplant when a patient is in remission or early in the disease, but there is a chance that cancer cells may also be collected. In order to return marrow that is as cancer-free as possible, some bone marrow transplant centers purge the marrow. One common technique for purging uses a cytotoxic agent to selectively damage cancer cells, but unfortunately it does not completely spare the undiseased marrow cells. Another technique, "negative selection," couples antibodies that recognize and capture specific cancer cell marker proteins to a solid matrix in a column or to magnetic beads. The sample then is mixed with the beads or run over the column and the cancer cells are captured and removed. A third, promising technique uses "positive selection" to capture stem cells and to remove cancer cells. This procedure uses an antibody column that binds to a $CD34^+$ marker on stem cells.

"In model studies," writes Gross, "bone marrow with 10% tumor cell contamination can be purged by a factor of 10^{-3} to 10^{-4}. In a more realistic example with 0.1% tumor cell contamination, about 3,000 tumor cells could be returned into the patient. To detect those cells in purged bone marrow before infusion requires a detection level of one tumor cell per 10^6 to 10^7 cells, a level not achieved so far. Present day methodologies . . . permit a level of detection by microscopy of one tumor cell per 10^5 cells at best."

Gross asserts that one major application for his technique is marrow sample testing to improve diagnostic capability. Unfortunately, a major roadblock for using this process is the time needed to analyze an entire marrow sample of 100 million cells. As a sample of cells drips through the laser, about 6,000 "events" (light scatter from a cell) per second are recorded by the detectors. It may take up to seven hours to analyze a typical sample, which is not a clinically useful timeframe.

To address this concern, a company in Palo Alto, California called SyStemix has developed a high-speed flow cytometry system designed to sort bone marrow cells. SyStemix, which explores stem cell biology and therapy, has developed a cytometer that can analyze about 50,000 events per second. In combination with a positive selection column that reduces the total number of cells in the sample to be sorted, this system reduces the sort time of a typical sample to about one to two hours. There is, however, a tradeoff between reduced analysis time and the possibility of increased stem cell damage that can result from manipulation. Other laboratory technology companies are also working to increase efficiency and decrease cost of purging methods.

Even though removal of cancer cells from reinfused marrow seems logical, purging is a controversial topic among researchers and clinicians. There is no solid evidence to support whether a relapse is caused by tumor cells in reinfused marrow or by original tumor cells that survive the ablation process. Many studies of autologous transplant patients have shown no difference in survival between patients that receive purged marrow versus those that receive nonpurged marrow.

A prospective clinical trial conducted by the European Bone Marrow Transplant registry is attempting to provide data to support or refute the benefits of marrow purging. All trial centers are testing a standardized antibody-linked magnetic bead technique. The results will not be available for years because a large number of patients must be recruited to complete the study.

Meanwhile, cancer patients who receive bone marrow transplants stand to benefit from improved procedures that will augment their quality of life and increase their life expectancy. Improved detection techniques will will also create new opportunities to research and study many types of cancer in hope of a cure.

Chris Edwards

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Suggested Reading

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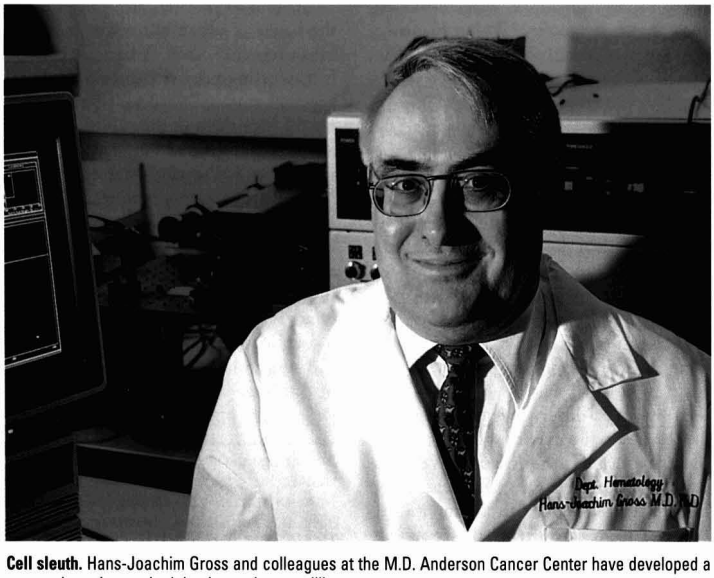

F. Carter Smith

Cell sleuth. Hans-Joachim Gross and colleagues at the M.D. Anderson Cancer Center have developed a cancer detection method that is one-in-ten-million.

Restoration of Urban Waterways and Vacant Areas: The First Steps Toward Sustainability

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Increased population pressure and human activities have significantly altered the effectiveness of functions of ecosystems ("ecosystem services") at the local and regional scale. Of primary importance is the decrease in water quality due to urban storm water runoff. A number of communities have initiated restoration strategies to improve water quality standards. One such strategy is the incorporation of riparian walkways with native flora. As a result of such restoration efforts, habitats for native fauna have improved, and the number and diversity of wildlife have increased in urban settings. Restoration of urban habitats also provides social and economic benefits to the surrounding community. Efforts to mitigate the loss of ecological resources by restoring native habitats on lots that cannot be developed or on abandoned lots hold a high, unrealized potential. Habitat restoration not only provides natural diversions to urban surroundings, but also enlightens and educates individual citizens about the importance of balanced ecosystems and the role of humans within ecosystems. Education is the primary step toward creating ecologically sustainable communities. ***Key words:*** **ecology education, habitat restoration, sustainability, urban renewal, waterways.** ***Environ Health Perspect*** **103:452–453 (1995)**

Most cities and towns have evolved along the banks and shores of waterways. Historically, the larger waterways functioned as major transportation corridors for humans as well as for other organisms. The numerous smaller waterways weaving through cities also functioned as sources of fresh water that provided food and habitat. Rapid urban expansion has dramatically changed the face of these waterways. Today, an estimated 93 million people reside in the coastal counties in the United States (*1*). Many water courses have been channeled, rerouted, paved over, transformed into storm sewers, or, in the case of wetlands, obliterated. Impervious surfaces, such as roofs, parking lots, roads, shopping malls, and industrial buildings, dramatically alter the flow of natural systems. Instead of percolating through the soil to groundwater aquifers or being transpired by vegetation, urban runoff shunted in abnormal patterns enters natural systems well beyond the urban areas from which the water originates. Additionally, the components of urban runoff, such as suspended solids, pesticides, nutrients, oil and grease, human and animal refuse, and pathogenic microorganisms, have significant impacts on the aquatic habitats they enter.

The National Research Council (*1*) estimates that approximately 85% of the 10 billion gallons per day of wastewater effluent discharged along the U.S. coasts enters bays and estuaries rather than open ocean. The ecological impacts of large-volume discharges into these slow-circulating habitats include sedimentation, anoxia, hypoxia resulting in aquatic plant die-back, and nuisance algal blooms, all of which adversely impact benthic populations such as shellfish. The Chesapeake Bay has seen dramatic declines in aquatic plant populations, which coincides with increased turbidity from agricultural and urban runoff. Aquatic plant communities are important nurseries that provide nutrients and shelter for molting crabs, juvenile fish, and shellfish, all of whose declines in the Chesapeake Bay are well documented. Residential, commercial, and industrial sites are all important contributors to urban runoff. Many of the contributing pollutants (such as refuse, oils, and solid materials) could easily be reduced with changes in urban lifestyle. With the water shortages we now face, particularly in the western United States, better management of water resources is mandatory. This can be accomplished while reacquainting urban dwellers with at least some of the attributes of natural systems.

The implementation of the 1972 Clean Water Act and its amendments in 1987 brought dramatic changes in point-source pollution, and society is only beginning to address the problems associated with nonpoint pollutants stemming from urban areas. Recognizing the importance of reducing nonpoint wastes, a number of creative and common-sense strategies have been developed. Unfortunately, no single "quick fix" or technology exists for reducing urban runoff, and a combination of innovative management policies and grassroots education is essential to improve water quality. Simple approaches, such as street sweeping and warnings posted on storm drains, may reduce urban pollutants, but to what extent is uncertain. In some cases, parking lot and gas station drains may be effectively retrofitted with oil and grit separators to remove hydrocarbons and heavy metals from storm water before its entry into storm sewers (*2*). San Francisco developed a combined sewer system in which all city water (including street runoff) is treated before its release (*3*).

The construction of wetlands to alleviate storm water pulses as well as to improve water quality is becoming increasingly popular. Wetlands (either engineered or natural), with dense vegetation and wide, shallow basins, slow the entry of storm water by forcing it to flow through a longer course (decreasing water velocity) and remain in the basin for a longer period of time so that trapping sediments is possible. Trapped sediments containing nutrients (such as nitrogen and phosphorus) are then used by plants during growing seasons or are broken down through biological processes such as denitrification. Wetlands have been extremely successful in reducing high pollutant loads in storm water. Samples from a constructed wetland in Auckland, New Zealand, reflect an 80–97% decrease in sediment concentrations of lead, total phosphorus, and hydrocarbons (*4*). In addition to improving water quality, wetlands serve as an attractive habitat for waterfowl and provide important ecosystem functions ("ecosystem services") to areas affected by urban development.

A number of cities are going beyond the banks of urban waterways to reduce urban runoff. Tucson, Arizona, is currently conducting a citywide storm water management study. This detailed analysis of the 59 watersheds in the city of Tucson is an effort to provide a long-range management plan for storm water quality and quantity. The plan promotes harvesting rain and grey water for landscape irrigation by private property owners and improved street and alley maintenance through increased street cleaning and waste removal. Tucson has a strict wash ordinance to protect washes from channeling and developing floodplains. Revegetation of disturbed floodplains and wash areas with native plant species is also encour-

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aged. In other areas, Tucson has created an extensive set of linear parks along its two major waterways, the Santa Cruz and Rillito rivers. Areas that were once graded and devoid of other vegetation are now lush with native mesquite (*Prosopis* sp.), palo verde (*Cercidium* sp.), ocotillo (*Fouquiera splendens*), and numerous small herbaceous plants. As a result of this endeavor, the linear parks are not only heavily used by humans (hiking and biking) but by native fauna as well. It is not uncommon to see horned lizards (*Phrynosoma modestum*), road runners (*Geococcyx californianus*), coyotes, and numerous species of birds and rodents foraging among the plants adjacent to the walkways. In addition to reducing urban runoff, the restoration of such disturbed riparian areas increases the opportunity for public environmental education. Surrounding businesses and residential areas also tend to benefit economically from similarly restored areas. The recent restoration of a downtown creek in San Luis Obispo, California, raised property values and enlivened business activity (*5*).

Strategies to reduce urban runoff have wide-reaching effects on community lifestyles and result in subtle improvements in the ecological condition of native plant and animal communities residing within the city. Integrated with strategies to decrease urban runoff are opportunities for urban ecological restoration. Urban ecological restoration need not be limited to riparian areas or wetlands. Although traditionally perceived as a linear process, urban development can be quite circular. Clothes, newspapers, and milk cartons are recycled; why not abandoned stores and empty lots? What would happen if abandoned or perpetually vacant commercial areas and empty lots were restored to natural habitat parks? As suburban malls, shopping strips, and housing developments continue to expand away from the city center, the remaining abandoned and vacant areas are ripe with restoration opportunities. The restoration of abandoned or vacant urban areas with native plant species may provide similar societal, as well as ecological, benefits as the community gardens and parks of the 1960s and 1970s. Urban restoration has the added benefit of reducing the impact of urban runoff, which is both a major ecological and societal problem (*6*).

The restoration of abandoned or vacant urban landscapes with native flora provides one means of replenishing ecological capital (e.g., fossil water and biodiversity). Additionally, revegetating graded areas and removing deteriorating buildings reduces suspended solids entering urban storm sewers. A number of valuable ecosystems already exist in heavily urbanized areas (e.g., Central Park, New York, and Amsterdam Bos, Holland) which further legitimizes the practice of environmental restoration in urban settings. Holland has pioneered the ecological restoration concept of landscape planning on a significant scale (*7*). Amsterdam Bos is a large, manmade forest. Bijlmereer is a 1960s housing project located on the flat polders southeast of Amsterdam. In England, volunteers from youth organizations and the Conservation Corps created the Ecological Parks Trust on two acres of abandoned warehouses and docks along the south bank on the Thames (*8*). Restored areas in close proximity (e.g., multiple lots on a city residential block) may function as habitat for small mammals, reptiles, and birds. Agencies such as state Game and Fish Departments and the federal Fish and Wildlife Service are establishing urban wildlife branches to determine the number and diversity of animal species residing in urban areas. These agencies also identify potential urban landscapes that may provide ecologically valuable habitat to nonhuman residents. On a subtle scale, all of these steps in ecological restoration represent steps toward sustainable use at the level of the individual.

To continue the trend toward sustainable resource use, society must pay attention to its influence at the level of the individual; its control of the rate of loss of ecological capital; overharvesting of renewable resources and exhaustion of non-renewable resources; deterioration of environmental quality; and extinction of species. First, the environmental literacy of most societies must be dramatically improved (*9*). The presence of restored floodplains, riparian zones, created wetlands, and grey water harvesting expose citizens to the environment at an approachable level. Second, society must understand what sustainability means. In its simplest form, sustainable resource use meets present needs without compromising the ability of future generations to meet their own needs. In fulfilling these needs, society must focus on both technological development and ecosystem services (*10*). Ecosystem services are those functions of natural systems perceived to be of value to human society, such as maintenance of water quality. Third, as identified by the National Research Council (*1*), integrated management strategies that identify the cost and consequences of resource use must be implemented. To achieve this goal, society must form a clear vision of the future of its communities and develop strategies toward that vision. It is essential that ecosystem protection and restoration measures be incorporated into the daily lives of individuals to maintain natural resources. In doing so, sustainable use practices may be realized.

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Resolving Intertracer Inconsistencies in Soil Ingestion Estimation

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In this article we explore sources and magnitude of positive and negative error in soil ingestion estimates for children on a subject-week and trace element basis. Errors varied among trace elements. Yttrium and zirconium displayed predominantly negative error; titanium and vanadium usually displayed positive error. These factors lead to underestimation of soil ingestion estimates by yttrium and zirconium and a large overestimation by vanadium. The most reliable tracers for soil ingestion estimates were aluminum, silicon, and yttrium. However, the most reliable trace element for a specific subject-day (or week) would be the element with the least error during that time period. The present analysis replaces our previous recommendations that zirconium and titanium are the most reliable trace elements in estimating soil ingestion by children. This report identifies limitations in applying the biostatistical model based on data for adults to data for children. The adult-based model used data less susceptible to negative bias and more susceptible to source error (positive bias) for titanium and vanadium than the data for children. These factors contributed significantly to inconsistencies in model predictions of soil ingestion rates for children. Correction for error at the subject-day level provides a foundation for generation of subject-specific daily soil ingestion distributions and for linking behavior to soil ingestion. *Key words*: dioxin, exposure assessment, risk assessment, soil ingestion. *Environ Health Perspect* 103:454–457 (1995)

Quantifying how much soil humans ingest became a major concern in the 1980s when soil ingestion estimates were needed to assess potential risk from sites contaminated by chemicals and radiation. The initial focus on the role of soil ingestion in health risk centered on dioxin contamination at Times Beach, Missouri; now soil ingestion estimates are routinely incorporated into all risk assessment procedures for contaminated sites (*1*). To aid in estimating soil ingestion, EPA has proposed daily soil ingestion rates for children and adults (*2*). Based on the nature of the contaminated site, estimated soil consumption has often been identified as one of the most significant routes of exposure affecting final risk assessment estimates (*1*).

The database on soil ingestion in humans is limited to five studies in children (*3–7*) and one study in adults (*8*). These studies used soil trace-element ("tracer") methodologies to estimate soil ingestion. The strengths and limitations of these studies and their capacity to provide defensible soil ingestion estimates have been assessed (*9*).

Of particular concern is that the soil ingestion studies demonstrated relatively poor intertracer consistency within a single study. As Table 1 indicates, the range of soil ingestion estimates can vary considerably among the tracers within each study. For example, in the Calabrese et al. (*5*) study, the median tracer-based soil ingestion values ranged from 9 to 96 mg/day, the mean from 21 to 459 mg/day, and the upper 95% boundary from 106 to 2100 mg/day, depending on the tracer used. Such divergent estimates could have any number of effects on the risk assessment process. A key problem has been determining which tracers provide the best estimates. The present study offers a quantitative solution to this problem of selecting tracers. We identify the principal sources of positive and negative error in mass-balance soil ingestion studies and quantify and correct the error by subject-day for each tracer. These adjustments are presented for the Calabrese et al. (*5*) report since this mass-balance study provided daily measurements of collected samples. The only other mass-balance soil ingestion study, which was published by Davis et al. (*7*), could not be corrected for positive and negative error using the developed methods because daily measurements were not taken and only three tracers were measured.

Choosing the Best Tracer

We previously conducted an "adult validation study" (*5*) using the same methods as the study in children. This validation study involved ingestion of known amounts of soil (100, 500 mg/day) by adult volunteers. Our purpose was to assess whether the study protocol could detect and precisely quantify soil ingestion in subjects when modest (100 mg/day) to substantial (500 mg/day) amounts of soil were ingested daily. In the adult validation study, the tracers that displayed close to 100% recovery were aluminum, silicon, yttrium, and zirconium. These elements were considered to be the most reliable tracers in the children's study (*5*). We initially assumed that tracers performing well in the adult tracer recovery study would also perform well in the children's soil ingestion study. Later we found that this assumption was unreliable (*9*): recovery is essentially a mathematical function of the amount of trace elements consumed in food compared to the amount ingested in soil. Tracers with low food-to-soil (F/S) ratios displayed better recovery. We developed a model to estimate the soil ingestion detection of tracers for varying sample sizes based on this concept (*10*).

Of particular interest was the large difference in F/S ratios for some tracers between children and adults. For example, the F/S ratio for titanium was nearly 10-fold lower in children than it was in adults (*9*). This suggested that even though titanium performed quite poorly in the adult tracer recovery study, it most likely had excellent recovery in the children's soil ingestion study. In fact, when applied to children's soil ingestion data, the soil ingestion detection model predicted that only two tracers (titanium, zirconium) displayed an acceptable estimated precision of recovery (100% ± 20%). These findings therefore led us to reject the original assumption that the most reliable tracers for the adult recovery studies would be the most reliable in the children's study.

However, there were still unresolved inconsistencies in estimates for titanium and zirconium. For example, if zirconium was such a reliable tracer in the children's study, why did it lead to highly inconsistent soil ingestion estimates for the one child that exhibited soil pica (*5*)? The soil ingestion estimates for this child for all tracers except zirconium were 5–6.5 g/day over a 2-week period, whereas the estimate based on zirconium, was 1.5 g/day for the same period. To have one of the two "best" tracers apparently underestimate the soil ingestion by 75% was troubling. The underestimation of soil ingestion by zirconium for the child exhibiting pica seemed to mirror the soil ingestion estimates for the entire sample, in which the median value for zirconium was about 70% less than that of titanium. How could the two "best" tracers differ substantially in the median (16 versus 55 mg/day), mean (25 versus 218 mg/day), and upper 95% (106 versus 1492 mg/day)? Questions were also raised about the reliability of the zirconium estimates, and an important source of error for titanium was determined, indicating that both children and adults most likely ingested quantities of titanium that were neither in food nor soil but from a different, unknown source that contributed to overestimates of soil ingestion in affected subjects (*11*). Such observations led us to rethink the question of which tracers provided the most reliable estimates of soil ingestion, with particular emphasis on understanding the basis for intertracer variability in estimating soil ingestion.

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One of the basic assumptions inherent in interpreting mass-balance soil ingestion studies is that positive and negative error will likely occur as a result of flaws in the study design. However, we assumed initially that the capacity for positive error would approximate negative error and they would cancel other out with respect to subject average values (*5*). In fact, negative soil ingestion values, which comprised 12–44% of soil ingestion estimates depending on the tracer in the children's study (*5*) was attributted to negative error, as it is not possible to have negative soil ingestion. However, we believed that positive error would also exist that would presumably offset the negative error. This assumption was never deeply explored in any of our original soil ingestion study reports. However, as we will show, this assumption appears to be of limited validity and leads to significant implications depending on the tracer.

We first provide a general framework for classifying various sources of error for soil ingestion. We follow this discussion with a description of a methodology for quantifying these sources. Finally, we present estimates based on implementing this methodology in our children's study (*5*).

Causes of Error

In mass-balance soil ingestion studies, positive and negative error are the result of a variety of causes. For example, if tracers are ingested in food but are not captured in the fecal sample as a result of either a slow transit time or because a fecal sample was not available for the final day(s) of the study, the soil ingestion estimate will have a negative bias. In addition, sample measurement errors, resulting in diminished detection of fecal tracers but not soil tracer levels, will negatively bias soil ingestion estimates.

Ingestion of high levels of tracers in the days before the study starts and low ingestion during the study could result in an overestimation of soil ingestion. Positive error can also occur if the subject ingests tracers from a source that is of neither soil nor food origin during the study period. For example, if a child eats a piece of paper that contains titanium in the printing material, this could lead to an overestimation of soil ingestion based on this particular tracer. If tracer was measured incorrectly in soil but not in the fecal sample, this could also result in positive error. Negative and positive error can be quantified for a single day or totaled for a subject-week.

In a previous paper (*12*), we reported that the quantification of negative and positive error led to improved daily soil ingestion estimates. In our previous reports, daily soil ingestion estimates were obtained by dividing the total soil ingestion observed by the number of days of study (e.g., 3–8) and not based on a particular day.

Quantifying Error

Obtaining the best estimate of soil ingestion for a given subject-day. To determine positive or negative error in soil ingestion estimates, it is necessary to develop a procedure for obtaining an unbiased estimate of soil ingestion. In the absence of direct knowledge of actual soil ingestion, the approach adopted in the present analysis was to: 1) Incorporate an assumed GI tract transit time of 28 hr for the passage of tracers ingested in food to the feces. This value was applied to all subject-day estimates. Inter- and intraindividual variation in GI transit time was not considered. 2) Estimate the daily soil ingestion rate for each tracer for each 24-hr day for which a fecal sample was obtained. We assume that the corresponding food ingestion period is a 24-hr period beginning 28 hr earlier than the start of the fecal sample period. 3) Determine the median tracer-based soil ingestion rate for each subject-day. Upper and lower bounds for the range of estimates were determined based on criteria formed using an assumption of the magnitude of the relative standard deviation as described elsewhere (*12*). Daily soil ingestion estimates falling outside of these upper and lower boundaries were assumed to be unreliable and were excluded from subsequent calculations. The median of the remaining tracer elements of the daily soil ingestion rates was deemed the best estimate of soil ingestion for the particular day. Tracers found to be unreliable displayed either positive or negative error depending on whether the tracer exceeded the upper or lower boundary. The magnitude of positive or negative error for a specific tracer for a day was then obtained by determining the difference between the value for the tracer and the median value. 4) Determine negative error due to missing fecal samples at the end of the study period. In the children's study (*5*), we estimated soil ingestion by developing an average daily tracer ingestion rate from food over 3 days. This average daily food tracer intake was subtracted from the average daily fecal tracer levels over the 4 days of fecal collection. The principal problem with this approach was that for 43 of 128 subject-weeks, there was no fecal sample for day 4 of the study. This would lead to an underestimation of soil ingestion (i.e., negative error). The situation became even more extreme for a smaller number of subjects for which no fecal samples were provided on days 3 and 4 (five subject-weeks) and on days 2, 3, and 4 (two subject-weeks). As expected, the likelihood of negative soil ingestion estimates for subjects with missing last-day fecal samples was markedly enhanced. In this case, negative error would have been minimized if the daily tracer intake from food were low or maximized if the daily tracer intake from food were high and transit time was sufficiently slow to prevent capture in the fecal sample. Thus, even though a day 4 fecal sample was not available, this would not directly lead to a large negative error, nor would availability of day 4 fecal sample automatically preclude this type of negative error. This reasoning is consistent with the observation (*9,10*) that a low F/S ratio was an important predictor of tracer recovery in the adult validation procedure.

Table 2 indicates the estimated magnitude of positive and negative error for six tracers in the children's study (*5*). The original mean soil ingestion estimates ranged from a low of 21 mg/day based on zirconium to a high of 459 mg/day based on vanadium. After correcting for positive and negative error, the range in soil ingestion estimates decreased to 97 mg/day based on yttrium to 208 mg/day based on titanium. This represents a change in the range from approximately 21-fold to approximately 2-fold. With the exclusion of titanium and vanadium, which were most susceptible to error, the range of the remaining four corrected tracers is from 97 to 136 mg/day. Consequently, correction for positive and negative error resulted in considerable intertracer agreement for esti-

Table 1. Soil ingestion estimates in children (mg/day)

	Binder et al. (*3*)		Van Wijnen et al. (*6*)		Davis et al. (*7*)		Calabrese et al. (*5*)	
Trace element	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Aluminum	181	121			40	25	153	29
Silicon	184	136			82	59	154	40
Titanium	1834	618			246	81	218	55
Barium							32	<0
Manganese							<0	<0
Vanadium							459	96
Yttrium							85	9
Zirconium							21	16
Limiting tracer method								
Day-care center			103	111				
Campers			213	160				

Table 2. Positive/negative error (bias) in soil ingestion estimates in the Calabrese et al. (1989) mass-balance study (*5*): effect on mean soil ingestion estimate (mg/day)[a]

Trace element	Negative error: Lack of fecal sample on final study day	Negative error: Other causes[b]	Negative error: Total negative error	Total positive error	Net error	Original mean	Adjusted mean
Aluminum	14	11	25	43	+18	153	136
Silicon	15	6	21	41	+20	154	133
Titanium	82	187	269	282	+13	218	208
Vanadium	66	55	121	432	+311	459	148
Yttrium	8	26	34	22	-12	85	97
Zirconium	6	91	97	5	-92	21	113

[a]How to read table: for example, aluminum as a soil tracer displayed both negative and positive error. The cumulative total negative error is estimated to bias the mean estimate by 25 mg/day downward. However, aluminum has positive error biasing the original mean upward by 43 mg/day. The net bias in the original mean was 18 mg/day positive bias. Thus, the original 156 mg/day mean for aluminum should be corrected downward to 136 mg/day.
[b]Values indicate impact on mean of 128-subject-weeks in milligrams of soil ingested per day.

mation of soil ingestion rates. Table 2 indicates that each tracer displayed some degree of positive and negative error. However, there were marked differences among the tracers with respect to their susceptibility to error. Titanium and vanadium displayed exceptionally high positive and negative, error; zirconium also displayed a high amount of negative error. The negative error attributed to missing last-day fecal samples affected the estimates of soil ingestion for all tracers to some extent, but most notably for titanium and vanadium, where the original mean was negatively biased by 82 and 66 mg/day, respectively. Negative error attributed to all other principal causes of error (e.g., input/output misalignment, sample loss) was also highly variable, with titanium being most susceptible (187 mg/day) followed by zirconium (91 mg/day) and vanadium (55 mg/day). The most likely cause of this negative error for titanium and vanadium is input/output misalignment because the daily ingestion of these tracers in food was highly variable. Such variable daily tracer intakes, coupled with transit times longer than 28 hr for a given subject, could have led to negative error.

In the case of zirconium, negative error may be more complex than simply input/output misalignment. Based on the pattern of negative soil ingestion estimates, the modest variability of zirconium in the diet (*13*), and the recognized difficulty of analyzing zirconium (*14*), we hypothesize that a substantial component of the 91 mg/day is attributed to sample measurement loss of fecal tracer levels.

Positive error was highest for vanadium (432 mg/day), followed by titanium (282 mg/day). The remaining four tracers displayed positive error <50 mg/day. The two principal causes of positive error are input/output misalignment and source error. Positive misalignment error would occur as a consequence of previous negative misalignment error. For example, if a subject displayed negative misalignment on day 2, it is likely that positive misalignment would occur on a subsequent day, although this would depend on the transit time in relation to the end of the observation period. Second, consumption of tracers in a nonfood/nonsoil source will contribute to positive bias. For example, subject 833 displayed low (<100 mg/day) soil ingestion for all tracers except vanadium (11 g/day) during week 2. This subject ingested about 10–15 µg/day vanadium in food. However, on day 4 of week 2, this subject excreted nearly 5000 µg vanadium in feces. This vanadium could not have come from food or soil. If so, other tracers would have indicated similarly high soil ingestion estimates. Thus, the high level of vanadium in feces came from an unknown source. This type of source-error was particularly apparent for titanium and vanadium.

Discussion

The present analysis identifies and quantifies element-specific sources of error in our children's study (*5*) that led to widely varying tracer-specific estimates. Correcting for such error at the individual level for each tracer provides substantially more reliable estimates of soil ingestion. The methodology leads to corrected soil ingestion estimates that provide similar mean estimates of soil ingestion across all tracers (Table 2). The range of mean tracer-based soil ingestion estimates for the six tracers has narrowed from 21 to 459 mg/day to 97 to 208 mg/day. This represents a marked improvement in estimation.

Despite the substantial improvement in intertracer estimation of subject-week soil ingestion estimates, the analysis revealed a sound basis on which to select the most reliable tracers and the most reliable subject-day estimates. The tracers requiring the least amount of error correction for a subject-week or subject-day would be expected to provide the most reliable estimates for that time.

Our findings indicate that aluminum, silicon, and yttrium, which displayed the least net bias along with modest and nearly equal positive and negative error, are the most reliable tracers in the children's study (*5*). These findings differ from our earlier reports (*9,10*), in which we argued that the most reliable tracers in the children's soil ingestion study were titanium and zirconium. Why should the biomathematical model which predicted tracer recovery with a high degree of precision based on the F/S ratio yield a different result? We believe that two factors contributed to the difference in tracer selection. First, the biostatistical model was developed using data for adults and was then applied to children. While the F/S ratios may be appropriately replaced by ratios for children, the pattern of fecal samples differs markedly between adults and children. Adults had daily fecal samples for all days in the study, while 39% of the children did not report fecal samples for the last days in the study week. This type of output misalignment was not accounted for in the biostatistical model, but it was in the present report.

Second, the biostatistical model used only the F/S ratio to evaluate the adequacy of tracer-specific soil ingestion. Although variability in tracer intake was probably related to the accuracy of soil ingestion estimates, this was not accounted for in the biostatistical model. In contrast, variability in tracer intake via food would lead to large intertracer differences between soil ingestion estimates for a given subject-day. Determining the best estimate for a specific day eliminates such extreme estimates. For these reasons, we believe that the present analysis [with soil ingestion estimates given earlier (*12*)] is clearly superior to soil ingestion estimates based on the original biostatistical model.

It should be noted that other approaches could be used to quantify and correct for error both on a subject-week and subject-day basis. We have explored several such options, including different time assumptions and various approaches for deriving the best estimate for error quantification. Comparisons of these approaches led to basically similar final, corrected mean estimates.

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Potential Impact of Global Climate Change on Malaria Risk

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The biological activity and geographic distribution of the malarial parasite and its vector are sensitive to climatic influences, especially temperature and precipitation. We have incorporated General Circulation Model-based scenarios of anthropogenic global climate change in an integrated linked-system model for predicting changes in malaria epidemic potential in the next century. The concept of the disability-adjusted life years is included to arrive at a single measure of the effect of anthropogenic climate change on the health impact of malaria. Assessment of the potential impact of global climate change on the incidence of malaria suggests a widespread increase of risk due to expansion of the areas suitable for malaria transmission. This predicted increase is most pronounced at the borders of endemic malaria areas and at higher altitudes within malarial areas. The incidence of infection is sensitive to climate changes in areas of Southeast Asia, South America, and parts of Africa where the disease is less endemic; in these regions the numbers of years of healthy life lost may increase significantly. However, the simulated changes in malaria risk must be interpreted on the basis of local environmental conditions, the effects of socioeconomic developments, and malaria control programs or capabilities. *Key words*: climate change, disability-adjusted life years, integrated modeling approach, malaria. *Environ Health Perspect* 103:458–464 (1995)

A potential consequence of anthropogenic climate change, foreseen for the coming century, is a change in the distribution and incidence of malaria (*1–7*). Although malaria eradication campaigns and socioeconomic development have caused malaria to disappear from many areas in which it had previously been endemic, in many tropical countries malaria remains a major cause of illness and death. Approximately 110 million clinical cases occur annually, and more than 1 million people, mostly children, die from malaria in tropical Africa (*8*).

Malaria incidence is determined by a variety of factors, particularly the abundance of anopheline mosquito species, human behavior, and the presence of malaria parasites. Anthropogenic climate change may directly affect the behavior and geographical distribution of the malaria mosquitoes and the life cycle of the parasite, and thus change the incidence of the disease. Indirectly, climate change could also have an effect by influencing environmental factors such as vegetation and the availability of breeding sites.

This study assesses, by integrated mathematical modeling, the effects of projected changes in temperature and precipitation on mosquito and parasite characteristics and their potential impact on malaria risk, and has followed two complementary approaches (*9*). One approach has sought to estimate the possible spatial shift in areas suitable for malaria transmission, using the critical vector density threshold as a comparative index. The other has considered possible changes in world malaria disease burden due to climate changes. Although the model only generates broad estimates of future trends and does not include all relevant factors which would influence the distribution of malaria (e.g., vaccination, pesticide use, and the emergence of drug resistance by the *Plasmodium* parasite), it addresses the question: If other things were held constant in the world, what would be the impact of climate change per se on the distribution and incidence of malaria?

Methods

Integrated Systems Approach

If the impact of a human-induced climate change on malaria risk is to be understood, the entire cause–effect chain must be described and analyzed comprehensively. The systems approach seems to be the only approach capable of adequately reflecting the complexity of the interrelationships between the climate system and mosquito and human population dynamics. The systems analysis not only studies the components of the various (sub)systems, but also the interactions and processes between them, rather than focusing on each subsystem in isolation. Given the complexity of the systems under consideration and the relative ignorance about the basic processes and interactions that determine their dynamics, the systems approach can help to foster understanding of the causal relationships between a human-induced climate change and changing malaria risks.

The model to assess the effects of climate change on malaria consists of several linked modules (i.e., systems): the climate system, the malaria system (divided into a human subsystem and a mosquito subsystem), and the impact system. The systems are linked in a straightforward manner; the output of one system serves as input to the next. The main climate factors that have a bearing on the malarial transmission potential of the mosquito population; are temperature and precipitation; i.e., factors derived from the climate system (Fig. 1). The interaction between the human system and the mosquito system determines the transition rates among the susceptible, the infected, and the immune. The impact system yields rough estimates of the health impact of climate change on malaria. This health impact is described by the disease burden due to malaria morbidity and mortality.

Climate Scenarios

To generate climate scenarios, we used the Integrated Model to Assess the Greenhouse Effect (IMAGE; Rotmans and Den Elzen, Bilthoven, The Netherlands). IMAGE (version 1.6) is a climate assessment model designed to simulate the entire cause–effect chain with respect to climate change and to develop scenarios of greenhouse gas emissions and their effect on global mean temperature. The model consists of a number of independent, but interlinked and integrated, submodels, each representing a separate component of the climate system (e.g., a world energy/economy model, land-use change model, atmospheric chemistry model, halocarbon model, carbon

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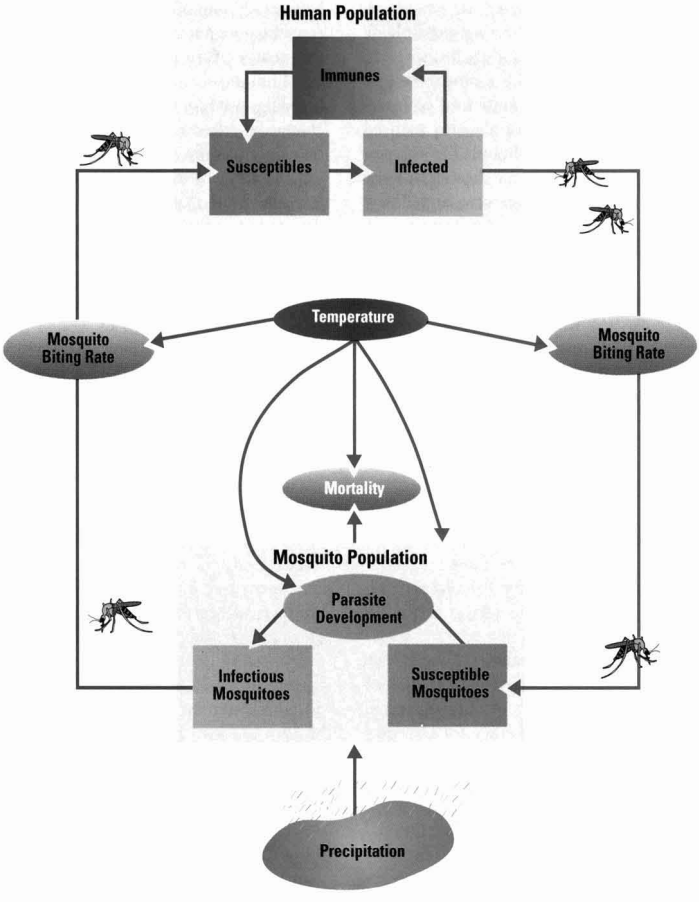

Figure 1. Diagram of the main population and rate processes involved in the life cycle of the malaria parasite.

cycle model, and climate model). A thorough description of the IMAGE model can be found elsewhere (*10,11*). Using the method of Santer et al. (*12*), the simulated global mean temperature changes are converted in time-dependent series of changes in regional seasonal temperature and precipitation by standardizing the output of a General Circulation Model (GCM). GCMs have been shown to simulate current temperature reasonably well, but they do not reproduce precipitation very accurately. They also cannot reliably project changes in climate variability, such as changes in the frequencies of droughts, which also could have a significant effect on vector-borne disease transmission. Nevertheless, GCMs currently provide the most advanced means of predicting the potential future climate consequences on a grid base (*13*).

The GCM used in this study is that of the UK Meteorological Office (*14*), using a grid resolution of 5° latitude by 7.5° longitude, with a climate sensitivity of 5.2. This equilibrium mean global temperature change of 5.2°C that would eventually occur if the CO_2 level were doubled falls beyond the current uncertainty range (1.5–4.5) projected by the Intergovernmental Panel on Climate Change (IPCC) (*11,15*). Although our projected changes in malaria transmission will be more pronounced compared to experiments using less sensitive GCMs, the direction of these changes will not be influenced significantly. The baseline climatology relies on precipitation and temperature data for the period 1951–1980.

New regional climate conditions are calculated using two widely used greenhouse gas standard scenarios: the business-as-usual (BaU) scenario and the accelerated policies (AP) scenario of the IPCC (*16*). BaU represents an ongoing trend of increasing fossil fuel-based energy use, agricultural use, and industrial growth, while AP entails increasing usage of renewable energy.

Epidemic Potential

Malaria is caused by species of the genus *Plasmodium* (of which *P. vivax* has the broadest geographic range and *P. falciparum* is the most dangerous clinically), and the vector responsible for malaria transmission is the mosquito of the genus *Anopheles*. The life cycle of the malaria parasite involves transmission both from mosquito to man and from man to mosquito, effected by the bite of a female mosquito. Inside the mosquito, the extrinsic development of the parasites takes several days.

A measure that summarizes many important processes in transmission of infectious diseases is the basic reproduction rate (R_0). For the malaria microparasite, R_0 is more precisely defined as the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible (*17*). The basic reproduction rate is measure of an individual parasite's reproductive potential, and enables us to simplify the epidemiology of malaria. Basically, if $R_0 > 1$, the disease will spread indefinitely; if $R_0 < 1$, the disease will die out.

The vector density is one parameter in the basic reproduction rate that is strongly related to local environmental conditions. Change in the number of existing malaria vectors with time varies greatly between species, being determined by numerous biological and physical factors such as the availability of species-specific breeding sites, the presence of predacious fish or other natural enemies, the hydraulics of bodies of water, and the type of vegetation present. It is impossible to estimate the change in vector abundance over large areas as a result of temperature, precipitation, and humidity changes using an aggregated model such as ours (*18*). However, the basic reproduction rate allows calculation of the critical density threshold of hosts necessary to maintain parasite transmission. The critical density for malaria transmission can be expressed as:

$$\frac{N_2}{N_1} = k\left[\frac{-\log(p)}{a^2 p^n}\right],$$

where N_2/N_1 is the number of malaria mosquitoes (N_2) per human (N_1), p is the survival probability of the mosquito, a is the frequency of taking human blood, and n is the incubation period of the parasite in the vector. The constant k incorporates variables assumed to be temperature independent (including the efficiency with which a mosquito infects a susceptible human and a human infects a susceptible mosquito; the propensity of the mosquito population to feed on humans; and the recovery rate in humans). We defined the epidemic potential of malaria as the reciprocal of the vectors population's critical density. This epidemic potential is a key summary parameter and is used as a comparative index to estimate the

effect on malaria risk of a change in ambient temperature and precipitation patterns, as simulated with the climate model. A high epidemic potential indicates that a smaller number of vectors or a less potent vector population may maintain a state of endemicity or give rise to occasionally epidemics in a given area.

Climate Effects

The distribution and population dynamics of malaria are probably more governed by abiotic than biotic factors (*19*). Of the possible abiotic influences on the transmission cycle of malaria, temperature and rainfall are the most important. Rainfall influences transmission by its role in the mosquito life cycle, while temperature acts as a regulatory force. Table 1 presents temperatures that are critical to malarial transmission.

The incubation period of the parasite in the vector must have elapsed before the infected vector can transmit the parasite. The relation between ambient temperature and latent period for different parasite species was calculated by using a thermal temperature sum as described by Detinova (*20*). The number of blood meals a mosquito takes from humans is the product of the frequency with which the vector takes a blood meal and the proportion of these blood meals that are taken from humans (the human blood index). The frequency of feeding depends mainly on the rapidity with which a blood meal is digested, which can be calculated by means of a thermal temperature sum, increasing as temperature rises (see Table 1).

The female mosquito has to live long enough for the parasite to complete its development. Between certain limits, longevity of a mosquito decreases with rising temperature and increases with increasing relative humidity (*21*). Mosquitoes prefer humidities above 60%, and optimum temperature for mosquito survival is in the range of 20–25°C. Excessive temperatures will increase mortality, and there is a threshold temperature above which death ensues. Similarly, there is a minimum temperature for the mosquito to become active. Based on data reported by Boyd (*22*) and Horsfall (*23*), we assumed a daily survival probability of 0.82, 0.90, and 0.04 at a temperature of 9, 20, and 40°C, respectively.

Rainfall plays a crucial role in malaria epidemiology because it provides the medium for the aquatic stages of the mosquito life cycle. Rain may prove beneficial to mosquito breeding if moderate, but if excessive it may flush out the mosquito larvae. Rainfall may also increase the relative humidity and hence the longevity of the adult mosquito. The relationships among changing temperatures, precipitation, and relative humidity, however, are complicated and the processes affecting atmospheric humidity suggest only a small change in relative humidity as the atmosphere gets warmer (*24*). The introduction of large-scale irrigation schemes has also reduced the significance of local rainfall in the epidemiology of vector-borne diseases to some extent (*25*). However, because rainfall may be a limiting factor in vector breeding, we imposed a minimum amount of precipitation needed for mosquito development. Using a minimum value of 1.5 mm per day allows us to exclude dry areas from malaria transmission, roughly coinciding with the present distribution limits of endemic malaria areas.

Uncertainties

Our estimate of the epidemic malarial potential, using *A. macullipennis* data on blood-digestion and a universal relationship between temperature and daily survival probability, contains many uncertainties. Ideally it should be calculated separately for each mosquito species in a given location. The epidemic potential of malaria is most sensitive to changes in mean survival probability and development time of the parasite. The effects of different values of maximum mosquito longevity and minimum temperature requirements for parasite development on epidemic malaria potential are illustrated in Figure 2. As temperature increases, epidemic potential increases until a maximum is reached. At high temperatures, the accelerated development of the parasite and the increased biting rate can no longer compensate for the decreasing mean life expectancy among the mosquitoes. The distributions shown in Figure 2 indicate that, in temperate climates, small increases in temperature can result in large increases in epidemic malaria potential, irrespective of the values chosen for the maximum daily survival probability (p_{max}) or minimum temperature for parasite development (T_{min}). Although the maximum values for the epidemic potential are found in the range 29–33°C, the actual transmission intensity also depends on vector abundance. Optimal temperature for the rapid expansion of a population of malarial mosquitoes is found between 20 and 30°C, which may increase transmission potential. Therefore, within this temperature range and with rainfall and humidity being optimal for mosquito breeding, our results will underestimate the change in transmission potential of mosquito populations due to climate changes. On the other hand, if the amount of rainfall (above the threshold limit of 1.5 mm day) is not optimal for mosquito breeding and development, our results are likely to overrate the changes in malaria risks.

Health Impact

We estimated the effect of anthropogenic climate change on malaria incidence and disease burden for highly endemic areas, mainly found in tropical Africa, and for areas of lower endemicity found in other parts of Africa, South America, and Southeast Asia. In tropical Africa attention has been restricted to *P. falciparum*, the predominant species responsible for most malaria mortality. In areas of lower endemicity, we have simulated changes in numbers of healthy years lost for both *P. vivax* and *P. falciparum*. Most developed countries will be in a position to take mitigating measures as malaria transmission potential increases; here the numbers of healthy life lost due to malaria infection will remain negligible compared with the endemic areas in the world.

The model framework used to describe the malaria transmission dynamics in the human population is based on a standard population model (*26*) combined with an epidemiological model for infectious diseases (*27*). The population model calculates future population figures on the basis of United Nations projections (*28*), including those for fertility. The human population at risk to malaria is defined for a younger age class from 0 to 4 years old, and an older age class of 5 years and older to account for age-specific differences in fatality rates (*29*). This population is divided into the three categories of the epidemiological model: susceptible, infected, and immune (see Fig. 1). The rate at which people become infected depends on the basic reproduction rate, which changes with climatic conditions. After entering the infected state a person

Table 1. Some important temperatures in malaria transmission[a]

	Extrinsic incubation cycle (*Plasmodium* species)		Digestion of blood meal (*Anopheles* species)
	P. vivax	*P. falciparum*	*A. maculipennis*
Degree-days (°C day)	105	111	36.5
Threshold temperature (°C)	14.5–15	16–19	9.9

[a]The time needed to complete the parasite's extrinsic development and for the digestion of a blood meal by the mosquito can be expressed in formula by $DD/(T\text{-}T_{min})$, where degree-days (DD) represent the accumulation of temperature units over time, and threshold temperatures (T_{min}) are those below which the process does not occur.

runs a standard risk of contracting malaria, since the general level of prophylaxis is, and probably will remain, low in the populations concerned.

Malarial morbidity and mortality, as modeled here, show the epidemiological features of an infectious disease leading to immunity. In areas with stable, highly endemic malaria, morbidity and mortality in the economically active age groups are expected to be relatively lower than in the younger persons because of the acquisition of long-term immunity by survivors. In areas of low to moderate endemicity the health impact is the same for practically all age groups. The social and economic consequences of malaria are directly related to its severity, mainly due to anemia and premature death.

Our simulation includes the concept of disability-adjusted life years (DALY) (*30*) to arrive at a single measure of the health impact of malaria. For each death, the number of years of life lost is defined as the difference between the actual age at death and the present upper life expectancy for humans as a reference. In the case of disability due to malaria, the incidence of the disease is multiplied with the expected duration of the condition and the severity of the disability. An average disability weight of 0.6 has been added to the periods spent with malaria (we assumed that a clinical attack lasts for 7 days, occurring twice a year), accounting for only a partial loss of functional independence. The death and disability losses are combined and allowance is made for an annual discount of 3% for future losses and for age weights.

Although actual prevalence and incidence figures are not very reliable in most endemic regions, a good estimate of the infection rate can be obtained from the rate of increase of prevalence with age in young children. In our calculations, the initial force of infection is 2.0 per annum for the year 1990 in highly endemic regions and 0.1 in areas of lower endemicity (*31,32*).

In the estimates of the excess disease burden in endemic areas, the malaria conditions are assumed to be in equilibrium in the year 1990 (equilibrium values for disease burden, calculated for the year 1990, are: highly endemic areas *P. falciparum*: 73.3; low endemic areas *P. falciparum*: 5.8 and *P. vivax*: 1.4 DALYs/1000 population). For the stable, highly endemic regions of tropical Africa, this assumption seems to be justified. However, for the unstable areas of lower endemicity, this assumption will often be inappropriate.

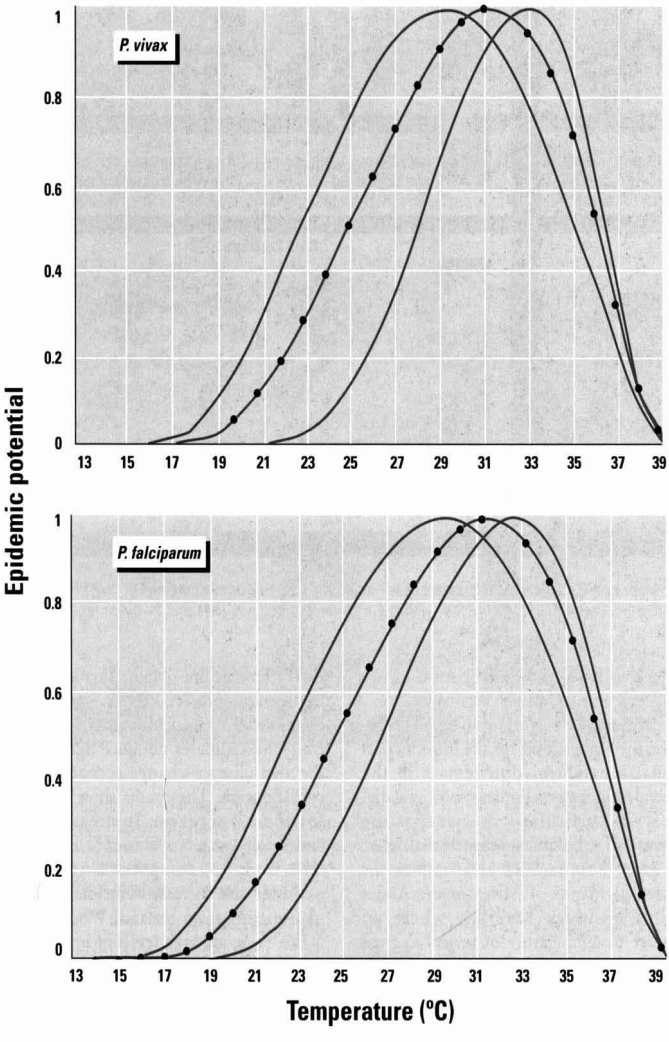

Figure 2. Epidemic potential (value 1 at maximum) as a function of temperature. The left-hand curve shows the epidemic potential for *P. vivax* with p_{max} = 0.8 and T_{min} = 14.5°C; for the central estimate the values are: p_{max} = 0.9 and T_{min} = 14.5°C; and for the right-hand curve: p_{max} = 0.95, T_{min} = 15°C. For *P. falciparum* the left-hand curve uses p_{max} = 0.8 and T_{min} = 16°C; central estimate: p_{max} = 0.9, T_{min} = 16°C; right-hand curve: p_{max} = 0.95, T_{min} = 19°C. For the central estimate the third-order polynomial coefficients used are: α = -4.40, β = 1.31 and γ = -0.03.

Results

We used the epidemic potential to estimate the effect potential of a change in average seasonal temperature and precipitation patterns on malaria transmission, as estimated using the UKMO-GCM. Figure 3 depicts the global distribution of the potential malaria risk areas and the estimates of absolute limits of the possible geographic extension of malaria transmission in the years 1990 and 2100 for the AP and BaU scenarios. The simulated 1990 malarial areas roughly agree with the global distribution of malaria transmission before the introduction of large-scale antimalaria campaigns (*21*). For *P. vivax* this includes large parts of the United States up to the Canadian border, southern and central Europe, Turkey, southern Russia, China, and Japan. *P. falciparum* malaria is restricted to more tropical areas because parasite development needs a minimum temperature of at least 16°C.

Comparing the potential geographic extent of malaria in 1990 to the actual malaria distribution indicates that the simulation of future risk areas must be interpreted to take account of local conditions and developments. In tropical and subtropical regions, climatic conditions are already favorable for mosquito breeding and reproduction, resulting in densities that exceed the critical value for a large portion of the year. However, in some regions "anophelism without malaria" exists, a phrase referring to the absence of malaria in the presence of both *Anopheles* and climate factors, in particular tempera-

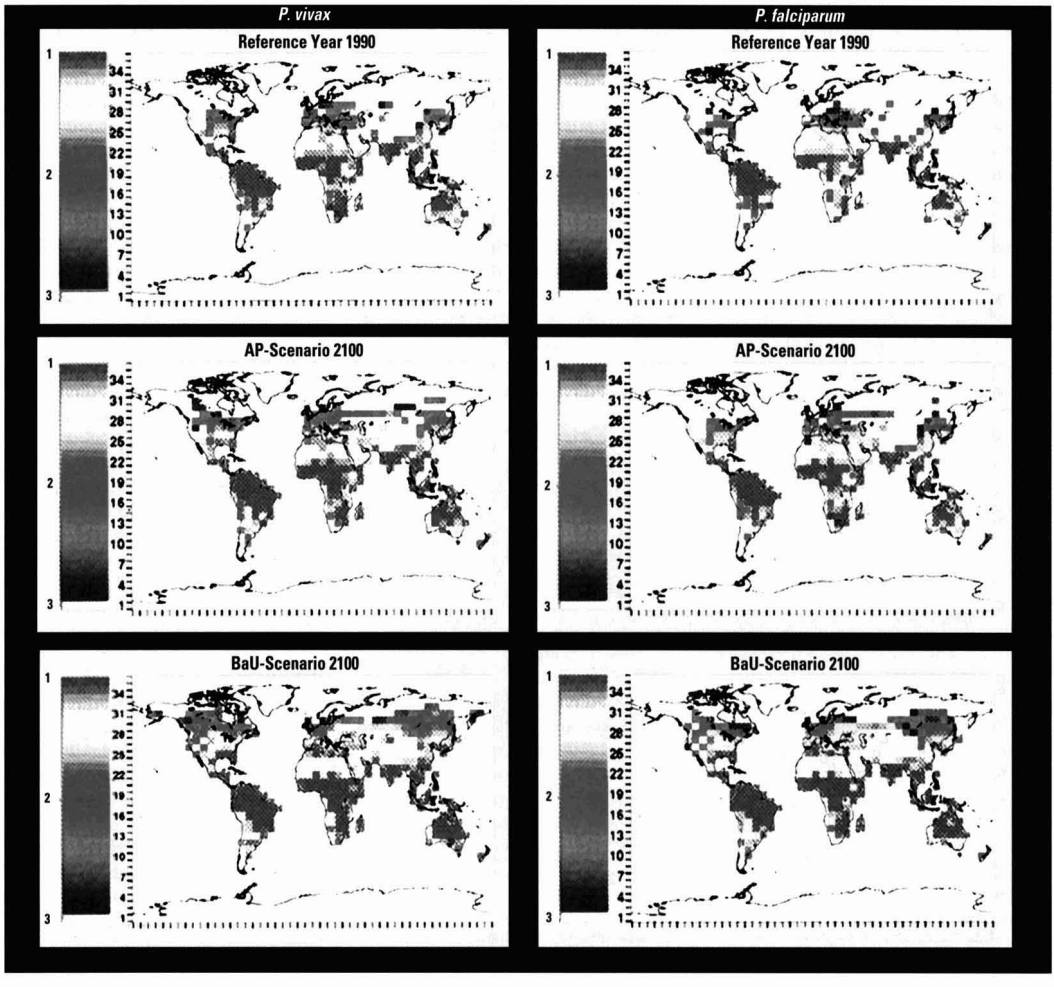

Figure 3. Potential malaria risk areas in 1990 and 2100 for *P. vivax* and *P. falciparum*, expressed as the logarithm of the epidemic potential [$-^{10}\log(EPI)$], based on the climate patterns generated by the UK Meterological Office–General Circulation Model with the accelerated policies (AP) and business-as-usual (BaU) greenhouse gas emission scenarios.

ture, that are apparently conducive to transmission. Effective vector control measures, the treatment of infected individuals, and the specific characteristics of the human and/or mosquito population may explain this phenomenon. In the Central and South Pacific, no potential vectors are present, establishing a malaria-free zone in this area.

Figures 3 and 4 show that an expansion of the geographical areas susceptible to malaria transmission and a widespread increase of potential malaria risk are to be expected as the climate changes. The main changes would occur in areas with temperate climates where mosquitoes already occur but where development of the parasite is limited by temperature. By the year 2100 in large parts of North America, Europe, and Asia, the potential for malaria transmission would exist even with a mosquito density a hundred or more times smaller than in 1990.

Because of their high potential receptivity, the highest risks for the introduction of malaria transmission remain in the nonendemic regions bordering on malarial areas. Of particular importance is the increase of epidemic potential at higher altitudes within malarial areas such as the eastern highlands of Africa or the Andes region in South America, where an increase in temperature of several degrees may raise the epidemic potential sufficiently to change normally nonmalarial areas to areas with seasonal epidemics.

Figure 5 presents the excess disease burden as climate changes according to the AP and BaU scenarios. Because disease burden is influenced by the population's demographic evolution, values for the disease burden attributable to the AP and BaU scenarios are obtained by subtracting the baseline projections; i.e. demographic changes within an unchanging climate, from the estimates obtained according to the two climate change scenarios under consideration. The results show that, even for the AP scenario, in areas of lower endemicity, a relatively small increase in malaria transmission potential may lead to a considerable increase in incidence of people suffering from malaria. Where malaria is rife, there are high levels of immunity in the population, and the change is far less pronounced. However, the major part of the disease burden due to high-fatality malaria will remain in the highly endemic countries of tropical Africa.

Discussion

Recent research assessing malaria risk in relation to climate changes has either been

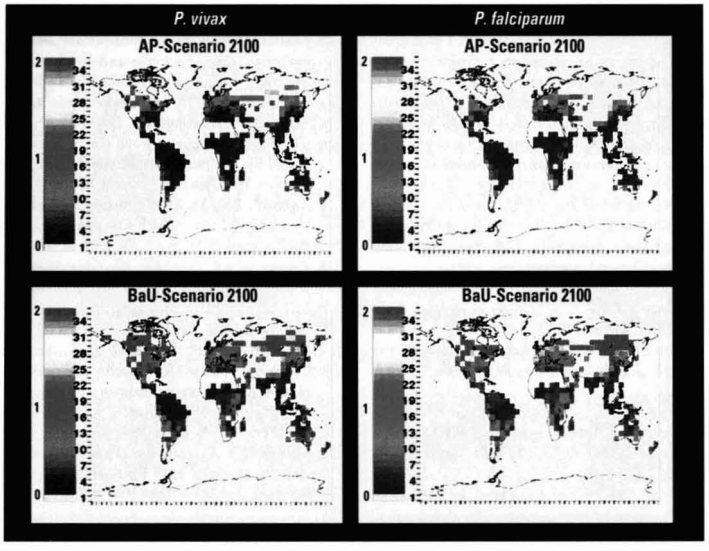

Figure 4. Estimated change of yearly mean epidemic potential (logarithmic scale) for *P. vivax* and *P. falciparum* in 2100 as compared with the year 1990 for the UK Meterological Office–General Circulation Model output with accelerated policies (AP) and business-as-usual (BaU) greenhouse gas emission scenarios.

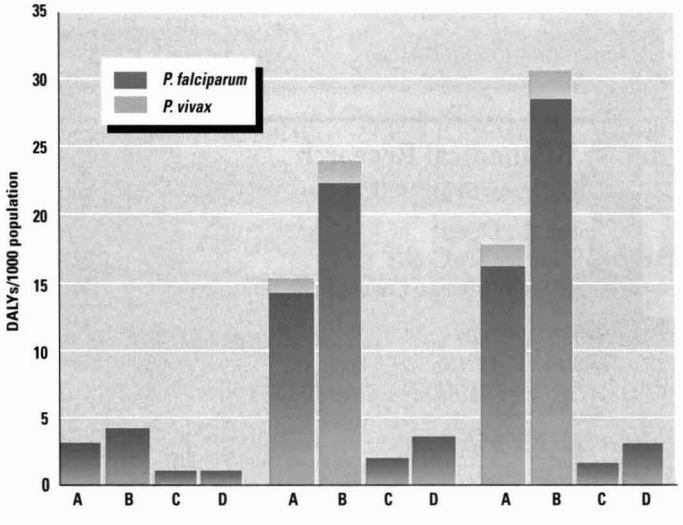

Figure 5. Projection of additional numbers of healthy years lost (*P. vivax* and *P. falciparum*) for highly endemic areas (HE) mainly found in tropical Africa, and areas of lower endemicity (LE) found in other parts of Africa, South America, and Southeast Asia. A, LE areas with accelerated policies (AP) scenario; B, LE areas with business-as-usual (BaU) scenario; C, HE areas with AP scenario; D, HE areas with BaU scenario]. DALY, disability-adjusted life years.

qualitative (*2,3,5*) or does not comprehensively model the cause–effect chain (*1,4,6*). In this study we combined and integrated the present state-of-the-art knowledge and expertise from various disciplines to obtain a global picture of changes in malaria risk areas and health impact, associated with the different climate scenarios. Studies such as this explore the sensitivity of malaria transmission dynamics on a global scale, as currently understood, to projected levels of climate change.

As climate changes in the direction predicted by the IPCC, simulation experiments show a widespread increase in transmission potential of the malaria mosquito population and an extension of the areas conducive to malaria transmission. A global mean temperature increase of several degrees in the year 2100 increases the epidemic potential of the mosquito population in tropical regions twofold and more than 100-fold in temperate climates. There is a real risk of reintroducing malaria into nonmalarial areas, including parts of Australia, the United States, and Southern Europe, associated with imported cases of malaria, since the former breeding sites of several *Anopheles* species still exist. However, because effective control measures are economically feasible in most developed countries, it is unlikely that anthropogenic climate changes would recreate a state of endemicity in these areas. Increased surveillance in previously malarial but not in *Anopheles*-free areas will be necessary, however.

A different situation can be expected in currently endemic areas and areas bordering on them in the subtropics, a result supported by other studies (*7,33*). In the highly endemic malarial areas of tropical Africa, the incidence of malaria and consequently the number of years of healthy life lost due to malaria may increase. In the malarial areas of lower endemicity, the incidence of infection is far more sensitive to climate changes. Therefore, anthropogenic climate change may have substantial effects on years of life lost in such areas.

The change in malaria risk as simulated must be interpreted within the framework of local conditions and developments, such as the health services, the parasite reservoir, and mosquito densities. The large-scale migration of populations from areas in which malaria is endemic into receptive areas, a movement induced by rural impoverishment and inevitably influenced by climatic changes, will play an important role in the dynamics of the disease. Therefore, the extent of an increase in malaria risk will be superimposed upon the change in malaria transmission associated with socioeconomic development, population growth, and the effectiveness of control measures. Given that resources are insufficient to deal adequately with malaria in the most affected regions, increased risk of malaria due to climate change may seriously affect human health in the next century.

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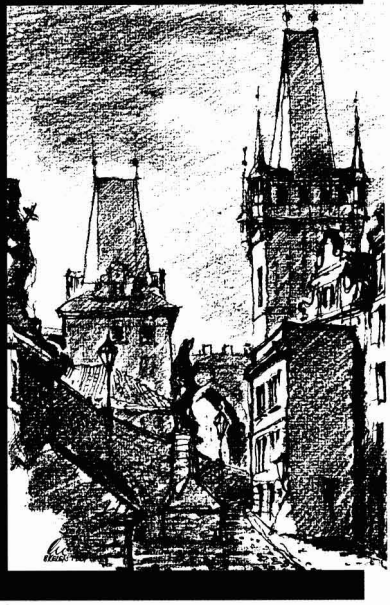

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AUGUST 20–25, 1995

Symposium Topics

1. Biomarkers of exposure and effects of mutagens and carcinogens
2. Genetic-environmental interactions on cancer susceptibility (polymorphism inductionladaptation)
3. Characterization of exposure to environmental mutagens in highly polluted areas
4. Genetic and cancer risk from accidental exposures
5. Reproductive and developmental effects of environmental mutagens
6. Advances in detection of genetic damage in germ cells and genetic risk estimation

Forum Topics

1. Identification of human populations at risk
2. Methodological problems in the design of epidemiological studies focused on environmental mutagens and carcinogens
3. Does exposure to environmental mutagens add significantly to the cancer burden
4. Should population monitoring andlor screening be routinely done on exposed workers
5. Future of human population monitoring

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Biomarker Monitoring of a Population Residing near Uranium Mining Activities

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We investigated whether residents residing near uranium mining operations (target population), who are potentially exposed to toxicants from mining waste, have increased genotoxic effects compared with people residing elsewhere (reference population). Population surveys were conducted, and 24 target and 24 reference residents were selected. The selected subjects and controls were matched on age and gender and they were nonsmokers. Blood samples were collected for laboratory studies. The standard cytogenetic assay was used to determine chromosome aberration frequencies, and the challenge assay was used to investigate DNA repair responses. We found that individuals who resided near uranium mining operations had a higher mean frequency of cells with chromosome aberrations and higher deletion frequency but lower dicentric frequency than the reference group, although the difference was not statistically significant. After cells were challenged by exposure to γ-rays, the target population had a significantly higher frequency of cells with chromosome aberrations and deletion frequency than the reference group. The latter observation is indicative of abnormal DNA repair response in the target population. *Key words*: chromosome aberrations, DNA repair, hazardous chemicals, population study, radiation. *Environ Health Perspect* 103:466–470 (1995)

Uranium has been mined in Texas (e.g., around Karnes County) since 1959. The process of refining the ore to produce high-grade uranium generates a large volume of hazardous residue, called tailings. This residue is often disposed of in open-air tailing piles. The tailing piles, however, contain most of the radionuclide species produced in the uranium decay chain as well as varying amounts of toxic chemicals present in the ore (e.g., heavy metals) or used in the extraction process (*1*). Through the tailings, radionuclides and toxic chemicals become more available for dispersal through hydrologic and atmospheric processes than in the original underground ore. An earlier investigation of the Karnes County Susquehana mine reported radioactive contamination of soil and water in areas beyond the mining sites (*2*). The tailings also release radon gas into the environment. For example, a 1987 survey (*3*) reported that 9.54×10^2 Ci/year of radon gas was released from a tailings site near Pana Maria, Texas. Populations residing near tailings and mining activities may be exposed to a variety of hazardous materials which may cause them to have increased risk for health problems. We conducted a cross-sectional study of a population residing adjacent to uranium mining activities and a population residing in an area free of uranium mining operations, using biomarkers to measure differences in chromosome aberrations and in DNA repair response after their lymphocytes are challenged *in vitro* with γ-rays.

Methods

Identification of mining sites and target residents. Active mine/mill operations, unreclaimed mine/mill sites, and sites that have been closed for less than 3 years in Karnes County, Texas, were identified, confirmed by site visits, and marked on a master map. As a result, 19 sites were selected. Households within 1.5 miles of each site were identified and marked on the same map. We identified 260 households. Residents who lived within 1 mile and downwind (in the northwest quadrant) from the uranium facilities or within 0.5 miles of the other three quadrants were defined as potentially exposed. Based on these criteria, 81 households were eligible for inclusion in this study phase.

We visited eligible households to document the residents and to inquire about their willingness to participate in our study. Volunteers were subsequently interviewed to document personal, occupational, and lifestyle information. A 37-page questionnaire was used; each interview took approximately 45 min. The interviewed participants were further selected based on our predetermined criteria.

Location of reference area residents. Reference (nonexposed) area residents lived south of the town of Kennedy, which is approximately 10 miles south of the mining area but within the same county. Background radioactivity in the reference areas was considered normal according to aeroradioactivity charts (U.S. Geological Survey of Department of the Interior) provided by the Texas Department of Health. Radioactive contour lines, as indicated from the charts, ranged from 170 to 370 cps in the reference area. These background radiation levels in the reference areas were similar to those areas inhabited by our target population. From our survey of the reference area, 137 dwellings were located. Residents were interviewed using procedures described earlier.

Selection of subjects. Enrollment in this study was restricted to nonsmokers who had never worked in the uranium industry, had not been exposed to radiographic procedures to soft tissues such as brain and abdominal scans, and had not undergone radiotherapy or chemotherapy with potent cytotoxic drugs. Inclusion in the target group was restricted to individuals who had resided in the uranium mining target area for 10 or more years. Inclusion in the reference group was restricted to individuals who had never resided in any of the uranium mining areas that we were able to identify. We also eliminated heavy drinkers from both the target and reference populations (daily consumption of more than two shots of hard liquor or four cans of beer) and matched reference and target subjects on age (±7 years) and gender.

We selected 154 residents (73 targets and 81 references) for interview. Among the target subjects, 10 refused to participate and 30 were ineligible based on our selection criteria. This left 33 qualified target individuals for our laboratory study. Among the 81 reference individuals, 17 refused to participate and 25 were disqualified. This left 39 qualified residents for our study. Although blood samples were collected from all of the qualified participants, only 24 pairs met our matching criteria. Due to the limited number of residents in the target area, the matching age was set at ±7 years. However, 19 out of 24 pairs were matched at ±4 years.

Radon monitoring. Residential radon levels were measured by placing radon canisters in the homes of reference study subjects for 2–3 days during early spring of 1991. Exposed canisters were shipped to

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the Radon Testing Corporation of America (New York) for analysis. We did not monitor homes in the target areas because they have been monitored routinely by the Texas Department of Health.

Radon levels in the houses of both the target and reference subjects ranged from 0.1–2.1 pCi/L air. These levels are well below the EPA established action levels of 4 pCi/L. The levels did not differ between target and reference homes.

Blood specimen and cytogenetic assay. Six to eight matched individuals were asked to donate blood samples each week. The collected samples were coded and sent by airline for same day delivery to our laboratories in Galveston, Texas.

Lymphocyte-enriched cultures (from buffy coat) were set up according to the procedure of Au et al. (*4*). The culture medium was made up of RPMI (Roswell Park Memorial Institute) 1640 medium (Gibco) supplemented with 10% heat-inactivated fetal bovine serum, 10% autologous plasma, 2% phytohemagglutinin (Wellcome, reagent grade, 9 mg/mL), 1% glutamine (stock concentration 10,000 U and 10,000 µg/mL, respectively), and 1% sodium heparin (stock concentration 1000 USP/U/mL). The cells from each donor and 25 mL of the culture medium were combined and mixed in a 50-mL sterile tube and then dispensed equally into five culture tubes. Three of the five tubes were unirradiated and used for the cytogenetic assay to determine the frequencies of chromosome aberrations. At 24 hr after initiation of cultures, one of the remaining two cultures was irradiated with 100 cGy of γ-rays, and the last one was irradiated with two doses of γ-rays (50 cGy per dose, separated by 1 hr). The latter two cultures were used for the challenge assay to detect abnormal DNA repair response. Bromodeoxyuridine was added to irradiated cultures immediately after irradiation and to unirradiated cultures at the same time to reach a final concentration of 5 µM. This chemical was used to label cells which have replicated DNA in culture. Only cells in the first metaphase after the beginning of culture were selected for chromosome analysis.

Cell culture harvest and chromosome analyses. Cell cultures were harvested according to our standardized procedures (*4*). Unirradiated cultures were harvested 48 hr after initiation of culture. The irradiated cultures were harvested at 51 hr. We added Colcemid (0.1 mL per tube; stock concentration 10 µg/mL) to each culture 1.5 hr before harvest to block cells at the metaphase stage of the cell cycle. Afterwards, cultures were centrifuged and culture medium was removed. Cells were treated with hypotonic solution and fixed

Table 1. Chromosome aberrations and demographic factors in reference population[a]

Individual no.	Dose (cGy)	No. of cells scored	% Aberrant cells	% Deletions	% Dicentrics	Sex	Residency (years)
1	0	600	1.7	0.4	0.5	F	18
	100	200	35.0	21.0	17.5		
	50 + 50	200	33.5	18.5	21.5		
2	0	600	1.8	0.5	0.2	F	12
	100	200	34.5	17.5	20.5		
	50 + 50	200	32.0	19.0	14.0		
3	0	600	1.7	0.7	0.2	F	28
	100	200	46.0	39.1	16.5		
	50 + 50	200	41.0	36.5	21.0		
4	0	600	2.7	0.5	0	F	28
	100	200	39.0	24.5	19.5		
	50 + 50	200	34.5	28.5	15.5		
5	0	600	2.4	0.2	0	F	13
	100	200	24.5	8.5	18.5		
	50 + 50	200	25.5	15.5	16.5		
6	0	600	1.8	0.5	0.3	F	14
	100	200	30.0	18.5	17.0		
	50 + 50	200	40.0	22.5	23.0		
7	0	600	0.7	0.2	0.2	F	12
	100	200	31.0	17.5	19.0		
	50 + 50	200	30.0	17.0	18.5		
8	0	600	0.8	0.5	0.5	F	15
	100	200	45.0	43.5	21.5		
	50 + 50	200	43.0	42.5	17.5		
9	0	600	1.2	0.3	0	F	15
	100	200	28.5	16.5	15.5		
	50 + 50	200	30.0	12.5	21.0		
10	0	600	2.3	0.8	0	F	15
	100	200	29.5	18.5	17.0		
	50 + 50	200	32.5	17.5	18.5		
11	0	425	2.7	0	0.2	F	14
	100	200	34.5	18.5	20.0		
	50 + 50	200	33.5	19.5	14.5		
12	0	600	02.9	0.7	0.8	F	14
	100	200	28.5	16.5	19.0		
	50 + 50	200	29.0	22.0	21.5		
13	0	600	2.3	0.7	0.7	F	13
	100	200	32.5	23.0	17.0		
	50 + 50	200	31.5	20.5	12.5		
14	0	600	1.0	0.2	0.3	F	31
	100	200	32.0	18.0	16.5		
	50 + 50	200	33.0	30.0	12.5		
15	0	600	1.0	0.2	0.2	F	40
	100	200	31.5	18.0	19.0		
	50 + 50	200	30.5	21.0	17.5		
16	0	600	3.5	0.1	0.7	F	28
	100	200	18.0	16.5	17.0		
	50 + 50	200	16.5	13.5	13.5		
17	0	600	1.4	0.2	0	F	17
	100	200	33.5	24.0	16.0		
	50 + 50	200	41.5	32.5	18.0		
18	0	600	2.3	0.5	0	F	40
	100	200	34.0	24.0	16.5		
	50 + 50	200	36.0	27.5	17.0		
19	0	600	1.5	0.2	0	F	20
	100	200	32.0	20.0	14.0		
	50 + 50	200	32.5	20.0	16.5		
20	0	600	2.3	0.8	0.3	F	19
	100	200	24.0	13.0	14.0		
	50 + 50	200	25.0	14.5	13.0		
21	0	600	0.5	0	0	F	12
	100	200	31.5	21.5	13.5		
	50 + 50	200	31.5	18.5	18.0		
22	0	600	1.8	0.8	0.2	M	26
	100	200	36.0	25.5	20.5		
	50 + 50	200	35.5	29.0	16.5		
23	0	600	0.7	0.5	0	M	16
	100	200	27.0	16.0	16.5		
	50 + 50	200	27.5	16.0	17.0		
24	0	600	1.0	0.2	0.2	M	14
	100	200	30.0	23.0	14.0		
	50 + 50	200	26.5	18.0	15.0		

[a]Dose = delivered dose of γ-rays from a cesium source, 50 + 50 is a split dose of 50 cGy each separated by 1 hr; % aberrant cells = % cells with any type of chromosome aberrations; % deletions = observed chromosome deletion events per 100 cells; % dicentrics = dicentric events per 100 cells. Mean age of population = 45.8 years; range, 23–71.

Table 2. Chromosome aberrations and demographic factors in target population[a]

Individual no.	Dose (cGy)	No. of cells scored	% Aberrant cells	% Deletions	% Dicentrics	Sex	Residency (years)
1	0	600	1.8	0.7	0	F	19
	100	200	52.0	45.5	18.5		
	50 + 50	200	46.0	42.5	19.0		
2	0	600	1.8	0	0	F	26
	100	200	42.5	36.5	19.5		
	50 + 50	200	35.0	26.0	15.0		
3	0	600	1.7	0	0	F	21
	100	200	36.5	23.5	18.0		
	50 + 50	200	37.5	33.0	15.0		
4	0	600	1.8	0.3	0	F	11
	100	200	43.5	42.0	22.5		
	50 + 50	200	37.0	29.5	16.5		
5	0	600	2.5	1.5	0	F	23
	100	200	32.0	28.5	13.5		
	50 + 50	200	35.0	26.5	15.5		
6	0	400	2.5	0.5	0.3	F	34
	100	200	37.0	20.0	18.0		
	50 + 50	200	44.5	24.0	17.0		
7	0	600	1.0	0.3	0.2	F	34
	100	200	31.5	17.5	16.0		
	50 + 50	200	30.5	16.0	18.0		
8	0	600	1.0	0.7	0	F	12
	100	200	45.5	34.0	23.5		
	50 + 50	200	33.5	27.0	16.0		
9	0	600	1.8	1.8	0	F	18
	100	200	34.0	22.0	18.5		
	50 + 50	200	31.5	22.0	16.0		
10	0	600	1.3	0.5	0.3	F	12
	100	200	43.0	40.5	18.0		
	50 + 50	200	42.0	38.0	15.0		
11	0	600	2.8	1.7	0.2	F	11
	100	200	28.5	14.5	17.0		
	50 + 50	200	30.0	11.5	17.5		
12	0	600	3.0	0.5	0.5	F	14
	100	200	38.0	28.0	17.5		
	50 + 50	200	34.5	27.0	16.5		
13	0	600	1.8	0.7	0	F	55
	100	200	35.0	16.0	21.0		
	50 + 50	200	31.5	18.5	19.5		
14	0	600	2.6	0	0	F	28
	100	200	28.5	27.5	12.0		
	50 + 50	200	26.5	17.5	13.0		
15	0	600	1.6	0.2	0.2	F	44
	100	200	32.0	19.0	18.5		
	50 + 50	200	27.5	24.0	21.5		
16	0	600	2.5	0	0.2	F	48
	100	200	36.0	23.5	18.5		
	50 + 50	200	34.5	22.5	14.5		
17	0	600	1.0	0.3	0	F	21
	100	200	43.0	32.5	17.0		
	50 + 50	200	46.5	33.0	20.5		
18	0	600	1.7	0.5	0	F	44
	100	200	45.0	43.0	19.5		
	50 + 50	200	41.5	42.0	15.5		
19	0	600	4.5	1.4	0.2	F	45
	100	200	42.0	28.5	21.0		
	50 + 50	200	38.5	28.0	18.0		
20	0	600	3.8	1.9	0.3	F	48
	100	200	38.0	32.0	18.5		
	50 + 50	200	37.5	22.0	22.0		
21	0	600	4.8	1.5	0.3	F	46
	100	200	30.0	16.5	17.0		
	50 + 50	200	28.0	20.5	17.5		
22	0	600	1.5	0.5	0	M	26
	100	200	37.5	23.0	15.5		
	50 + 50	200	36.5	31.0	17.0		
23	0	600	1.3	0.3	0	M	12
	100	200	42.5	18.5	16.5		
	50 + 50	200	38.5	37.0	19.5		
24	0	600	1.5	0.3	0.3	M	12
	100	200	43.5	34.5	19.5		
	50 + 50	200	39.0	22.0	20.0		

[a]Dose = delivered dose of γ-rays from a cesium source, 50 + 50 is a split dose of 50 cGy each separated by 1 hr; % aberrant cells = % cells with any type of chromosome aberrations; % deletions = observed chromosome deletion events per 100 cells; % dicentrics = dicentric events per 100 cells. Mean age of population = 46.7 years; range, 19–71.

with Carnoy's fixative. Cytological preparations were air-dried and stained. The stained slides were coded and divided among at least two technicians for analyses. For slides from unirradiated cultures, each technician scored 300 cells. For each of the irradiated cultures, 100 cells were analyzed by each of the two technicians. Unusual and questionable cells were reviewed before decisions were made. The data from the two scorers were added together and used for statistical analysis.

Experimental design and statistical analysis. Concerning the sensitivities of the study, when assuming that the dicentric frequency (from unchallenged cells) in the reference population is 0.15%, fixing the type I error at 0.05 and using a one-sided critical region, the study (with analysis of two metaphase cells per donor) would have had an 80% probability of detecting a target group mean frequency of 25% or larger when sample sizes of over 20 and 20 were used (*5,6*).

We analyzed the cytogenetic data using both parametric and nonparametric analysis of variance methods and the paired *t*-test to compare statistically the average chromosome aberration frequency in the target and reference groups of residents. The nonparametric method used was the Kruskal-Wallis comparison of average ranked frequencies (*7*). When the parametric and nonparametric significance levels differed, we used the Kruskal-Wallis test results because of the indication that requirements for the parametric analyses were not met. Usually, the violated requirements concerned different magnitudes of variability (SD) in the two groups being compared.

Results

Although participants who were exposed to therapeutic or excessive diagnostic radiation were disqualified, the accepted participants had diagnostic radiation to chest, hand, ankle, back, etc. The frequencies of the diagnostic radiation during the last 10 years are similar for the target and the reference groups. Only 7 out of 24 people from the target group and 8 out of 24 people from the reference group reported no exposure to diagnostic radiation during the last 10 years.

The collected demographic information relevant to the cytogenetic data is presented in Tables 1 and 2. The female-to-male ratios for study subjects in both the target and reference groups are identical (7:1). The reason for this high ratio is that many male residents were disqualified because of work-related exposure to uranium or other hazardous chemicals. In addition, more males than females refused to participate in the study.

Table 3. Cytogenetic data from matched study and reference residents[a]

Dose (cGy)	Types of abnormalities	Mean frequency of reference group (SEM)	Abnormalities in target group (SEM)	p-value[b]	p-value
0	% Aberrant cells	1.75 (0.16)	2.15 (0.21)	>0.05	0.12
	Deletions/100 cells	0.40 (0.05)	0.67 (0.12)	>0.05	0.07
	Dicentrics/100 cells	0.23 (0.05)	0.13 (0.03)	>0.05	0.06
100	% Aberrant cells	32.00 (1.23)	38.22 (1.24)	0.002	0.0004
	Deletions/100 cells	20.94 (1.51)	27.80 (1.89)	0.008	0.0055
	Dicentrics/100 cells	17.33 (0.46)	18.13 (0.52)	0.440	0.25
50 + 50	% Aberrant cells	32.17 (0.12)	35.96 (1.14)	0.015	0.013
	Deletions/100 cells	22.19 (1.55)	26.71 (1.63)	0.033	0.032
	Dicentrics/100 cells	17.08 (0.61)	17.31 (0.48)	0.522	0.77

[a]The data from analysis of 24 study residents and 24 matched reference residents are presented.
[b]From parametric and nonparametric analysis of variance (see text for details).
[c]From paired t-test (see text for details).

The mean age of the target and reference groups were 46.7 and 45.8 years, respectively. The age ranges for the two groups were 19–71 and 23–71, respectively. The mean age and the range of ages for both populations are similar.

Our criteria required that the target residents live in the uranium belt continuously for more than 10 years and that the reference residents did not live near any uranium-mining areas during the last 10 years. The mean and range of residency data as shown in Tables 1 and 2 are consistent with our criteria. Statistical analysis of the demographic data indicates that the average and distribution of age, gender, and duration of residence are similar for the two groups.

Tables 1 and 2 show the cytogenetic data for each subject from the target and reference populations. The measured chromosome abnormalities are classified into three categories: percentage of aberrant cells, which represents the frequency of cells having any type of chromosome aberrations; deletions/100 cells, which contains the rate of chromosome-type deletions (excessive acentric fragments); and dicentrics/100 cells, which contains the rate of dicentric chromosomes.

A summary of the cytogenetic data is shown in Table 3. As shown in the table, target residents have a higher spontaneous frequency of abnormal cells and cells with chromosome deletions than reference residents (2.15 and 0.67 versus 1.75 and 0.40, respectively). The spontaneous dicentric frequencies from both groups are very low, and the target group has a lower frequency (0.13 and 0.23, respectively). None of the spontaneous frequencies between the target and the reference groups are significantly different from each other. With the challenge assay, the frequencies of aberrant cells, deletions, and dicentrics in lymphocytes from the target residents are consistently higher than those from the controls (e.g., for 100 cGy dose: 38.22, 27.80, and 18.13 versus 35.96, 26.71, and 17.31, respectively). The difference for the first two cateogries are significantly different from each other, whereas there is no difference in the last category.

Analyses of the cytogenetic data were conducted using both parametric and nonparametric analysis of variance methods for independent samples to compare statistically the average abnormality frequencies in the target and reference groups of residents. The results from both analyses were consistent with each other. For spontaneous chromosome aberrations, there were no significantly increased frequencies of aberrant cells, dicentrics, and deletions. For cells challenged with 100 cGy γ-rays, the significance of difference for percentage of aberrant cells, deletion per 100 cells, and dicentrics per 100 cells between the target and the reference groups are p = 0.002, 0.008, and 0.440, respectively. The p-values for the same analyses for cells irradiated with 50 + 50 cGy are 0.015, 0.033, and 0.522, respectively. The cytogenetic data were further evaluated by paired analyses. For the paired analyses, each target resident was paired with the reference counterpart. The data were evaluated using paired t-tests. A summary of the evaluation is shown in Table 3. The data show that the target group has a higher mean frequency of total aberrations and deletions but lower mean frequency of dicentrics than the reference group. The differences were not significant (p = 0.12, 0.07, and 0.06, respectively). The data from the challenge assay show that the study group had more problems in the repair of DNA damage which produced more total aberrations and deletions than the reference group (p-values range from 0.032 to 0.0004).

Discussion

Few studies have been conducted using biomarkers to monitor populations (residents) exposed to toxicants from disposal sites. Heath et al. (*8*) reported a lack of increased chromosome aberrations in persons living near Love Canal. Perera et al. (*9*) and Lakhanisky et al. (*10*) reported increased sister chromatid exchanges in persons exposed to chemicals. To our knowledge, we are the first to report biomonitoring of a population who may have been exposed to toxicants such as radioactive particulates, radon, and heavy metals from uranium mining operations. Exposure to elevated levels of residential radon has been reported to be associated with an increase of gene mutation in peripheral lymphocytes of residents (*11*).

Exposure to environmental toxicants can cause DNA damage, leading to DNA repair problems. For example, lymphocytes from leukemia patients had reduced O^6-alkylguanine-DNA-alkytransferase activites after receiving methylating agents for therapy (*12*). Occupational exposure to toxicants caused hospital workers and tire-storage workers to be defective in the same repair enzyme (*13*). Lymphocytes from smokers and drug addicts have altered unscheduled DNA synthesis after *in vitro* challenge with UV-light or 2-acetylaminofluorene (*14–16*). In a series of cytogenetic challenge studies like ours, Hsu et al. (*17*) and Bondy et al. (*18*) used bleomycin, and Knight et al. (*19*) used X-rays in their challenge assay to detect abnormal cytogenetic response. They concluded from their studies that individuals with the abnormal response are defective in DNA repair and have an associated increased risk for cancer. We have found that cigarette smokers and butadiene workers have abnormal DNA repair responses as shown by our challenge assay (*4,20,21*). In addition, the latter study revealed a significant correlation between abnormal repair and exposure to butadiene as shown by urine metabolite analysis, suggesting a cause–effect relationship (*21*). Exposure to environmental toxicants can cause DNA repair problems, and our cytogenetic challenge assay can be used to identify exposure-related abnormal DNA repair response.

The results from our study, as shown in Tables 1–3, show that the target residents who reside nearby uranium mining activities have higher baseline frequencies of aberrant cells and chromosome-type deletions but lower dicentric frequency than the reference residents. These differences border on being statistically significant. Results from our challenge assay show that target residents have significantly higher frequencies of aberrant cells and chromosome deletions, indicating abnormal DNA repair response.

The data from both assays reinforce each other because increased abnormalities are often observed in the target group compared with the reference group. Our study indicates that the residents who live around uranium mining activities have exposure to hazardous agents. However, the exposure is below the level needed to

cause a significant increase in chromosome aberrations as shown by our standard cytogenetic assay. Based on the sensitivity of the standard assay, the exposure level needed is of the order of maximum permissible occupational doses (*22*). The exposure for the target population is, however, high enough to cause abnormal DNA repair response. Although the mechanism for induction of such response is not known, we suggest that the abnormality may be caused by mutation of genes which code for DNA repair enzymes or by blockage of repair processes on DNA (e.g., adducts) (*20*). These possibilities need to be investigated further using molecular assays.

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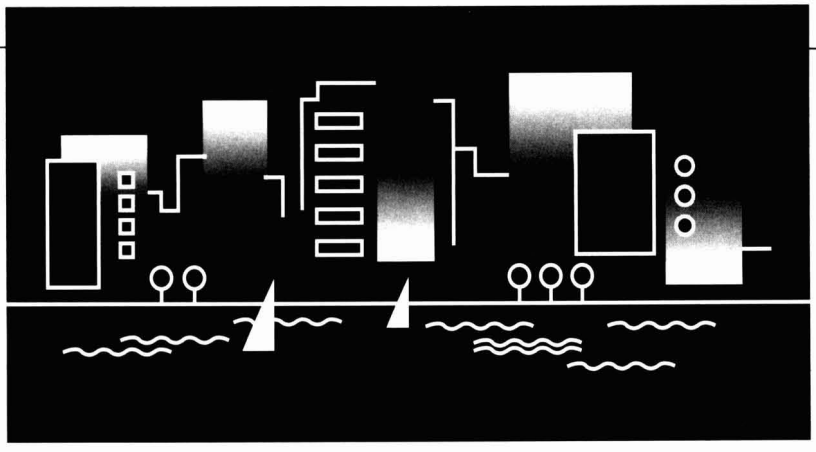

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Health Effects of Particulate Air Pollution: Time for Reassessment?

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Numerous studies have observed health effects of particulate air pollution. Compared to early studies that focused on severe air pollution episodes, recent studies are more relevant to understanding health effects of pollution at levels common to contemporary cities in the developed world. We review recent epidemiologic studies that evaluated health effects of particulate air pollution and conclude that respirable particulate air pollution is likely an important contributing factor to respiratory disease. Observed health effects include increased respiratory symptoms, decreased lung function, increased hospitalizations and other health care visits for respiratory and cardiovascular disease, increased respiratory morbidity as measured by absenteeism from work or school or other restrictions in activity, and increased cardiopulmonary disease mortality. These health effects are observed at levels common to many U.S. cities including levels below current U.S. National Ambient Air Quality Standards for particulate air pollution. *Key words*: **air pollution, particulate pollution, health effects, respiratory disease.** ***Environ Health Perspect*** **103:472–480 (1995)**

Many investigators have reported associations between particulate air pollution and respiratory disease. Early studies focused on severe air pollution episodes including an episode in Meuse Valley, Belgium, in December 1930 (*1*); an episode in Donora, Pennsylvania, in 1948 (*2*); and several episodes in London, the most notable occurring in December 1952 (*3*). Although few data were available regarding concentrations of air pollutants during these episodes, large increases in sickness and death demonstrated severe health effects of air pollution.

Two other important observations were made. First, Martin noted that in the greater London region, overall annual respiratory mortality (as opposed to episodic mortality increases) was significantly related to smoke level (*4*). Second, Holland and Reid (*5*) made a cross-sectional comparison of British male postal employees in London and in smaller country towns, where levels of SO_2 and particulate pollution were about half those in the metropolis. Accounting for cigarette smoking, significant decrements of FEV_1 (forced expiratory volume in 1 sec) in London employees compared to those in the provinces were reported. With our present knowledge of the remarkable predictive capability of FEV_1 for survival (*6*), this finding also suggests that longevity was adversely affected by pollution levels prevailing at that time. This type of air pollution from coal burning has been greatly reduced in the western industrialized nations, but it is still present in Eastern Europe and China. A recent study (*7*) of nonsmoking women in different areas around Beijing shows similar decrements of FEV_1 in areas of higher pollution as were first demonstrated by Holland and Reid (*5*).

By the 1970s, a link between respiratory disease and particulate air pollution and/or sulfur oxide pollution had been well established. There remained disagreement about what levels of pollution significantly affected human health. For example, Holland and several other prominent British scientists (*8*) reviewed research on the health effects of particulate pollution that had been published between 1968 and 1977. They concluded that particulate and related air pollution at high levels pose hazards to human health, but that health effects of particulate pollution at lower concentrations that existed in the United States and Britain by the 1970s could not be "disentangled" from health effects of other factors (*8*). Shy (*9*) responded that this review systematically discounted evidence of pollution-related health effects at contemporary pollution levels. Shy and other reviewers (*9–12*) contended that the cumulative weight of evidence suported the belief that particulate pollution may adversely affect human health even at relatively low concentrations. There has been a great increase in vehicular traffic over the past 20 years. The larger particles resulting from uncontrolled coal burning have been replaced in the urban environment by relatively high concentrations of much smaller particles, commonly 0.2 μm in size.

Much additional research has been conducted since the mid 1970s. While earlier research was useful in documenting the substantial health effects associated with large, dramatic pollution episodes, recent epidemiologic studies have provided more quantification of subtle health effects associated with particulate pollution common to contemporary cities in the developed world. Recent epidemiologic research has generally had better definitions and measures of pollution exposures and health endpoints. Advanced biostatistical and econometric techniques for longitudinal or cross-sectional analysis have greatly expanded opportunities to evaluate health effects of particulate pollution and have increased the analytical rigor of recent studies. For example, recent advances in autoregressive Poisson and logistic regression analysis have permitted the evaluation of pollution associations in panels or other small populations.

This review focuses on approximately 80 recently published epidemiologic studies, most since 1985, which evaluated effects of particulate pollution at concentrations commonly observed in contemporary cities in the developed world. For convenience, these studies are subdivided into general categories based on health endpoint and research methodology and are summarized in Tables 1–5. Separate critiques of each of the key papers are beyond the scope of this review. Although individual studies necessarily have limitations imposed by data deficiencies or by problems in analytical methods, when the whole body of contemporary research is viewed, it is possible to form a judgment concerning the validity of adverse health outcomes as a consequence of particulate pollution.

Acute Morbidity

Numerous studies evaluated acute morbidity effects of particulate pollution by examining short-term temporal associations between lung function measures and/or respiratory symptoms and pollution. Measures of lung function including forced vital capacity (FVC), FEV_1, and peak expiratory flow (PEF) were used. Most of these studies used formal daily time-series analysis, but some of them used periodic time-series analysis across one or more pollution episodes. A summary of the results of many of these studies is presented in Table 1.

Negative associations with particulate pollution and lung function measures were often observed. The particulate pollution effect on lung function was generally physiologically small but statistically signifi-

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cant. Because various measurements of particulate pollution were used, precise comparisons between the studies are difficult. Results of most of the studies suggest, however, that a 10 $\mu g/m^3$ increase in respirable particles (particulate matter ≤10 μm; PM_{10}) resulted in less than a 1% decline in lung function. Nevertheless, in several studies, 24-hr PM_{10} concentrations would occasionally exceed 150 $\mu g/m^3$. During such episodes lung function declined by as much as 7%. In addition to declines in lung function, many of these studies observed increases in respiratory symptoms. A 10 $\mu g/m^3$ increase in PM_{10} was typically associated with a 1–10% increase in symptoms such as cough, combined lower respiratory symptoms, and asthma attacks. These effects were also observed at comparable PM_{10} levels near or even below 150 $\mu g/m^3$.

An important limitation of these studies is that acute effects of particulate pollution on lung function are on average physiologically small and transient, remaining for a few days up to a few weeks. The importance of these small transient effects on a person's long-term well being is unclear. Furthermore, there is concern that these pollution effects may be due to confound-

Table 1. Selected time-series studies on acute effects of particulate pollution on lung function and respiratory symptoms

References	Health endpoints	Study area	Summary of findings
Braun-Fahrlander et al., 1992 (*13*)	Respiratory symptom episodes of 625 children	Basel and Zurich, Switzerland	Particulate pollution (TSP) was associated with incidence and duration of respiratory symptom episodes. No such associations were observed with SO_2 or ozone.
Dassen et al., 1986 (*14*)	Lung function (FVC, FEV_1, PEF) of 636 children	Ijmond, The Netherlands	Significant declines in lung function of 3–5% were observed during an episode of moderately elevated TSP and SO_2. Reductions remained for 16 (but not 25) days.
Dockery et al., 1982 (*15*); Brunekreef et al., 1991 (*16*)	Lung function (FVC, $FEV_{.75}$) of approx. 200 children	Steubenville, OH	Small, significant decreases in lung function were observed after TSP/SO_2 pollution episodes. The association was strongest with previous 5-day mean TSP concentrations.
Johnson et al., 1982 (*17*)	Lung function (FVC, FEV_1, FEF_{25-75}) of children	Missoula, MT	Declines in lung function of 1–3% were associated with a "normal" urban air pollution episode. Comparable declines were not associated with a volcanic ash episode.
Johnson et al., 1990 (*18*)	Lung function (FVC, FEV_1, FEF_{25-75}, PEF) of children	Five Montana cities	Transient declines in lung function were associated with particles. In some cities sources were mostly wood smoke and entrained dust with low levels of SO_2 or O_3.
Hoek and Brunekreef, 1993 (*19*)	Lung function (FVC, FEV_1, PEF, MMEF) of children	Wageningen, The Netherlands	Negative associations between lung function and particulate pollution were observed. Consistent associations with respiratory symptoms were not observed.
Koening et al., 1993 (*20*)	Lung function (FVC, FEV_1) of 326 children	Seattle, WA	Lung function declines were associated with fine particulate air pollution for asthmatic children, but not for nonasthmatic children.
Kinney et al., 1989 (*21*)	Lung function (FVC, $FEV_{.75}$, MMEF, $Vmax_{75}$) of 154 children	Kingston/Harriman, TN	Small decrements in lung function were associated with O_3 but not with particulate pollution, which had low concentrations with little variability.
Krupnick et al., 1990 (*22*)	Respiratory symptoms of 1000+ children/adults	Los Angeles, CA	Respiratory symptoms in both adults and children were associated with particulate pollution. An association with O_3 was observed for adults but not children.
Lebowitz et al., 1985 (*23*)	Lung function (PEF) and symptoms of 229 children/adults	Tucson, AZ	Declines in PEF were associated with elevated concentrations of TSP and O_3. Associations with smoking, gas stove use, and outdoor NO_2 concentrations were also observed.
Ostro et al., 1991 (*24*)	Respiratory symptoms of 207 adult asthmatics	Denver, CO	Several respiratory symptoms including cough and shortness of breath were associated with airborne acidic particulate pollution (H^+). Cough was also associated with $PM_{2.5}$.
Pope et al., 1991 (*25*); Pope and Dockery, 1992 (*26*)	Lung function (PEF) and symptoms of 100+ children and asthma patients	Provo/Orem, UT	Elevated PM_{10} levels were associated with significant declines in PEF, increases in respiratory symptoms, and increased use of asthma medication. Lagged associations were observed for up to 5 days. Particle acidity, SO_2, and O_3 levels were low.
Pope and Kanner, 1993 (*27*)	Lung function (FVC, FEV_1) of smokers with COPD	Salt Lake City, UT	Small transient negative associations between PM_{10} levels and lung function (FEV_1, FEV_1/FVC) were observed. This association was not entirely obscured by participants' smoking habit.
Raizenne et al., 1989 (*28*)	Lung function (PEF, FEV_1) in 112 girls	Girl's camp in Ontario	Maximum average declines in FEV_1 and PEF equal to 3.5 and 7%, respectively, were associated with elevated acid aerosol episodes.
Schwartz et al., 1994 (*29*)	Respiratory symptoms in children	Six U.S. cities	Cough and lower respiratory symtoms were positively associated with PM_{10}.
Whittemore and Korn, 1980 (*30*)	Asthma attacks of 443 asthmatics	Los Angeles, CA	Increased asthma attacks were observed on days with elevated levels of TSP and/or O_3.

Abbreviations: TSP, total suspended particulates; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 sec; PEF, peak expiratory flow; FEF, forced expiratory flow; PM_{10}, particulate matter ≤10 μm; COPD, chronic obstructive pulmonary disease.

ing by weather or some other factor that is not adequately accounted for in the analysis. This concern is partially mitigated by the fact that similar effects have been observed in locations with differing weather conditions including locations where particulate concentrations are high in the summer and where they are high in the winter. For example, effects were observed in studies from Switzerland, the Netherlands, Ohio, Montana, southern California, Arizona, Colorado, Utah, and southern Ontario. Effects were observed in communities where most of the pollution was from wood burning, steel mills, and related industry, or was composed of a complex mixture of aerosols and other particles that are characteristic of urban air pollution. Effects were observed in studies both with and without high concentrations of acid aerosols, sulfur dioxide, and ozone. Effects were observed for both children and adults. Effects were generally observed across areas where the primary source of particulate pollution was combustion, but very small or no effects were associated with large volcanic ash particulate concentrations (*17*).

Numerous studies have also evaluated acute morbidity effects of particulate pollution by examining short-term temporal associations between particulate air pollution and hospital admissions, health care visits, or other measures of restricted activity due to illness (Table 2). These studies usually used formal time-series analytical methods. Statistically significant associa-

Table 2. Selected studies on acute effects of particulate pollution on respiratory morbidity as measured by hospital admissions, health care visits, or other measures of restricted activity due to illness

References	Health endpoints	Study area	Summary of findings
Bates and Sizto, 1987, 1989 (*31,32*); Lipfert and Hammerstrom, 1992 (*33*)	Hospital admissions for 79 hospitals	Southern Ontario	Statistically significant associations between respiratory hospital admissions and sulfates and ozone were observed during summer months. No such associations with nonrespiratory admissions were observed.
Bates et al., 1990 (*34*)	Hospital emergency visits to 9 hospitals	Vancouver, British Columbia	Particulate concentrations were low, and associations with pollution variables were inconsistent. For ages 15–60, asthma and all respiratory visits were significantly correlated in summer with SO_2 and SO_4 levels.
Burnett et al., 1995 (*35*)	Admissions for 168 hospitals	Ontario	Significant positive associations were observed between respiratory and cardiac hospital admissions and previous-day sulfate levels.
Schwartz et al., 1993 (*36*)	Asthma emergency visits	Seattle, WA	Asthma visits were associated with PM_{10} (but not SO_2 or O_3) even at PM_{10} levels below 100 μg/m^3. An increase in PM_{10} equal to 30 μg/m^3 was associated with a 12% increase in asthma visits.
Thurston et al., 1992 (*37*)	Respiratory emergency visits	Buffalo, Albany, New York, NY	Associations between elevated summer haze pollution, including acid particles, particulate sulfate, and ozone, and total respiratory and asthma admissions were observed.
Lutz, 1983 (*38*)	Outpatient clinic visits	Salt Lake City, UT	Strong positive associations were observed between weekly particulate pollution levels and the percentage of patients with a diagnosis of respiratory tract or cardiac illnesses.
Ponka, 1991 (*39*)	Hospital admissions for asthma attacks	Helsinki, Finland	Hospital admissions for asthma were associated with NO_2, NO, SO_2, CO, O_3, and TSP. Associations were strongest for adults of working age, followed by the elderly.
Pope, 1989, 1991 (*40,41*)	Respiratory hospital admissions	Provo/Orem, UT	Strong, statistically significant associations between PM_{10} and respiratory admissions (especially children's bronchitis and asthma admissions) were observed.
Samet et al., 1981 (*42*)	Emergency room visits	Steubenville, OH	Statistically significant but small increase in respiratory emergency room visits were associated with elevated levels of TSP and SO_2.
Schwartz, 1994 (*43*)	Hospital admissions for elderly	Birmingham, AL	Admissions for pneumonia and COPD were associated with particulate air pollution and less strongly associated with ozone.
Schwartz, 1994 (*44*)	Hospital admissions for elderly	Minneapolis/St. Paul, MN	Admissions for pneumonia and COPD were associated with both particulate and ozone air pollution.
Schwartz et al., 1991 (*45*)	Medical visits for croup or obstructive bronchitis	Five areas in Germany	Associations between croup cases and TSP and NO_2 were observed. An increase in TSP from 10 to 70 μg/m^3 was associated with a 27% increase in croup cases. No associations with obstructive bronchitis and pollution were observed.
Schwartz, 1994 (*46*)	Hospital admission for elderly	Detroit, MI	Admissions for pneumonia and COPD (other than asthma) were associated with particulate and ozone air pollution.
Sunyer et al., 1991 (*47*)	Hospital emergency room visits for COPD	Barcelona, Spain	Emergency visits for COPD were consistently associated with particulate pollution (black smoke) and SO_2, even at 24-hr levels less than 100 μg/m^3.
Ostro, 1983, 1987, 1990 (*48–50*); Ostro and Rothschild, 1989 (*51*)	Restricted activity days of up to 12,783 adult workers	Cities in U.S. Health Interview Survey (HIS)	Respiratory morbidity was consistently associated with particulate pollution. Morbidity was often more strongly associated with the fine, respirable, or sulfate component of particulate pollution. Lagged pollution effects of 2–5 weeks were observed.
Ransom and Pope, 1992 (*52*)	Grade school absences	Provo/Orem, UT	Significant robust associations between grade-school absenteeism and PM_{10} were observed. These effects persisted for up to 3–4 weeks.

Abbreviations: PM_{10}, particulate matter ≤10 μm; TSP, total suspended particulates; COPD, chronic obstructive pulmonary disease.

tions between hospital/health care visits for respiratory illnesses and particulate pollution were observed in most, but not all, of these studies. Most of the studies suggested that a 10 $\mu g/m^3$ increase in PM_{10} on the day of the visit or 1 or 2 days before the visit was typically associated with a 1–4% increase in hospital visits. Significant associations between respiratory hospital admissions or related health care visits and particulate pollution were observed in many study areas including southern Ontario, British Columbia, Washington, Utah, Finland, New York, Ohio, Germany, and Spain.

A major concern about using hospital databases to evaluate effects of air pollution is the reliability of diagnoses and other information. Some studies have concluded that when only broad diagnostic classes are used, hospital databases provide reliable information for research on air pollution effects (*53*). Nevertheless, most air pollution studies have used existing databases without specifically evaluating data reliability.

Another concern about interpreting these studies is that the length of the lead-lag relationship of particulate pollution effects differed across studies. These differences may be partially due to disparities in type of health care visit and health care delivery systems across study areas. It may also be due to data analysis that only evaluated short-term effects. The study of inpatient admissions for respiratory disease in Utah Valley (*40,41*) found associations between admissions and air pollution levels up to a month or more before the visit. Several studies that used other measures of respiratory morbidity also observed long lead-lag times. Associations between particulate pollution in Utah Valley and absences of elementary schoolchildren had lead-lag relationships up to 4 weeks (*52*). Also, a series of studies by Ostro (*48–51*) observed that the association between particulate air pollution and days of respiratory morbidity serious enough to restrict activity (including loss of work, confinement to bed, or other restrictions) had a lead-lag time of 2 or more weeks.

Chronic Morbidity

Measures of lung function and incidence rates of respiratory symptoms have also been compared across communities or neighborhoods with different levels of particulate air pollution. Given the cross-sectional design of these studies and because pollution measures are averages over relatively long periods of time (1 year or more), these studies are often interpreted as evaluating chronic or cumulative effects of exposure rather than acute effects. Approximately 35 cross-sectional studies of lung function and/or respiratory symptoms were initially reviewed. Most reported associations between particulate pollution and either respiratory symptoms, lung function, or both. However, many of these studies included only a small number of communities and did not have individual data but relied only on aggregate measures of illness, limiting the amount of confidence that can be given to their results. In this paper, only studies using more sophisticated analysis and individual data for several or more study areas are included and are summarized in Table 3.

Small deficits in lung function (FVC, FEV_1, PEF) were generally associated with higher levels of particulate pollution and were often statistically significant. The results suggest that a 10 $\mu g/m^3$ increase in PM_{10} was typically associated with a decline of less than a 2% in lung function. Respiratory disease, including emphysema and chronic bronchitis, and the incidence of respiratory symptoms were also associated with particulate pollution. The results suggest that a 10 $\mu g/m^3$ increase in PM_{10} was typically associated with a 10–25% increase in bronchitis or chronic cough.

The major limitation of these studies may be the lack of true long-term individual exposure data. An individual's cumulative or long-term exposure to particulate pollution can only be estimated by using available data for the individual's area of residence. Even when available pollution databases allow for adequate estimation of pollution concentrations for a given area, there may be bias in exposure estimates due to selective migration from or into more polluted areas. For example, if persons most sensitive to pollution are more likely to move from polluted areas to less polluted areas, pollution effects would be underestimated.

Acute Mortality

Some of the most striking studies of health effects of particulate air pollution are those that observed changes in daily death counts associated with short-term changes in particulate air pollution (Table 4). Because various measurements of particulate pollution were used, precise comparisons between studies is difficult, but results of most of the studies suggest that a 10 $\mu g/m^3$ increase in

Table 3. Selected cross-sectional studies on chronic effects of particulate pollution on respiratory morbidity

References	Health endpoints	Study areas	Summary of findings
Chestnut et al., 1991 (*54*)	Lung function (FVC, FEV_1) of adults	49 U.S. cities from NHANES I	Small, statistically significant associations between lung function and TSP were observed.
Schwartz, 1989 (*55*)	Lung function (FVC, FEV_1, PEF) age 6–24	44 U.S. cities from NHANES II	Lung function was negatively associated with TSP, NO_2 and O_3, but not with SO_2
Vedal et al., 1991 (*56*)	Lung function and symptoms in children	Port Alberni, British Columbia	Particulate pollution was associated with prevalence of chronic respiratory symptoms, but not lung function.
Dockery et al., 1989 (*57*); Ware et al., 1986 (*58*); Speizer, 1989 (*59*)	Lung function (FVC, FEV_1, $FEV_{.75}$, MMEF), respiratory symptoms of 5422 children	Portage, WI; Topeka, KS; Watertown, MA; Kingston, TN; St. Louis, MO; Steubenville, OH	Chronic cough, bronchitis, and chest illness were associated with particulates. Associations were stronger for children with a history of wheeze or asthma. Associations with lung function were negative but statistically insignificant.
Euler et al., 1987 (*60*)	Nonsmoking adult COPD symptoms	Areas in California	COPD symptoms were associated with particulate pollution and less strongly with SO_2 pollution.
Portney and Mullahy, 1990 (*61*)	Chronic respiratory disease	Cities in U.S annual Health Interview Survey (HIS)	Particulate pollution was associated with emphysema, chronic bronchitis, and asthma. Ozone was more associated with sinusitis and hay fever.
Schwartz, 1993 (*62*)	Chronic respiratory disease	53 U.S. Cities from NHANES I	Chronic bronchitis and respiratory diagnosis by a physician were associated with particulate pollution.

Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 sec; NHANES, National Health and Nutrition Examination Survey; TSP, total suspended particulates; PEF, peak expiratory flow; MMEF, maximal midexpiratory flow rate; COPD, chronic obstructive pulmonary disease.

PM_{10} was associated with an increase in daily mortality equal to 0.5–1.5%. In some studies, lagged pollution effects of up to approximately 5 days were observed.

A few studies divided mortality by cause of death. Figure 1 presents relative risk ratios of mortality associated with similar increases in particulate air pollution in Philadelphia (*69*) and Utah Valley (*77*). Respiratory disease deaths were most strongly associated with particulate pollution levels, but statistical associations were also observed for cardiovascular disease deaths. Why cardiovascular mortality is associated with particulate air pollution is unclear. Reasons may include diagnostic misclassification, acute bronchiolitis precipitating heart failure, and/or effects of pollutants on lung permeability. A recent detailed examination of cardiovascular deaths on days with high particulate air pollution reported that most of the increase in cardiovascular deaths also had respiratory disease as a contributing factor (*70*).

These daily time-series studies have been partially summarized and reviewed (*81,82*). The daily time-series studies suggest that the association between particulate pollution and mortality are not due to confounding by weather, SO_2, or ozone. They also provide information on the age pattern of early deaths and causes of death. Most of them used Poisson regression analysis, allowing a comparison of effect-size estimates on a common scale. Time-series studies have observed effects in varied locations such as California, Utah, Michigan, Missouri, Tennessee, and Alabama in the United States, as well as England, Germany, Greece, and Brazil. It is highly unlikely that such concordance across so many locations could have occurred due to confounding or by chance. Many studies are in locations where particulate concentrations peak in the summer while others are in areas with winter peaks. In locations with winter peaking of particulate concentrations, ozone can be eliminated as a potential confounding factor. Most of the studies examined SO_2. The relationship between mortality and particles was generally independent of SO_2, while the SO_2 relationship disappeared when particles were considered. In Utah Valley and Santa Clara, California, SO_2 concentrations were low. Almost all the studies examined nonlinear relationships with weather factors. Both warm and cold climates and dry and humid locations have reported positive associations between air-

Table 4. Selected daily time-series studies on acute effects of particulate pollution on mortality

References	Study area	Summary of findings
Ostro, 1984 (*63*); Schwartz and Marcus, 1990 (*64*); Ito et al., 1993 (*65*)	London	Daily mortality was associated with particulate pollution (British smoke) and SO_2. The association seemed to be primarily due to particulate pollution but the overall air pollution effect could not be assigned to a specific pollutant with certainty. No threshold level was observed.
Schwartz, 1993 (*66*)	Birmingham, AL	Daily mortality was associated with PM_{10}. The association was strongest for respiratory deaths. An increase in PM_{10} equal to 100 $\mu g/m^3$ was associated with an 11% increase in mortality.
Ozkaynak and Spengler, 1985 (*67*)	New York, NY	Daily mortality was associated with particulate pollution (COH) and SO_2. Data limitations provided little opportunity to estimate separate effects of particles and SO_2.
Wyzga, 1978 (*68*)	Philadelphia, PA	An association between daily mortality and particulate pollution (COH) was observed. The estimated total deaths due to pollution equaled approximately 6%.
Schwartz and Dockery, 1992 (*69*) Schwartz, 1993 (*70*)	Philadelphia, PA	A 100 $\mu g/m^3$ increase in TSP was associated with an increase in mortality due to COPD, pneumonia, and cardiovascular disease equal to 19, 11, and 10%, respectively. On high pollution days, COPD, pneumonia, and dead-on-arrival deaths were disproportionately increased.
Shumway et al., 1988 (*71*) Kinney and Ozkaynak, 1991 (*72*)	Los Angeles, CA	Associations between daily mortality and particulate pollution were observed. Because of multicollinearity between pollutants, independent effects could not be estimated but mortality was not significantly associated with SO_2.
Mazumdar and Sussman, 1983 (*73*)	Three areas in Pittsburgh, PA	Small associations between daily mortality and particulate pollution (COH) were observed only for the area with the highest pollution levels. Emergency hospital admissions were also significantly associated with particulate pollution.
Dockery et al., 1992 (*74*)	St. Louis, MO; Kingston, TN	Mortality was associated with PM_{10}. The association was statistically significant only in St. Louis, yet in both areas an increase in PM_{10} of 100 $\mu g/m^3$ was associated with an approximately 17% increase in mortality. Associations with SO_2, aerosol acidity, or O_3 levels were not observed.
Schwartz, 1991 (*75*)	Detroit, MI	Daily mortality was associated with TSP levels. The association seemed to be independent of SO_2 and existed even at very low levels of pollution. A 100 $\mu g/m^3$ increase in PM_{10} was associated with a 6% increase in mortality.
Fairley, 1990 (*76*)	Santa Clara County, CA	Daily mortality was associated with particulate pollution (COH) at levels below 150 $\mu g/m^3$. Lagged effects were observed for at least 2 days. The association was stronger for respiratory mortality than for mortality due to other causes.
Pope et al., 1992 (*77*)	Provo/Orem, UT	Daily mortality was associated with PM_{10} pollution. The strongest association was with 5-day moving average PM_{10}. An increase in PM_{10} equal to 100 $\mu g/m^3$ was associated with an increase in deaths/day equal to 16%. The association was largest for respiratory disease deaths, next largest for cardiovascular deaths, and smallest for all other deaths.
Schwartz and Dockery, 1992 (*78*)	Steubenville, OH	An association between daily mortality and TSP was observed. This association seemed to be independent of SO_2 and was observed at particulate levels below current standards.
Saldiva et al., 1995 (*79*)	Sao Paulo, Brazil	Mortality of elderly persons was associated with PM_{10}, NO_x, SO_2, and CO. Only the association with PM_{10} was independent of other air pollutants.
Wichmann et al., 1989 (*80*)	North Rhine-Westfalia Germany	During a moderate pollution episode, mortality in the more polluted area was elevated by 8%. Hospital admissions were also elevated. Effects on cardiovascular diseases were larger than on respiratory disease.

Abbreviations: PM_{10}, particulate matter ≤10 μm; TSP, total suspended particulates; COPD, chronic obstructive pulmonary disease.

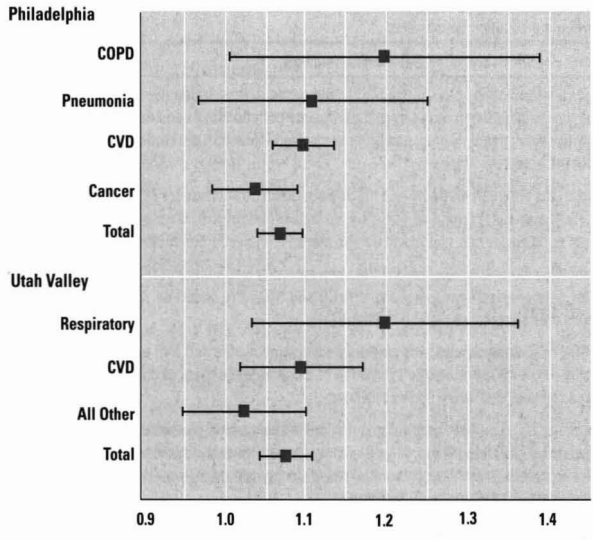

Figure 1. Relative risks of mortality in Philadelphia associated with a 100 μg/m^3 increase in total suspended particulates and in Utah Valley associated with a 50 μg/m^3 increase in suspended particles ≤10 μm diameter. COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

borne particles and mortality. They also covered over an order of magnitude range in airborne particle concentrations. Despite substantial variations in all of the potential confounding factors, the quantitative relationships between particles and daily mortality were essentially the same.

A particulate pollution threshold was not generally observed in these studies. Regression results remained relatively consistent even when pollution episodes that exceed air quality standards were excluded. Several studies, such as those in St. Louis and eastern Tennessee, were conducted in locations that never exceeded two-thirds of the ambient air quality standard, and all provided evidence of an exposure-dependent increase in mortality with particle concentration.

Chronic Mortality

Mortality effects of long-term or chronic exposure to particulate air pollution have been studied using two basic cross-sectional study designs. Population-based (ecologic) cross-sectional studies have correlated city-specific mortality rates with particulate air pollution (Table 5). These studies generally observe a positive association between mortality and various measures of particulate pollution. Most of the population-based cross-sectional studies observed strongest associations with fine particulate pollution or sulfate particulate matter. One of these studies evaluated health effects based on sources of particulate pollution and suggested that particles from the iron/steel industry or coal combustion are relatively more hazardous than soil-derived particles (*87*). These studies typically estimate that 2–9% of total mortality was associated with particulate pollution.

The major limitation of the cross-sectional population-based studies is their ecologic design, which does not permit direct control of individual differences in cigarette smoking and other risk factors. The strength of the relationship between mortality and particulate pollution was often sensitive to model specification, socioeconomic, demographic, and other risk factors included in the analysis and the choice of study areas included in the analysis.

Cross-sectional differences in mortality and air pollution were also studied in a prospective cohort study of 8,111 adults in 6 cities (*92*) and a larger study of over 500,000 adults in 151 cities (*93*). The prospective cohort design allowed for direct control of individual differences in age, sex, cigarette smoking, and other risk factors. In both studies fine particulate air pollution or sulfate particle concentrations were associated with mortality. Adjusted risk of mortality was approximately 15–25% higher in cities with the highest levels of fine particulate pollution compared to cities with the lowest levels. The results suggest that a 10 μg/m^3 increase in average PM_{10} exposure was associated with an increase in daily mortality equal to 3% or more. The strongest associations were observed with cardiopulmonary disease and lung cancer deaths, with only small, insignificant associations with death due to other causes.

Discussion

There are important concerns pertaining to these studies that reflect legitimate skepticism about inherent limitations imposed upon epidemiologic studies. Limitations and concerns relating to these studies tend to fall in three categories: 1) issues related to methodological or analytical bias, 2) issues relating to biological significance or plausibility, and 3) concerns about confounding.

It is unlikely that the overall effects of particulate air pollution are due to systematic methodological or analytical bias because the reasonably consistent findings from many differing study designs, data sets, and analytical techniques used. Many of the studies used simple, straightforward comparative statistical analysis coupled with more sophisticated statistical modeling techniques. Generally, the simple and the more sophisticated analysis observed similar associations between particulate air pollution and the health endpoint. Furthermore, recent reviews have noted considerable consistency across studies, especially the daily time-series mortality studies (*81,82,94*).

The epidemiologic studies, taken individually or as a whole, are severely limited with regard to establishing biological plausibility or providing information on specific biological mechanisms responsible for the observed effects (*95*). Recently, Bates (*96*) has noted the importance of biological plausibility but suggested that the coherence of epidemiologic studies of the health effects of particulate air pollution provide a convincing pattern. A recent review of the acute health effects of particulate air pollution also noted substantial coherence across various health endpoints (*94*). Clearly, biological plausibility is enhanced by the observation of a coherent cascade of respiratory health effects and by the fact that non-cardiopulmonary health endpoints were not typically associated with particulate pollution. Also, several authors have offered biological explanations for the observed relationship between fine-particulate air pollution and cardiopulmonary disease (*6,97*).

The most fundamental concern about the validity of these epidemiologic studies pertains to issues of confounding. Confounding may result when another risk factor that is correlated with both exposure and disease is not adequately controlled for in the analysis, resulting in spurious correlations. One proposed confounder is cigarette smoking. Although cigarette smoking contributes to baseline or underlying respiratory disease rates in a population, it could not be a common confounder across all the studies. For example, cigarette smoking would not be a confounder in the short-term time-series studies because 1) lung function, respiratory symptoms, and school absences studies were generally conducted among nonsmoking children; 2) the largest association between respiratory hospitalizations and pollution was often

Table 5. Selected cross-sectional studies on chronic effects of particulate pollution on mortality

References	Study areas	Summary of findings
Lave and Seskin, 1970 (*83*); Chappie and Lave, 1982 (*84*); Lipfert, 1984 (*85*); Evans et al., 1984 (*86*)	U.S. SMSAs	Statistical associations between mortality and particulate pollution were observed. The strength of the relationship between mortality and particulate pollution was sensitive to model specification, choice of social, demographic, and other variables included in the models, and the choice of SMSAs used in the analysis.
Ozkaynak and Thurston, 1987 (*87*)	U.S. SMSAs	Associations between mortality and particulate concentrations were relatively strong and consistent with sulfate and fine particles. Particles from the iron/steel industry and coal combustion seemed to be larger contributors to human mortality than soil-derived particles.
Mendelsohn and Orcutt, 1979 (*88*)	U.S. county groups	Statistically significant associations between mortality and sulfate particulates were observed. Smaller, less consistent associations with CO and SO_2 were observed. An estimated 9% of total mortality was associated with air pollution.
Lipfert et al., 1988 (*89*)	U.S. cities	SO_4, SO_2, NO_x, fine particles, and particulate trace metals (Fe and Mn) were associated with mortality. The data did not allow estimation of independent effects of these pollutants, but effects of SO_4 and fine particles were fairly consistent.
Bobak and Leon 1992 (*90*)	Czech Republic districts	Infant mortality, especially post-neonatal infant mortality, was consistently associated with particulate air pollution (PM_{10}). After adjusting for differences in socioeconomic characteristics, the relative risk of respiratory post-neonatal respiratory mortality was approximately 3.00 for most polluted areas versus least polluted areas.
Archer, 1990 (*91*)	Three counties in Utah	Spatial and longitudinal differences in death rates in three counties with low smoking rates and the introduction of a major pollution source were evaluated. It was estimated that 30–40% of respiratory disease deaths (approximately 5% of all deaths) were associated with the air pollution in the most polluted county.
Dockery et al., 1993 (*92*)	Six U.S. cities	Prospective cohort study directly controlled for individual differences in age, sex, cigarette smoking, and other risk factors. Statistically significant and robust associations between particulate air pollution and mortality were observed.
Pope et al., 1995 (*93*)	151 U.S. cities	Prospective cohort study included over >500,000 subjects followed up for 8 years. After controlling for individual differences in age, sex, cigarette smoking, and other risk factors, fine and sulfate particulate pollution was associated with mortality (mostly cardiopulmonary mortality).

Abbreviations: SMSA, standard metropolitan statistical area; PM_{10}, particulate matter ≤10 μm.

between young, nonsmoking children; and 3) cigarette smoking does not change day-to-day, week-to-week, or month-to-month in positive correlation with air pollution. Cigarette smoking is a more plausible confounder in some of chronic morbidity and mortality studies. However, even in these studies, smoking is an unlikely common confounder because the estimated pollution effects were observed after analytically controlling for cigarette smoking or restricting the analysis to never-smokers.

Another set of proposed confounders are socioeconomic factors. As with cigarette smoking, socioeconomic status in a population does not change day-to-day in correlation with air pollution. Therefore, socioeconomic status was not a potential confounder in the short-term time-series studies looking at lung function, respiratory symptoms, school absences, outpatient visits, and mortality.

Temporal multicollinearity makes confounding by weather and seasonal variables a concern. The studies often observed various weather and seasonal effects. Several observations pertaining to the studies as a whole mitigate the prospect of weather and/or seasonal variables being common confounders: 1) daily, seasonal, or annual changes in weather were not potential confounders in the chronic mortality and morbidity studies; 2) in most of the shorter-term time-series studies, at least some attempts to control for weather and/or seasonal effects were part of the analysis; 3) the study period for some of the acute studies were conducted only during single seasons, eliminating potential confounding by seasonal or annual changes in weather; and 4) the estimated pollution effects are reasonably consistent for areas with different climates and weather conditions.

It is extremely unlikely that several different confounders for the different studies would coincidentally cause spurious correlations that were coherent across the different studies and different health endpoints. The most likely common confounder that could be responsible for the effects observed is another pollutant or combination of pollutants that are highly correlated with particulate pollution. However, it is difficult to determine which other pollutant(s) may be the confounder. Similar particulate-related health effects have been observed in areas where sulfur dioxide, ozone, and aerosol acidity levels are low or poorly correlated with particulate pollution compared with areas with relative high levels of these pollutants. Given current data, proposing additional potential confounding pollutants is largely speculative. It may be that the true culprit pollutant is a constituent of particulate mass such as combustion particles, sulfate particles, fine- or ultra-fine particles. It may also be possible that various measures of particulate exposure are serving as proxies for an unknown or unmeasured pollutant or combination of pollutants.

Conclusions

There is substantial body of contemporary epidemiologic research that has explored health effects of particulate air pollution at levels common to contemporary cities in the developed world. Observed health effects of respirable particulate pollution include: increased incidence of respiratory symptoms, decreased lung function, increased hospitalizations and other health care visits for cardiopulmonary disease, increased respiratory morbidity as measured by absenteeism from work or school or other restrictions in activity, and increased cardiopulmonary disease mortality. Health effects are observed at levels common to many U.S. and Canadian cities, including levels well below current U.S. National Ambient Air Quality Standards. There is no clear evidence of a safe threshold level. Many studies observe that health effects increase monitonically with pollution levels, often with a near-lin-

ear dose–response relationship.

When a substantial body of epidemiologic evidence indicates that a material to which people are commonly exposed may be having serious adverse health effects the burden of proof may be deemed to have shifted from those who draw a causal inference, to those who maintain no causal inference is possible (*98*). The latter should be required to explain the consistency and coherence of the large body of evidence and put forward alternative hypotheses to explain the findings.

Based on our evaluation of this recent research, there is enough consistency and coherency of results across a large number of studies and a wide range of expected outcomes, methodologies, study areas, and researchers to merit a reassessment of the importance of fine and/or respirable particulate pollution on cardiopulmonary health. A research emphasis should be directed at elucidating the mechanisms behind the epidemiological data. It is unclear why morbidity and mortality should be so closely linked to respirable particulate pollution. Nonetheless, Sir Austin Bradford Hill (*99*), in his famous lecture in 1965, warned us that we should not require mechanistic understanding before making the inference of causality from associative epidemiological studies.

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Applications wanted for Research on the Biological Effects of EMFs

In section 2118 of the 1992 Energy Policy Act, the National Institute of Environmental Health Sciences (NIEHS), an institute of the National Institutes of Health (NIH), has been designated as the lead agency for coordinating and conducting the health effects studies on the possible adverse health effects, if any, of exposure to 60 Hz electric and magnetic fields (EMFs) from the generation, transport and use of electricity. As part of the national program, the NIEHS is required to competitively solicit and select applications to conduct research and communication activities. With the funds provided by this act, the NIEHS established a Research and Public Information Dissemination (RAPID) Program to meet the obligations of this law. In fiscal year 1995 (FY95), the NIEHS is again soliciting grant applications for the NIH Program Announcement 91-53, Research on the Effects of Power Frequency Electric and Magnetic Fields.

PRIORITY AREAS FOR THE FY 95 RAPID PROGRAM

In the FY95, the NEIHS RAPID Program is encouraging investigators to pursue research areas which may be important for understanding the biological actions and possible health effects of exposure to 60Hz EMFs. The following have been identified as priority research areas:

1. Identification and characterization of any biological mechanisms that might lead to adverse health effects in animal models (*in vivo* studies).
2. Identification of any significant changes in normal biological function caused by EMFs that may be plausibly involved in the processes leading to leukemia, breast and brain cancer, and reproductive and neurologic dysfunctions.
3. Validation (and to the extent possible, replication) of bioeffects reported in the peer-reviewed literature related to the mechanisms underlying the diseases listed in item 2.
4. Use of laboratory-based approaches to identify and characterize the specific physical characteristics of EMFs that might be biologically active.
5. Development of scientifically sound risk assessment models and criteria for determining the human health hazards of EMFs.

EMF EXPOSURE SYSTEMS

Many of the problems with exposure systems that have hindered the participation of investigators wishing to pursue research on this problem have been minimized with the recent development of commercial exposure commercial exposure units for *in vitro* and *in vivo* studies. NIEHS can provide investigators a list of commercial vendors and engineers who have expertise and information about EMF exposure units. In addition, NIEHS, through the Department of Energy (DOE), is willing to assist successful investigators by providing advice, helping to identify potential problem areas, and visit laboratories to monitor the functioning of exposure units. NIEHS and DOE have also established regional exposure facilities staffed with knowledgeable investigators who may also be able to provide advice on exposure systems to investigators interested in working in this field.

Application receipt date for FY95:
June 1, 1995

A copy of the program announcement can be obtained by either writing or faxing your mailing address to:

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Measurement of Acidic Aerosol Species in Eastern Europe: Implications for Air Pollution Epidemiology

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A large number of studies have indicated associations between particulate air pollution and adverse health outcomes. Wintertime air pollution in particular has been associated with increased mortality. Identification of causal constituents of inhalable particulate matter has been elusive, although one candidate has been the acidity of the aerosol. Here we report measurements of acidic aerosol species made for approximately 1.5 years in Erfurt, Germany, and Sokolov, Czech Republic. In both locations, the burning of high-sulfur coal is the primary source of ambient air pollution. Twenty-four-hour average measurements were made for PM_{10},[particulate matter with an aerodynamic diameter (d_a) ≤10 μm], as well as fine particle (d_a <2.5 μm) H^+ and SO_4^{2-} for the entire study. Additionally, separate day and night measurements of fine particle H^+, SO_4^{2-}, NO_3^-, and NH_4^+ and the gases, SO_2, HNO_3, HONO, and NH_3 were collected with an annular denuder/filter pack system over a 7-month (late winter–summer) period with additional measurements during pollution episodes the following winter. At both sites, 24-hr SO_2 (mean concentrations of 52 μg/m^3, with peak levels of >585 μg/m^3) and PM_{10} (mean concentration 60 μg m^3) concentrations were quite high. However, aerosol SO_4^{2-} concentrations (mean concentration of approximately 10 μg/m^3) were not as great as expected given the high SO_2 concentrations, and acidity was very low (mean concentration of <1 μg/m^3, with peak levels of only 7 μg/m^3). Low acidity is likely to be the result of NH_3 neutralization and slow conversion of SO_2 to SO_4^{2-}. These data, along with evidence that aerosol acidity exposures are significantly lower than ambient levels and the reported association between fine particulate air pollution and health outcomes in regions where little aerosol acidity has been measured, suggest that particulate acidity alone is not the primary component defining fine particulate air pollution toxicity. *Key words*: acid aerosols, air pollution, Eastern Europe, epidemiology, particulates. *Environ Health Perspect* 103:482–488 (1995)

Beginnning more than 50 years ago, winter episodes of high levels of air pollution were associated with excess mortality in a number of locations, such as London; Donora, Pennsylvania; and the Meuse Valley in Belgium. Although comprehensive air quality data were often not available for these episodes, analysis suggested that although all fine particle concentrations were elevated, acidic aerosols in particular, in addition to sulfur dioxide, were the constituents associated with effects (*1,2*). The potential effect of acidic aerosol exposure has been investigated in North America, where in the summer acidic species are produced via photochemical oxidation mechanisms (*3*). One motivating factor for focusing on summer acid aerosol episodes in North America was the suggestion that the historical winter fog episodes produced high levels of acidic aerosols (*1,4*).

As a result of severe air pollution episodes, control strategies were implemented to reduce the burning of coal for residential heating in London, high-sulfur coal was replaced with low-sulfur varieties, and emission control strategies were implemented, such as the addition of tall stacks which emit above inversion layers. These strategies have greatly reduced the severity of localized wintertime episodes in western Europe and North America. In contrast, the use of tall stacks and the increased demand for summertime power (for air conditioning, for example) has led to long-range transport of sulfur oxides above inversion layers. As this is a summertime phenomenon, photochemical oxidation mechanisms are responsible for production of acidic aerosol species (*3*). Therefore, although the production mechanisms are different, the same agent that was suspected in earlier winter episodes has also been investigated for North American summer situations, even though typical summertime levels of aerosol acidity in North America are significantly lower than in the historical winter fog episodes.

Recently, several studies have attempted to examine the relative importance of aerosol acidity for the health effects of air pollution. Pope and colleagues have shown that wintertime air pollution, especially fine particulate matter ≤10 μm in diameter (PM_{10}, $d_a \leq 10$ mm), is associated with excess mortality, as well as increased school absences and hospital admissions in an area of Utah (*5–8*). Although these studies showed elevated levels of wintertime air pollution, levels of acidic aerosols were extremely low (*7*). Dockery et al. examined the association among PM_{10}, aerosol acidity, and gaseous pollutants with daily mortality in eastern Tennessee and St. Louis, Missouri (*9*). The authors found associations of similar magnitude for PM_{10} in both locations and weaker associations with aerosol acidity (*9*). The consistency of the PM_{10} associations with daily mortality is striking given that mean aerosol acidity levels in eastern Tennessee were more than three times higher than the mean levels in St. Louis, although PM_{10} and aerosol sulfate concentrations were similar. It is also important to note that in eastern Tennessee and St. Louis, PM_{10} concentrations peak during the summer months, whereas in the Utah Valley, elevated PM_{10} is a winter phenomenon.

Dockery and colleagues also reported on the relationship between mortality and air pollution in six U.S. cities (*10*). In this analysis, mortality was more strongly associated with levels of fine and inhalable particulates, as well as sulfate particles, than it was with aerosol acidity (*10*). Somewhat different results were presented by Thurston et al. for analysis of Toronto, Ontario, data: aerosol acidity showed a stronger relationship to summer hospital admissions than did other particle measures such as aerosol SO_4^{2-}, PM_{10}, or $PM_{2.5}$ (*11*). Such results are perplexing, especially when one considers that even when aerosol acidity is measurable in the ambient air, exposure is likely to be low due to neutralization in indoor environments (*12,13*).

Another opportunity to investigate the impact of aerosol acidity and the epidemiological association between winter smog and health came with the end of Communist rule in Eastern Europe. A major air pollution epidemiology study was undertaken in former East Germany and in the Czech Republic. An initial analysis of data from the period 1980–1989, just before the reunification of Germany, has associated excess mortality in Erfurt, Germany, with levels of SO_2 and suspended particulates (*14*). Although air pollution data were available for these pollutants, there were no measurements available of fine particulates nor of the

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chemical composition (such as acidity) of the particulates. With the reunification of Germany in 1989 and the end of Communist rule in the neighboring Czech Republic, the opportunity arose not only to conduct a more detailed epidemiological study, but also to collect measurements of aerosol acidity and fine particulate matter (*15*). During 1990–1992, the effect of ambient SO_2 and total suspended particulates (TSP) on peak flow, medication intake, and daily respiratory symptoms in a population of 160 asthmatic children and 110 adults with asthma or chronic bronchitis was analyzed. A small but consistent decrease in evening peak flow and an increase in daily symptoms was associated with elevated levels of SO_2 and TSP, whereas the effects of aerosol acidity and SO_4^{2-} were generally weaker (*15*).

In the Czech Republic, several studies have indicated effects of ambient air pollution on health. Bobak and Leon report an ecological study in which associations were observed between PM_{10}, and to a lesser extent SO_2 and NO_x, and post-neonatal respiratory mortality in Czech infants (*16*). Lower pulmonary function and a higher prevalence of respiratory symptoms in 2nd-, 5th-, and 8th-grade children living in the highly polluted region of northern Bohemia were observed when compared to the lung function and respiratory symptoms of children living in the less polluted area of southern Bohemia (*17*). In northern Bohemia, high levels of PM_{10} and SO_2 (12-hr averages of 800 and 1100 μg/m^3) were measured in a 1993 winter episode. During this period SO_4^{2-} levels were also quite high (200 μg/m^3) and the fine aerosol was acidic, although only a few percent of the SO_4^{2-} was in the form of sulfuric acid (Stevens RK, personal communication).

Ambient air measurements of PM_{10}, acidic aerosols, acidic gases, and NH_3 were conducted for approximately 1.5 years in Erfurt, Germany, and Sokolov, Czech Republic. This study provided a unique opportunity to examine levels of acidic aerosol species in environments directly impacted by both local and regional sources of high sulfur (up to 5%) lignite "brown coal." Monitoring was specifically focused on winter inversions during which pollutant concentrations were expected to be highest. Here we report on these measurements and compare them to our substantial database of acid aerosol measurements in North America and the available data for Europe. We also compare characteristics of the chemical composition of these Eastern European winter atmospheres to other coal-burning regions and with summer episodes in North America. Our purpose was to determine if aerosol acidity can be measured in wintertime air pollution episodes in locations where the burning of high-sulfur coal is a major air pollution source. Our primary hypothesis was that the health effects associated with wintertime air pollution in similar settings are associated with acidic aerosols. Extensive measurements of acidic aerosol species were collected to support an indirect test of this hypothesis.

Methods

Two cities were selected for air monitoring, Erfurt, in the former East Germany, and Sokolov, in the Czech Republic. Both Erfurt and Sokolov were reported to be subject to winter inversions, which resulted in poor ambient air quality (high TSP and SO_2 concentrations) and reduced visibility. Erfurt (population approximately 220,000) is northwest of Frankfurt, approximately 100 km east of the former east–west border, and is a regional center of commerce. The city has an older, central area where the primary heating source is individual coal furnaces. The outer areas of the city contain large apartment complexes with steam heat supplied by a large coal-burning power plant located several kilometers east of the city center. Erfurt is situated on a flat plain bordered by a 100-m high ridge on all sides but north. The sampling site was 1 km from the town center, 15 m from the nearest structure, and 30 m from the nearest major road. Sampler inlets were located approximately 2 m above ground level.

Sokolov (population approximately 60,000) is an industrial town in a coal-mining region of the Czech Republic, 100 km east of the German–Czech border, at the southern edge of the northern Bohemia region where some of the largest SO_2 sources in Europe are located. In the immediate vicinity of Sokolov are several power plants and large industrial complexes in the region, in addition to a coal gasification plant. Sokolov is in the broad Ohre river valley, which is bordered by 400-m high valley walls. The sampling site was located on the terrace of a two-story building approximately 2 km from the central district. Sampler inlets were located 2 m above the terrace surface.

Particulate acidity (measured in the $PM_{2.5}$ particulate size fraction) and PM_{10} samples were collected with the Harvard Impactor (with the addition of a citric acid-coated honeycomb denuder for acidity sampling) (*18,19*). The Harvard-EPA Annular Denuder System (HEADS) was used to measure gaseous and particle species during some portions of the study. Sampling and analysis procedures are reported in detail elsewhere (*20,21*). Daily or every second day 24-hr samples of fine particulate (d_a <2.5 μm) mass, H^+, and SO_4^{2-} were collected from December 1990–June 1992, and 24-hr PM_{10} samples were collected February 1991–June 1992. Annular denuder measurements were made twice daily (0800 hr–1600 hr, 1600 hr–0800 hr) from February 1991 to September 1991 and during episode periods from October 1991 to April 1992. Detection limits for 12-hr denuder measurements were 16.2 μg/m^3, 1.2 μg/m^3, 0.8 μg/m^3 (as H_2SO_4), 2.3 μg/m^3, 0.6 μg/m^3 and 0.3 μg/m^3, for SO_2, NH_3, H^+, SO_4^{2-}, NH_4^+, and NO_3^-, respectively. The detection limit for PM_{10} was 9 μg/m^3, and the Harvard Impactor 24-hr detection limits were 0.4 (as H_2SO_4) and 1.4 μg/m^3 for H^+ and SO_4^{2-}, respectively.

One of the features of the annular denuder system is a multistage filter pack which includes a Teflon filter to collect the fine particles as well as backup Na_2CO_3 and citric acid-coated filters to collect gaseous HNO_3 and NH3, respectively, that have evolved from the collected particles as the result of artifact reactions (*22*). Backup filters are used to determine whether any aerosol acidity has been "lost" due to particle–particle interactions. For example, acidic sulfate aerosols that react with NH_4NO_3 aerosols will be neutralized, and gaseous HNO_3 will be liberated (Eq. 1). An additional source of volatilized HNO_3 is from the dissociation of particulate NH_4NO_3 into gaseous HNO_3 and NH_3 (Eq. 2).

$$H_2SO_4\,(p),\ NH_4HSO_4\,(p),\ (NH_4)_3H(SO_4)_2\,(p) + (NH_4)NO_3\,(p) \rightarrow (NH_4)_2SO_4\,(p) + HNO_3\,(g) \quad (1)$$

$$NH_4NO_3\,(p) \rightarrow NH_3\,(g) + HNO_3\,(g) \quad (2)$$

By quantifying the amount of HNO_3 (as NO_3^-) and NH_3 (as NH_4^+) on the backup filters, the measured acidity can be corrected for any acidity that is lost due to particle–particle neutralization reactions.

Results and Discussion

Tables 1–3 present summary statistics and compare the winter and summer concentrations measured in Erfurt and Sokolov to those measured in 23 North American communities as part of a major epidemiological study (*23*). These sites were used for comparison because the studies used the same or equivalent measurement and analytical techniques for aerosol acidity as the Eastern European sites, measurements were collected over an entire year, and all measurements were of 24-hr duration. Additional measurements of aerosol acidity in North America have been reported previously (*3*) and demonstrate that the 23 North American communities used for comparison represent a reasonable description of the range of aerosol acidity and

Table 1. Summer (May–September) and winter (November–March) concentrations of particulate matter ≤10 μm (PM_{10}; μg/m^3) measured in Sokolov, Erfurt, and 23 communities in the United States and Canada[a]

	Summer						Winter				
Site	*N*	Mean	SD	Min	Max	Site	*N*	Mean	SD	Min	Max
Penn Hills, PA	73	46.3	24.6	6.4	119.3	**Erfurt**	**76**	**63.5**	**42.9**	**12.2**	**208.9**
Erfurt	**53**	**44.3**	**19.6**	**16.5**	**89.3**	**Sokolov**	**72**	**54.2**	**34.7**	**3.2**	**171.2**
Sokolov	**36**	**40.9**	**19.7**	**9.2**	**84.1**	Monterey, CA	72	32.6	11.2	13.7	61.1
Simi Valley, CA	71	39.8	11.7	15.2	73.5	Livermore, CA	74	30.6	17.2	3.1	83.8
Morehead, KY	71	39.5	17.9	8.6	77.1	Parson, WV	73	29.6	17.7	5.2	93.6
Zanesville, OH	65	39.2	17.1	10.9	84.9	Simi Valley, CA	74	28.9	14.4	6.8	64.6
Springdale, AZ	65	37.3	13	0	67.9	Hendersonville, TN	68	27.9	12.7	8.9	60.2
Hendersonville, TN	75	37.1	15.7	10.6	77.3	Uniontown, PA	72	27.8	11.5	10.9	70.5
Uniontown, PA	76	36.5	19.3	14.5	116.5	Penn Hill, PA	61	26.4	11.9	4.9	76.7
Athens, OH	76	34.8	16.4	10.7	99.5	Springdale, AZ	71	26	15	0	89.3
Blacksburg, VA	73	30.9	11.4	5	60.5	Morehead, KY	68	24.9	9.2	8.5	49.5
Parson, WV	76	30.5	14.5	8.1	73.3	Leamington, ON	70	23.4	11.5	7	78.5
Dunville, ON	68	30.3	18.8	0	83.3	Newtown, CT	59	23.3	11.9	0	58.5
Oak Ridge, TN	64	29.6	11.3	13.3	64.4	Athens, OH	75	23	9.4	5.2	49.6
Leamington, ON	77	28.6	13.1	9.5	78.8	Blacksburg, VA	70	22.7	8.7	5.5	41.9
Charlottesville, VA	74	27.2	12.6	7	61.3	Oak Ridge, TN	65	21.8	10	3.6	53.7
Newton, CT	73	27.1	17.7	0	79.4	Zanesville, OH	66	21	10.3	1.7	58.1
State College, PA	73	26.8	13.1	0	67.3	Penticton, BC	72	19.9	9.9	6.5	47.6
Livermore, CA	70	26.3	10.9	4.8	53.2	Charlottesville, VA	62	19.8	8.2	7.5	60.1
Aberdeen, SD	78	25	11.4	5.3	74.2	Dunville, ON	58	17.1	9.5	0	47.7
Egbert, ON	77	23.2	13.5	0	70.8	Egbert, ON	68	16.7	9.4	4.6	51.3
Yorktown, SK	73	22.8	9.7	5.1	48.6	State College, PA	72	16.6	6.8	0	38.6
Pembroke, ON	75	21.2	14.2	0	64	Aberdeen, SD	67	16.5	8.4	3.4	41.2
Monterey, CA	71	20.3	9.8	0	45.5	Pembroke, ON	47	16.1	11.4	0	51.1
Penticton, BC	73	18.9	9.1	4	47	Yorktown, SK	60	14.1	6.1	1.7	34

[a]For each season, the sampling sites are listed in order of highest mean concentration.

Table 2. Summer (May–September) and winter (November–March) concentrations of aerosol strong acidity (μg/m^3 as H_2SO_4) measured in Sokolov, Erfurt, and 23 communities in the United States and Canada[a]

	Summer						Winter				
Site	*N*	Mean	SD	Min	Max	Site	*N*	Mean	SD	Min	Max
Uniontown, PA	69.0	4.3	5.3	0.1	39.1	Oak Ridge, TN	65.0	1.3	1.5	0.0	8.8
Parson, WV	71.0	4.0	4.7	0.0	19.2	Uniontown, PA	71.0	1.2	1.1	0.2	6.5
Morehead, KY	72.0	3.8	3.3	0.1	14.8	Parson, WV	68.0	1.1	1.0	0.1	4.5
Athens, OH	75.0	3.8	4.0	0.1	24.6	Hendersonville, TN	71.0	1.1	1.2	0.0	7.2
Penn Hills, PA	66.0	3.4	4.2	0.0	19.4	Morehead, KY	69.0	1.1	1.0	0.2	5.3
Oak Ridge, TN	70.0	3.3	2.9	0.0	14.3	State College, PA	71.0	1.0	0.9	0.0	4.1
State College, PA	66.0	3.3	3.2	0.4	16.5	Charlottesville, WV	68.0	0.9	0.9	0.0	4.5
Zanesville, OH	59.0	3.2	3.7	0.0	17.8	Zanesville, OH	70.0	0.8	1.0	0.0	6.7
Hendersonville, TN	70.0	3.2	2.5	0.2	10.9	Athens, OH	75.0	0.7	0.7	0.0	4.2
Charlottesville, VA	66.0	3.1	2.7	0.0	15.5	Pembroke, ON	43.0	0.6	0.5	0.0	1.7
Blacksburg, VA	72.0	2.9	2.2	0.3	10.9	Blacksburg, VA	71.0	0.6	0.6	0.0	2.8
Dunville, ON	57.0	2.6	3.4	0.0	13.9	Simi Vally, CA	70.0	0.6	0.9	0.0	5.6
Newtown, CT	70.0	2.0	2.2	0.0	9.1	Newton, CT	63.0	0.6	0.5	0.0	2.2
Leamington, ON	73.0	1.5	2.1	0.0	13.5	Livermore, CA	72.0	0.6	0.4	0.0	1.6
Pembroke, ON	64.0	1.4	2.2	0.0	13.3	Leamington, ON	73.0	0.5	0.6	0.0	3.0
Springdale, AR	71.0	1.0	0.6	0.0	2.6	Monterey, CA	72.0	0.5	0.3	0.1	1.5
Simi Valley, CA	68.0	0.9	0.6	0.0	3.0	Penn Hills, PA	63.0	0.5	0.5	0.0	2.4
Sokolov	**74.0**	**0.5**	**0.3**	**0.0**	**1.5**	Penticton, BC	70.0	0.4	0.3	0.0	1.4
Livermore, CA	73.0	0.5	0.4	0.0	1.9	Dunville, ON	54.0	0.4	0.4	0.0	2.3
Egbert, ON	48.0	0.5	1.2	-0.4[b]	6.0	**Sokolov**	**72.0**	**0.3**	**0.6**	**0.0**	**4.8**
Monterey, CA	72.0	0.4	0.3	0.0	1.5	Springdale, AZ	67.0	0.3	0.3	0.0	1.0
Penticton, BC	69.0	0.4	0.2	0.0	1.1	**Erfurt**	**74.0**	**0.2**	**0.3**	**0.0**	**1.7**
Erfurt	**75.0**	**0.4**	**0.3**	**0.0**	**1.4**	Aberdeen, SD	66.0	0.0	0.1	-0.3	0.4
Aberdeen, SD	74.0	0.2	0.2	-0.2	0.9	Yorktown, SK	30.0	0.0	0.1	-0.3	0.2
Yortown, SK	75.0	0.0	0.2	-1.2	0.5	Egbert, ON	16.0	-0.1	0.1	-0.4	0.1

[a]For each season, the sampling sites are listed in order of highest mean concentration.
[b]Negative values indicate alkaline samples.

aerosol SO_4^{2-} concentrations found in North America.

European measurements are extremely limited and more difficult to compare because of different sampling and analytical techniques and small sample sizes. Using similar techniques to those described here, Hoek et al. found low levels of aerosol acidity (0–8.8 μg/m^3 as H_2SO_4) and aerosol SO_4^{2-} (1–24 μg/m^3) in an extensive monitoring study conducted in The Netherlands (*24*), and Kitto and Harrison measured aerosol acidity levels of 0–8.7 and SO_4^{2-} concentrations of 1–48 μg/m^3 in a coastal area of southeast England (*25*). In a limited series of measurements, Puxbaum, et al. (*26*) measured 6- to 12-hr averages of wintertime aerosol acidity and SO_4^{2-} concentrations in Ljublijana (formerly Yugoslavia), in a rural site in Italy (Po Valley), and at a suburban

Table 3. Summer (May–September) and winter (November–March) concentrations of aerosol sulfate (μg/m^3) measured in Sokolov, Erfurt, and 23 communities in the United States and Canada[a]

	Summer						Winter				
Site	*N*	Mean	SD	Min	Max	Site	*N*	Mean	SD	Min	Max
Penn Hills, PA	62.0	12.1	9.2	0.0	42.6	**Erfurt**	**74.0**	**8.4**	**6.5**	**0.9**	**30.5**
Uniontown, PA	70.0	10.4	8.1	0.0	51.5	**Sokolov**	**72.0**	**7.7**	**5.4**	**1.4**	**23.8**
Morehead, KY	72.0	10.1	5.4	1.7	27.4	Athens, OH	74.0	4.6	2.4	0.4	12.0
Athens, OH	74.0	10.0	7.7	0.0	43.1	Uniontown, PA	71.0	4.4	2.2	1.2	11.9
Zanesville, OH	60.0	9.9	7.7	0.0	37.5	Oak Ridge, TN	66.0	4.2	2.4	0.9	12.9
Hendersonville, TN	69.0	9.6	5.1	2.4	22.5	Penn Hills, PA	63.0	4.1	2.1	0.0	10.7
Blacksburg, VA	72.0	9.4	5.3	1.2	23.8	State College, PA	71.0	4.0	2.4	0.5	10.0
Dunville, ON	59.0	9.1	7.9	0.0	30.6	Morehead, KY	69.0	3.8	2.2	1.1	9.7
State College, PA	67.0	9.1	7.0	0.6	29.5	Zanesville, OH	70.0	3.8	2.2	0.7	11.3
Parson, WV	71.0	8.6	7.7	0.0	33.8	Parson, WV	67.0	3.8	1.8	1.0	10.3
Oak Ridge, TN	70.0	8.6	5.7	0.0	29.4	Blacksburg, VA	70.0	3.6	1.7	0.6	9.9
Sokolov	**67.0**	**8.6**	**5.0**	**1.4**	**21.2**	Hendersonville, TN	73.0	3.5	2.4	0.0	13.2
Charlottesville, VA	67.0	8.2	5.4	0.0	26.4	Charlottesville, VA	68.0	3.5	1.9	0.7	9.2
Erfurt	**69.0**	**8.0**	**4.7**	**1.5**	**21.5**	Leamington, ON	73.0	3.4	1.9	0.0	8.7
Newtown, CT	69.0	6.3	6.0	0.0	26.0	Newtown, CT	61.0	3.3	2.0	0.0	9.7
Leamington, ON	74.0	6.3	5.9	0.0	33.1	Dunville, ON	53.0	3.3	1.7	0.0	8.2
Springdale, AR	72.0	4.8	2.9	0.0	12.8	Egbert, ON	16.0	2.4	1.5	0.6	6.8
Egbert, ON	48.0	4.7	7.2	0.0	30.7	Springdale, AR	66.0	2.4	1.6	0.0	8.2
Pembroke, ON	67.0	4.4	5.6	0.0	27.8	Simi Valley, CA	70.0	2.2	3.3	0.0	14.8
Simi Valley, CA	63.0	4.0	2.5	0.0	10.0	Pembroke, ON	41.0	2.2	1.3	0.0	6.1
Aberdeen, SD	74.0	2.4	3.2	0.3	20.4	Aberdeen, SD	66.0	1.4	1.2	0.0	5.5
Livermore, CA	73.0	1.6	1.1	0.0	5.7	Monterey, CA	71.0	1.1	0.9	0.0	5.3
Monterey, CA	66.0	1.4	0.7	0.0	3.1	Livermore, CA	72.0	1.0	0.8	0.0	3.7
Yorktown, SK	76.0	0.8	0.7	0.0	4.3	Yorktown, SK	30.0	0.8	0.8	0.0	3.5
Penticton, BC	68.0	0.7	0.5	0.0	2.3	Penticton, BC	69.0	0.7	0.6	0.0	3.2

[a]For each season, the sampling sites are listed in order of highest mean concentration.

site in Vienna. Concentrations of SO_4^{2-} and acid aerosols in Ljublijana were comparable to those measured in this study, after accounting for the different sampling durations. Due to the limited number of European measurements available, we chose to compare our measurements primarily to the more extensive North American database, as well as other measurements collected in coal-burning areas (*10,27,28*) (Table 4).

Erfurt and Sokolov report aerosol acidity concentrations that are at the low end of the observations in North America and much lower than those measured in London during the 1963–1972 period (Tables 2 and 4). Winter PM_{10} and SO_2 concentrations at both eastern European sites were also much lower than those measured in London (*28*), but well above concentrations observed in the North American communities used for comparison (Tables 1, 3, and 4).

Mean concentrations of PM_{10} in Erfurt and Sokolov were significantly higher in the winter than in summer (Table 1), which is consistent with the occurrence of winter inversions and increased coal burning (particularly in Erfurt) for residential heating. Although the record of SO_2 sampling was not complete, concentrations also appeared to be higher in winter than in summer. During 1991, two consecutive 12-hr samples were collected daily in both Erfurt and Sokolov with the HEADS sampler. In Erfurt during February–April, the mean 24-hr SO_2 concentration was 125 μg/m^3 (SD = 122, range: 27–656, N = 35), while in May–September, the mean was 22 μg/m^3 (SD = 21, range: 3–93, N = 55). In Sokolov the February–April 24-hr mean SO_2 concentration was 76 μg/m^3 (SD = 45, range: below detection–205, N = 31), while in May–September, the mean was 31 μg/m^3 (SD = 22, range: 3–97, N = 46). Aerosol acidity was slightly higher in the summer than in winter at both sites (Table 2). This contrasts with observations from North America in which summer acidity levels are much greater than those measured in the winter (*3*) (Table 2).

Although acid aerosol levels were very low, comparisons to the North American database of SO_4^{2-} measurements (Table 2) indicates that the eastern European sites presented somewhat higher SO_4^{2-} concentrations, particularly during the winter period. As SO_4^{2-} concentrations can be viewed as "potential acidity," it is evident that little of the aerosol SO_4^{2-} was acidic, suggesting substantial neutralization. H^+/SO_4^{2-} ratios were below 0.4 for all samples except for one 24-hr winter sample collected in Erfurt (ratio = 1.25) and two winter samples collected in Sokolov (ratios = 0.60 and 0.65).

As suggested by the observations of low aerosol acidity and high SO_4^{2-} concentrations, levels of NH_3 were elevated (Table 4) in Sokolov and Erfurt. Ambient NH_3 measurements are indicative of the extent to which acid aerosols may be neutralized into nonacidic species, since NH_3 neutralizes acidic sulfate aerosols to produce neutral salt species. Although the record of NH_3 concentrations is less complete than

Table 4. Summary statistics of ambient concentrations (μg/m^3) measured in Sokolov and Erfurt and comparisons to measurements in Wuhan, China (*27*), Steubenville, Ohio (*10*) and historical measurements in London (*28*)

Site	Mean	SD	Peak
Aerosol acidity (as H_2SO_4)			
Sokolov	0.5	0.6	7.6
Erfurt	0.4	0.4	8.1
Wuhan	0.7	NA	2.4
Steubenville	1.2	NA	NA
London	6.5	6.7	134
SO_4^{2-}			
Sokolov	9.6	6.0	36.4
Erfurt	11.0	9.0	74.1
Wuhan	50.4	NA	94.1
Steubenville	12.8	NA	NA
NH_3			
Sokolov	2.6	3.2	23.6
Erfurt	1.7	1.1	13.9
SO_2			
Sokolov	52	63.7	592
Erfurt	60	94.5	715
Wuhan	42	NA	73
Steubenville	63	NA	NA
London	317	163	1298
Pariculate matter ≤10 μm (PM_{10})			
Sokolov	59	35	171
Erfurt	66	45	269
Wuhan	NA	NA	350
Steubenville	47	NA	NA
London[a]	92	71	709

NA, data not available from references.
[a]London PM_{10} measurements are estimated from British smoke measurements where British smoke is assumed to be equal to PM_{10} as a lower bound (*43*). Mean measurements of acidity and SO_4^{2-} from Erfurt and Sokolov are from Harvard impactor (24-hr) measurements; peak measurements for all species except PM_{10} are from HEADS (12-hr) measurements.

the aerosol acidity and sulfate measurements, mean concentrations during the sampling periods were consistently high (>1.4 μg/m^3) throughout the year. Annual averages in North American communities are typically below 1 μg/m^3, with only rural sites reporting annual means above 1.4 μg/m^3.

The observation of higher SO_4^{2-} levels in Wuhan, China (*27*) than in Erfurt or Sokolov is indicative of low conversion of SO_2 to SO_4^{2-}, given the higher SO_2 levels measured in Erfurt and Sokolov (Table 4). SO_2 levels in Erfurt and Sokolov were well below those measured in London, but significantly higher than those measured in China. In contrast, the Wuhan environment may have presented more complete conversion, but acidity appeared to be controlled by neutralization. In both the Wuhan study and this study, levels of aerosol acidity were surprisingly low, given the high measured concentrations of SO_2 and PM_{10}. PM_{10} concentrations in Erfurt and Sokolov were similar to concentrations measured in Wuhan. Although these comparisons are limited, they suggest that the conditions encountered in Erfurt and Sokolov may be typical of regions in which high-sulfur coal is burned during the winter. In such situations, although SO_2 levels may be greater than concentrations observed in North America, aerosol acidity levels are very low.

Sampling and Analytical Issues

One explanation for our inability to observe aerosol acidity lies with the measurement itself. Were the measurements used in this study unable to measure acidity that was present in the atmosphere, or were the studies in London in the 1950s and afterwards measuring acidity produced via artifact reactions? Although few data are presented, the analytical method used in London was apparently insensitive to artifact formation of acid from SO_2, even though only a small amount of SO_2 would need to react on the filter to produce a relatively large artifact of sulfate (*29*). At the levels of SO_2 measured in London (Table 4), this artifact could easily account for all of the measured aerosol acidity. In future studies in similar environments it would be advisable to attempt to directly replicate the measurement method of Commins (*29*).

Although there was no measured acidity, we examined the possibility that the high particle concentrations led to particle–particle interactions on the filter which resulted in an apparent loss of measurable acidity. For this analysis we used the data (approximately 230 samples) from the multistage filter pack of the HEADS (Table 5). The acid correction is minimal, although there is a tendency for a negative correction due to higher NH_4^+ on the backup filter. These results are consistent with those reported by Koutrakis et al., who found little correction for samples collected in six locations in North America (*22*). Although NH_4^+ concentrations were quite high, most of the NH_4^+ and NO_3^- was found on the Teflon filter and not on the backup, suggesting only minimal volatilization of NH_4NO_3. Ion balances ($[H^+] + [NH_4]/2$ ($[SO_4^{2-}] + [NO_3]$) on the Teflon filter were only slightly less than 1, suggesting that all anions associated with acidity were accounted for (Table 5).

Alternatively, although the method used in the measurements reported here is suitable for generated atmospheres of acidic sulfate species (*30*) and for acidic aerosols produced during summer photochemical processes (*18*), it may not adequately measure aerosol acidity that is likely produced via heterogeneous mechanisms and associated with carbon particles. This question remains unanswered because all applications of this method in winter pollution situations (*7,27*), including our study, have measured little or no acidity, while the method has only been evaluated for aerosols likely to resemble those produced in summer conditions.

We also investigated the possibility that in the humid environments with high concentrations of particles characteristic of winter episodes, acidity was present in larger size fractions than collected by our sampler. Measurements of SO_4^{2-} in the PM_{10} fraction were made on a subset of the samples collected in Erfurt (N = 35) and Sokolov (N = 45). SO_4^{2-} in the PM_{10} and $PM_{2.5}$ fraction were highly correlated (r^2 = 0.94), and there was little indication of additional SO_4^{2-} in the PM_{10} fraction. This limited analysis suggests that no additional aerosol acidity would be associated with particles of aerodynamic diameter >2.5 μm.

Acid Production and Neutralization

Another explanation for our observation of low aerosol strong acidity is the effect of low SO_4^{2-} production or neutralization of acidic sulfate species by ambient NH_3. The meteorological conditions of local winter inversions suggests that SO_2 and consequently SO_4^{2-} ("potential acidity") concentrations and NH_3 will peak at the same times, limiting the opportunity for acidic particles to avoid neutralization. This contrasts with North American summer episodes, for which it is believed that convective mixing replaces stagnant surface-level air (high ammonia content) with acid-laden air that has been transported above inversion layers where it is protected from neutralization (*3,31*). The situation in eastern Europe also differs in terms of the proximity of the sources, with local sources emitting SO_2 below inversion layer heights and therefore in close proximity to NH_3 sources, providing ample opportunity for neutralization.

Further, the SO_2 conversion reactions are expected to differ between the (eastern European) winter and the North American summer, where photochemical reactions predominate. In North America, emissions are typically above the height of inversion layers under conditions of low particle concentrations, facilitating transport of gaseous species at heights where slow conversion may occur while the air mass is protected from neutralization by surface level sources of NH_3. The predominant conversion mechanism in North America is photochemical, based on the reaction of hydroxyl radical with SO_2 in the presence of water (*32*). In eastern Europe, where winter inversions reduce the impact of photochemistry and where high particulate concentrations provide sufficient surface area, heterogeneous reactions are expected to predominate.

Aqueous-phase oxidation mechanisms may explain our observations of lower than expected sulfate levels at a given SO_2 concentration, as well as the high levels of NH_4^+ ion observed (mean concentrations >4 μg/m^3). In the winter inversion setting, concentrations of oxidizing species may be quite low and conversion of SO_2 limited. Homogeneous gas-phase conversions, associated with North American summertime acidity, occur at rates of 0.3–2%/hr, while aqueous phase (nonmetal catalyzed) oxidation is slower (0.2%/hr) (*33*).

The extent of SO_2 conversion may be estimated by the $[SO_4^{2-}/SO_4^{2-} + SO_2]$ ratio. Much like the North American situation, the ratios in Erfurt and Sokolov were lower in the winter than in the summer. Ratios

Table 5. Summary statistics for denuder/filter pack measurements of particulate species[a]

Site	H^+ uncorrected	H^+ correction	H^+ total	Ion balance	SO_4^{2-} (teflon)	NO^{3-} (teflon)	NH_4^+ (teflon)	NO_3^- (backup)	NH_4^+ (background)
Sokolov	13.6	-8.4	15.9	0.95	99.3	51.9	225.0	8.1	14.6
Erfurt	8.9	-19.3	12.9	0.89	109.7	48.8	245.6	14.6	37.8

[a]All concentrations in nmol/m^3. All values are mean values for the (approximately) 230 denuder samples collected (i.e., the H^+ total is the mean of the 230 H^+ total measurements, not the sum of the mean H^+ uncorrected + mean H^+ correction). H^+ correction refers to F2 NO_3^- – F4 NH_4^+. H^+ total = H^+ uncorrected + H^+ corrected.

were typically below 0.25 in the winter, and reached peaks of 0.6 or higher in the summer. While these ratios suggest considerable conversion in the summer, SO_2 concentrations were low during this period. In the winter, when SO_2 concentrations are elevated, $[SO_4^{2-}/SO_4^{2-} + SO_2]$ ratios were below mean ratios of 0.4–0.6 seen in summer acidic atmospheres in North America (*21,31*), suggesting the impact of slower SO_4^{2-} production processes.

Implications

Analysis of aerosol acidity as a causal factor distinct from fine particulate matter is particularly important for North America because levels of fine particulates may be elevated throughout the year and in regions without high acid aerosol levels. In contrast, aerosol acidity is elevated during the summer, and high concentrations are usually only found in the eastern portion of the continent (*3*). The comparisons presented in this article suggest that while aerosol acidity may be present in elevated concentrations during summertime episodes in eastern North America, there are few other settings with similar levels of aerosol acidity. In particular, areas where high-sulfur coal was burned showed low levels of acid aerosols. Additionally, short-term acidity concentrations typically measured in North America are well below levels shown to elicit effects in controlled chamber experiments (*3*). These findings when viewed along with the observation that in summer episodes in North America acid particles are inherently correlated with fine particulate levels, makes it difficult to distinguish the acidic fraction as a causal agent. Therefore, analysis of the health impact of inhalable particulates in settings with elevated particle concentrations (*5–8,14,34,35*) where acidity is low suggests that aerosol acidity may not be the primary particulate parameter associated with increased morbidity and mortality.

Further evidence for the absence of aerosol acidity as a causal factor in air pollution health studies comes from its low indoor:outdoor ratio (*12,13*). Although fine particles penetrate efficiently indoors so that indoor:outdoor ratios are approximately 0.8 (*36,37*), acid levels are quite low indoors as a result of indoor ammonia, which neutralizes aerosol acidity. Indoor:outdoor ratios of sulfate are also near 0.8 (*12,38*). Accordingly, outdoor concentrations of fine particles and sulfates are likely to be better indicators of total exposure than are acid aerosols because their indoor:outdoor ratios are high and since the majority of an individual's time is spent indoors.

Much of the epidemiological evidence also does not support aerosol acidity as the primary causal factor in the health effects of particulate air pollution. In addition to the comparative analysis of St. Louis and Kingston-Harriman Tennessee (*9*), Dockery and colleagues analyzed the Harvard Six-Cities Study and reported that mortality was more strongly associated with levels of fine and inhalable particulates, as well as sulfate particles, than it was with aerosol acidity (*10*). One of the cities included in this analysis, Steubenville, Ohio, had air quality levels which were quite similar to those measured in this study (Table 4). These data, along with the Utah Valley (*5–8*) and Seattle (*35*) studies, and results presented here indicate either stronger associations between health effects and PM_{10} mass than aerosol acidity or relationships between particle pollution and health in areas where aerosol acidity levels are low.

In an investigation of hospital admissions in Toronto, Thurston and colleagues (*11*) found a stronger relationship with aerosol acidity than with either fine particles or inhalable particles; however, this result is not in direct conflict with studies that show weaker relationships with aerosol acidity than with other particle metrics. As Thurston et al. have discussed (*11*), aerosol composition may differ dramatically even in locales where significant associations were observed between inhalable particulates and health effects. In the Toronto area, during summer episodes the submicrometer aerosol is dominated by acidic sulfate aerosols. It is plausible that in this setting aerosol acidity merely acts as a surrogate for the submicrometer aerosol which most fully penetrates into indoor environments. In regions such as Erfurt and Sokolov where submicrometer aerosols are not acidic, other particle metrics may be associated with health effects. Future epidemiological studies should collect more detailed information on size-fractionated particle composition, with special emphasis placed on the $PM_{2.5}$ fraction which penetrates indoors.

As Dockery and Pope have suggested (*39*), the available epidemiological data indicate that the associations observed between particulate air pollution and health effects are due to the mass concentration of the particle mix common to urban areas rather than to specific chemical species within the mix. Even in locales where particle composition, as it is traditionally measured, is quite different, and where major particle sources are different (auto exhaust, woodsmoke, steel mill emissions, transported power plant emissions), relationships between particle concentrations and measured health outcomes appear to be remarkably consistent. One common feature of the particulates in these studies is that they are produced in combustion processes. Studies of naturally produced particles show a much smaller impact on health outcomes for a given particle concentration (*40*). These data support the hypothesis that any particulate air pollution produced by combustion will be associated with adverse health outcomes. The implication of this hypothesis is that particulates are associated with adverse health effects in all settings with combustion air pollution, or essentially all urban areas.

Although the identification of specific inhalable particle components associated with adverse health outcomes is important for understanding air pollution epidemiology and for implementing control strategies, perhaps the most compelling reason to investigate the relationship between particle composition and health outcomes is to understand the biological mechanism by which airborne particulates may cause effects. The epidemiological evidence which suggests that aerosol acidity is not the primary particle parameter associated with health effects implies that the biological mechanism associated with particulate air pollution may be different from that experienced in animal and controlled chamber studies with sulfuric acid aerosol exposures. That adverse health effects may be found in settings where aerosol acidity is not observed indicates that other particle parameters in addition to aerosol acidity should be investigated in both epidemiological and mechanistic studies. For example, recent evidence from *in vitro* studies suggests that iron present on the surface of particles may promote lung injury (*41,42*). For epidemiologists it is important to identify settings with different particle compositions and to investigate whether the health effects are still observed. In particular, thorough analysis of particle composition for PM_{10} samples collected during routine monitoring is recommended, especially for locations where particle-associated health effects have already been observed.

Conclusions

A large number of studies have indicated associations between particulate air pollution and adverse health outcomes. Wintertime air pollution in particular has been associated with increased mortality. Identification of causal constituents of inhalable particulate matter has been elusive, although one candidate has been the acidity of the aerosol. Here we report on low levels of aerosol acidity in relatively polluted environments which were directly impacted by the burning of high-sulfur coal. These measurements, along with reported associations between fine particulate air pollution and health outcomes in other regions where little aerosol acidity

has been measured, suggest that particulate acidity alone is not the primary component defining the toxicity of fine particulate air pollution.

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The Use of Trout and Zebra fish in Biomedical Toxicology

July 10 and 11, 1995
Oregon State University, Corvallis, Oregon

Objectives of the Workshop

This workshop is designed to provide hands-on experience in the care and use of trout and zebrafish, and in the design and performance of toxicology studies employing fish as animal models. The information will be state-of-the-art, but it will be targeted dso that researcher with no prior experience in the use of fish models will also benefit.

The workshop will consist of morning lectures followed by afternoon laboratory sessions. Registration will be limited so hands-on experience is available to all participants.

Lecture topics will include:

- Facilities and procedures for spawning and rearing trout and zebrafish, including water quality, computerized facility monitoring, and photoperiod manipulation to produce biannual spawning in rainbow trout.
- Developmental toxicity studies using chlorinated hydrocarbons as the example.
- Production of genetically altered fish, such as isogenics, transgenics, and triploids

Combination laboratory-lecture topics will include:

- Exposure protocols (embryo microinjection, water bath, and dietary exposures) and the design of tumor studies.
- Pharmacokinetic studies in fish
- Phase I and Phase II metabolism in fish
- Histopathology in fish, with emphasis on phenotyping neoplasms
- Techniques for assessing genetic damage including DNA adduct analysis and determination of oncogene and tumor suppressor gene mutations.

For more information contact:

Ms. Sandy Ernst
Marine/Freshwater Biomedical Center
Oregon State University
Wiegand Hall 232
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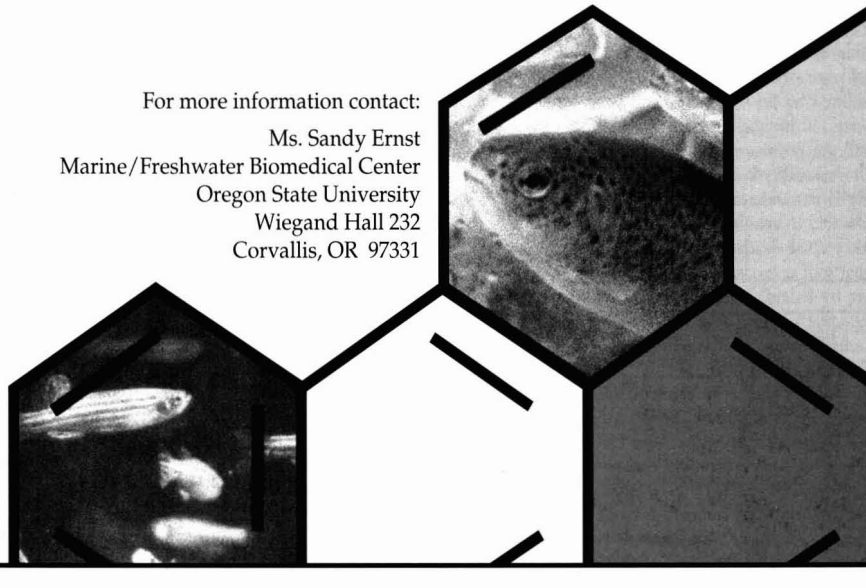
An intensive two day workshop sponsored by the Oregon State University NIEHS Marine/ Freshwater Biomedical Sciences Center and the Society of Toxicology



Effect of Outdoor Airborne Particulate Matter on Daily Death Counts

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To investigate the possible relationship between airborne particulate matter and mortality, we developed regression models of daily mortality counts using meteorological covariates and measures of outdoor PM_{10}. Our analyses included data from Cook County, Illinois, and Salt Lake County, Utah. We found no evidence that particulate matter ≤10 μm (PM_{10}) contributes to excess mortality in Salt Lake County, Utah. In Cook County, Illinois, we found evidence of a positive PM_{10} effect in spring and autumn, but not in winter and summer. We conclude that the reported effects of particulates on mortality are unconfirmed. *Key words*: causal inference, model selection, observational data, PM_{10}, Poisson regression, semi-parametric modeling. *Environ Health Perspect* 103:490–497(1995)

To determine if airborne particulates contribute to excess mortality, researchers have adopted multiple regression techniques to measure the effects of particulates on daily death counts (*1,2*). Other factors, such as extreme temperatures, can affect mortality, and regression techniques are used to adjust for these other known influences. Though many factors could be involved, research has generally limited attention to meteorological sources such as temperature and humidity. In some cases, other air pollution measures such as sulfur dioxide and ozone are included. The regression coefficient corresponding to a measure of particulate level is then interpreted as the effect of particulate pollution on mortality, accounting for stress from the other influences. If this coefficient is a statistically significant positive number, the conclusion is that mortality increases with increasing levels of particulates. This association is then elevated to a causal interpretation: particulates cause death, and researchers estimate that soot at levels well below the maximum set by federal law "kills up to 60,000 in U.S. each year" (*3,4*), and similar calculations "put the annual toll in England and Wales at 10,000" (*5*).

Studies vary as to the particulate measures used and the locations analyzed. In the analyses presented here, we used PM_{10}, which specifies particulate matter with an aerodynamic diameter ≤10 μm (*6*). The current U.S. EPA standard is based on this measure. The locations we analyzed, Cook County, Illinois, and Salt Lake County, Utah, both have relatively long records of PM_{10} monitoring. The monitoring data are discussed in more detail in Methods.

The data used in the analyses (meteorological conditions, particulate levels, death counts) are observational; that is, data that are measured and recorded without control or intervention by researchers. Deducing causal relationships from observational data is perilous. A practical approach described by Mosteller and Tukey (*7*) involves considerations beyond regression analysis. In particular, consideration should be given to whether the association between particulate levels and mortality is consistent across "settings," whether there are plausible common causes for elevated particulate levels and mortality, and whether the derived models reflect reasonable physical relationships.

There is a high degree of association of PM_{10} with meteorology, and a high degree of association of mortality with weather. For example, in the summer in Cook County the correlation coefficient between the daily average of PM_{10} and daily mean temperature is 0.52 and the correlation between daily elderly (age 65 or older) mortality and mean temperature is 0.25. The confounding effects of weather as a partial cause of both particulate levels and mortality may not be controllable by standard regression methods; the appearance of an effect for particulates, i.e., a positive coefficient for the PM_{10} term, may, as a result, be spurious (see Appendix B). We have not addressed the issue of errors in variables, which can also be a cause for spurious relationships. The concern about errors in variables arises from the differences between measured PM_{10} and the actual PM_{10} exposure experienced by the population. PM_{10} measurements are taken outdoors, but people tend to spend most of their time indoors, especially the sick and elderly who are believed to be the most vulnerable. Similarly, the meteorological covariates we include represent outdoor conditions. And again, when explanatory variables are measured with error, the result is not necessarily attenuation of the regression surface. In multiple regression, the result can be an artificial increase in the magnitude of the estimated coefficients.

The results for Cook County and Salt Lake County show that the appearance and size of a PM_{10} effect is quite sensitive to model specification. In particular, the treatment of season affects the estimates of the PM_{10} effect. In Cook County, we found a significant interaction between the time of year and PM_{10}. Using a standard Poisson regression model, we found that PM_{10} appears to be significantly associated with mortality in the spring and fall, but not in the winter and summer. Using a semi-parametric model (Appendix A), we found that only the months of May and September exhibit a particulate effect. In Salt Lake County, the semi-parametric model suggests a similarly isolated PM_{10} effect limited to the month of June, but we found no evidence of a PM_{10} effect in any model using Poisson regression. Hence, we conclude there is no evidence of a consistent association between particulates and mortality.

Several studies carried on at various locations in the United States have reported small yearly increases in mortality resulting from increases in particulates. In our Cook County analyses, the effect of PM_{10} in the spring and fall induces a similar positive yearly increase in mortality from increases in particulates, but the increase is from one-half to one-third the size usually reported in other studies depending on the analyses performed. In Salt Lake County, the size of the yearly effect is far smaller and statistically insignificant. What remains unexplained is why, in Cook County, effects should appear in the spring but not in the summer, and in the fall but not in the winter. Neither is it clear why the effect of particulates on mortality should not appear in any season in Salt Lake County.

The appearance of a PM_{10} effect in the spring and fall in Cook County led to the speculation that pollen may be implicated, but no such evidence was found using pollen data monitored in the city of Chicago, the major population component of Cook County. Other analyses carried out for the fall season in Cook County on different subgroups of the population produced no definitive differences among subgroups.

The inconsistency of the regression analyses, the unresolved status of plausible common causes of particulate levels and mortality, the confounding effects of weather, and the unavailability of plausible biophysical mechanisms to explain the

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empirical analyses prevent us from concluding that there is an effect between "today's" mortality and "yesterday's" particulates. The question appears to be unresolved.

Methods

Data

The data used for the statistical studies have three main components: mortality counts, particulate levels, and meteorology. The sources of the data are described in this section along with some summary statistics.

Mortality data. Daily death counts for the period 1985 through 1990 came from death certificate records for Cook and Salt Lake County residents, collected by the National Center for Health Statistics, and made available to us by John Creason, EPA. Although mortality data are available for longer periods, PM_{10} data are unavailable before 1985. Each death record contains a cause of death code and some basic demographic information. In compiling daily death counts, we excluded all deaths from accidental causes, as well as deaths of county residents occurring in other locations. We refer to the remaining number of deaths as total deaths. The main analyses were performed with total deaths among the population aged 65 or older (elderly deaths). We carried out additional analyses for total deaths, unrestricted by age, for deaths classified by specific causes, and for selected population subgroups such as elderly blacks and elderly males. We classified the disease-specific causes of death by the International Classification of Diseases (ICD) codes that appear on the mortality records. We adopted the classification scheme detailed in Fairley (*8*), extracting cancer deaths (ICD categories 140–209), circulatory deaths (ICD categories 390–459), and respiratory deaths (ICD categories 11, 35, 472–519,710.0, 710.2,710.4).

In Cook County, there was an average of 117 nonaccidental deaths per day for all ages. Among residents aged 65 and over, there was an average of 83 deaths per day. Death counts vary by time of year, with higher numbers in winter and fewer deaths in summer. In Salt Lake County, there was an average of 9 nonaccidental deaths for all ages and 7 nonaccidental deaths for residents 65 and over. As in Cook County, there are slightly more deaths in the winter. Table 1 displays some summary statistics for both Cook County and Salt Lake County mortality.

Particulate data. In current monitoring efforts, particulates are measured throughout the United States. There are both 24-hr and annual ambient air quality standards for particulate matter (*6*). In the first case, the standard is attained when the expected number of days per calendar year with a 24-hr average concentration above 150 $\mu g/m^3$ is equal to or less than one. In the second case, the standard is attained when the expected annual arithmetic mean concentration is less than or equal to 50 $\mu g/m^3$. To comply with these standards, it is sufficient to collect samples from each monitoring site only once every 6 days, though there are a few locations with monitors that operate on a daily basis. For Cook County, the particulate data come from a network of PM_{10} monitors reported in the EPA Aerometric Information Retrieval System (AIRS) for the period 1985 through 1990. During this time, there were 20 separate monitors in operation, though several monitors were operated for only a brief period of time. The Cook County network includes one daily station where PM_{10} samples are collected on a daily basis. The remaining stations collected samples every sixth day. The daily station observations are frequently missing, with 69% of the values recorded once the monitoring station began operation in April 1985. To fill in some of the missing values, we used the daily means of all available monitoring data as the basis for constructing our measures of PM_{10}. With all available data, there are observations for 75% of the days after 1 April 1985. Since many of the 20 monitoring stations were in operation for a short period, there is a maximum of 12 observations on any single day. Furthermore, the 6-day monitoring stations tend to operate on the same schedule, so many of the days have only the single daily monitor contributing to the daily mean.

In Cook County, PM_{10} levels are generally highest in the summer. Figure 1 shows the distribution of daily PM_{10} values by month. It is clear that mean levels are generally well below the EPA standard of 150 $\mu g/m^3$. In Table 2, the daily means from all available stations are compared with the values from the single daily monitoring station. These show close agreement, with three observations over the EPA standard for the daily station and two observations over 150 for the daily means.

In Salt Lake County, there were six PM_{10} monitors operating between June 1985 and December 1990. The monitoring network includes two daily stations. We use the observations from just one of the daily stations, station 12, in this analysis. Station 12 is centrally located in Salt Lake County. The second daily monitor is located in a more remote section of the county and was considered to be unreliable to use in measuring general exposure levels. Figure 1 shows the distribution of daily PM_{10} values by month for the centrally located daily station (station 12). The distribution of PM_{10} in Salt Lake County differs slightly from the distribution in Cook County. The overall levels are similar, though there are more days in Salt Lake County with PM_{10} levels over 150 $\mu g/m^3$. Unlike Cook County, there is an increase in overall levels in winter (December–February), though isolated occurrences of high particulate levels occur throughout the spring and summer. In Table 2, we present some summary statistics from the single daily station used in this analysis.

Meteorological data. The meteorological data used in this study are based on hourly surface observations taken at O'Hare International Airport (Cook County) and Salt Lake City International Airport (Salt Lake County). We extracted the data from the National Climatic Data Center's National Solar and Meteorological Surface Observation Network (1961–1990) database, which contains hourly surface observations in addition to solar radiation data. Our primary analyses concentrated on three meteorological variables: temperature, specific humidity, and barometric pressure. We excluded other variables such as solar radiation, cloud cover, wind speed, and wind direction. These variables were omitted to make our primary analyses more directly comparable with other research and because factors like wind may have more direct connection with PM_{10} than those included. For each variable we did include, we calculated the daily mean, based on hourly values. And, because weather may have a lagged effect on mortality, we also included the values of temperature, humidity, and pressure

Table 1. Mean daily mortality for nonaccidental causes of death

	Cook County					Salt Lake County	
	Elderly[a]	Total[b]	Circulatory[c]	Cancer	Respiratory	Elderly	Total
Winter	90.4	126.7	62.5	28.9	11.8	7.4	10.2
Spring	82.3	116.7	56.3	28.3	10.2	6.8	9.2
Summer	77.0	110.6	52.6	28.4	8.8	6.3	8.5
Fall	81.5	115.6	54.9	29.2	9.6	6.6	8.9

[a]Elderly mortality indicates the subset of these deaths among county residents aged 65 and older.
[b]Total mortality indicates the mean number of daily deaths of county residents of all ages, excluding accidental deaths, homicides, and suicides.
[c]Circulatory, cancer, and respiratory deaths are classified by the primary cause of death code listed on residents' death certificates.

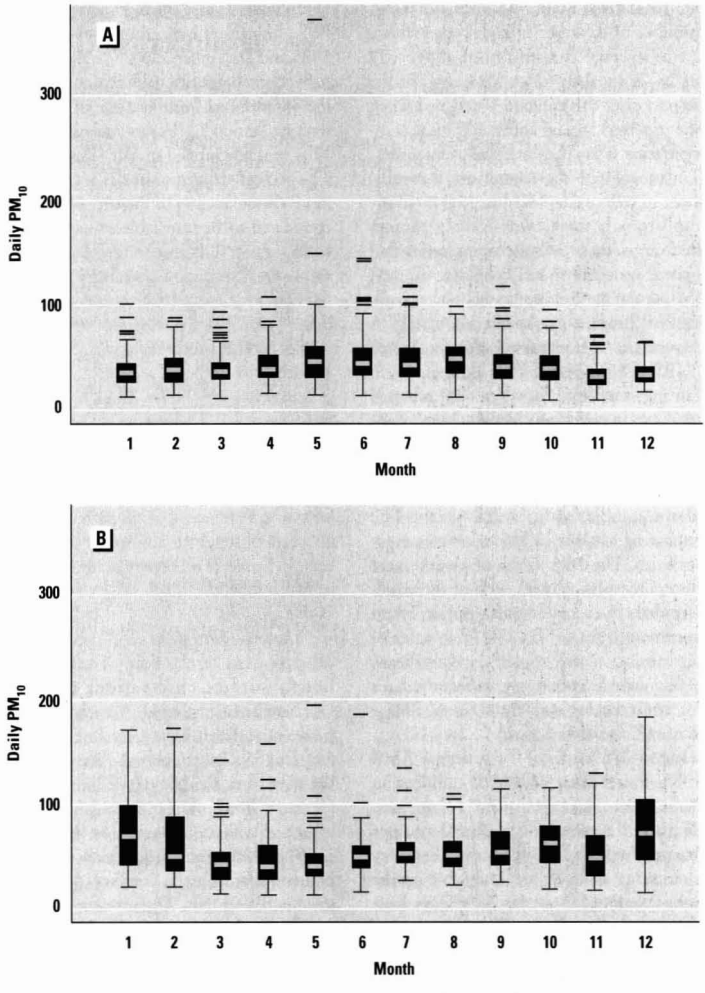

Figure 1. Daily particulate matter ≤10 μm (PM_{10}) by month for (A) Cook County and (B) Salt Lake County. Box plots by month showing the distribution of the daily network averages of PM_{10} observations for Cook County, and the observed values from the centrally located daily station in Salt Lake County.

Table 2. Summary of particulate matter ≤10 μm (PM_{10}) values[a]

	Min	25th Percentile	Median	75th Percentile	Max	No. days over 150 μg/m^3
Cook County						
Daily station	3	28	38	51	365	3
Network mean	4	27	37	50	365	2
Salt Lake County						
Daily station no. 12	9	33	48	67	194	13

[a]Statistics listing the minimum, 25th, median, 75th, and maximum PM_{10} values for daily stations in Cook and Salt Lake Counties, and the corresponding network averages for all available monitoring data. [b]The number of days with PM_{10} values >150 μg/m^3 is listed in the final column.

from the 2 previous days. In other analyses, we considered the effect of wind chill in the winter and solar radiation and a heat index in the summer. These variables did not improve the prediction of mortality; the analyses are not included. The inclusion of wind speed and lagged wind speed in Cook County did not change the results from any of the models fit without wind.

Table 3 presents a summary of the meteorological data considered in various analyses. The data set containing the original hourly observations for these variables had only a few (nonsequential) missing values. We filled in the missing hourly observations by assigning the value from the previous hour, and then computed the daily mean values based on 24 observations.

Pollen data. Pollen data were obtained from the pulmonary unit at Grant Hospital, Chicago, Illinois, courtesy of Judith Young. During the study period, pollen counts were recorded on a daily basis, except for weekends and holidays, when cumulative samples were taken. To fill in daily pollen values from the cumulative values, we used a model to predict daily pollen from local meteorological conditions and then distributed the total pollen amounts to the individual days based on this model. We considered pollen from trees, mold spores, and ragweed.

Model Formulation

Our primary analyses modeled daily death counts as a Poisson process. For most analyses, we split the data by 3-month seasons and fit separate models within each season. Winter is taken as December–February; spring as March–May, etc. All season-by-season models include a yearly factor and a within-season trend (day) component. The specification of the trend component differs by season. For each season, we considered either a polynomial or a piecewise linear trend component and selected the shape that fit the data best. Although the covariates differ for different analyses, the basic model assumes that the daily death counts (Y) are Poisson-distributed with

$$\log(EY) = X\beta$$

where X contains terms corresponding to a yearly factor, a within-seasonal trend component, relevant meteorological covariates, and a measure of particulates. The parameters of the model were fit by the iterative, reweighted least-squares algorithm in the statistical software package Splus (MathSoft, Inc., Seattle, Washington) (*9*).

To account for a possible lagged effect of PM_{10}, we focused primarily on the 3-day PM_{10}, the average of the current day's PM_{10} together with the values for the 2 preceding days. Missing values were ignored, so the mean values were based on any available observations. We compared the results from these models with models that incorporated each of the 3 single-day values. We also did analyses using only the current day, a 2-day PM_{10} (today and yesterday), and a 5-day PM_{10} (today and 4 previous days). In essence, the results using the 3-day PM_{10} are consistent with these other choices of PM_{10} measures, so we only report a typical result from Cook County using the 5-day PM_{10} in the fall.

Auxiliary to the Poisson regression models used is a semi-parametric model which, through its nonparametric character, avoids the necessity of specification of special forms while allowing a reasonably

Table 3. Description of meteorological variables

Variable	Description
t_{mean}	Average daily temperature (°C) from hourly observations
*t*lag-1	Average temperature from 1 day before
*t*lag-2	Average temperature from 2 days before
q_{mean}	Average daily specific humidity (g/kg) from hourly observations
*q*lag-1	Average specific humidity from 1 day before
*q*lag-2	Average specific humidity from 2 days before
pr	Average daily station pressure (millibars) from hourly observations
*pr*lag-1	Average station pressure from 1 day before
*pr*lag-2	Average station pressure from 2 days before

Table 4. Candidate covariates for Poisson regression analyses based on results from semi-parametric modeling on elderly mortality

Month[a]	Cook County	Salt Lake County
January	day[b]	*pr*[c], t_{mean}, day
February	q_{mean}, *q*lag-1, *pr*, *pr*lag-2	day, *pr*lag-1, *pr*lag-2
March	day, 3-day PM_{10}[d]	
April		
May	t_{mean}, *q*lag-2, 3-day PM_{10}	
June	*pr*	day, 3-day PM_{10}
July	t_{mean}	*q*lag-1, *pr*lag-2, 3-day PM_{10}
August	*t*lag-1, *pr*, *q*lag-1	
September	*q*lag-2, *pr*, *pr*lag-2, 3-day PM_{10}	day, t_{mean}
October	*pr*	
November	*q*lag-2	
December	day, *q*lag-1, *pr*lag-1	day, *t*lag-1

PM_{10}, particulate matter ≤10 μm.
[a]Active variables appearing in the month-by-month analyses using the semi-parametric model described in Appendix A.
[b]The variable day is the day of month (1–31).
[c]The meteorological variables are described in Table 3.
[d]The 3-day PM_{10} is the simple average of the observed network daily means for the concurrent day and 2 previous days.

accurate selection of important covariates. The details of the model as it was used are given in Appendix A. This model is used in several ways. Primarily, it was used to select relevant meteorological covariates and to focus on potentially important interactions as well as nonlinear functional forms for some of the covariates. Models selected in this fashion tend to be more parsimonious than models selected with standard stepwise procedures, with no loss of explanatory power. In addition, a month-by-month analysis using the semi-parametric model revealed that PM_{10} was usually an inactive factor.

By focusing on the months where PM_{10} does appear active, a possible connection with pollen was suggested. Accordingly, we obtained pollen data from the City of Chicago and introduced it in the month-by-month analyses of May and September, as well as in additional analyses covering August 15 to September 15, the ragweed season. In no case did any pollen variables appear as active factors in the semi-parametric model. Given the available pollen monitoring data, the observed PM_{10} effect in May and September is not explained by the presence of pollen particles.

With the focus on 3-day PM_{10}, the meteorological covariates that were considered at the first stage include the current day's values as well as values for the preceding 2 days. The particular covariates included for a season's analysis incorporated those found in the monthly analyses by the semi-parametric model. Table 4 shows the set of active factors for each month in both Cook County and Salt Lake County in the semi-parametric model. We considered each of these covariates as the candidate variables for inclusion in the Poisson regression models, along with the functional forms and interactions suggested by the fitted response surfaces from the semi-parametric model. To illustrate this use of the semi-parametric model, we include some plots of estimated effects of 3-day PM_{10}, temperature, pressure, and day-of-year for some selected months (Fig. 2). These effects are computed by conditioning the remaining variables on their median values, that is, by fixing them equal to their median values. The plots show the so-called Christmas effect on mortality, with a spike in the number of deaths around the beginning of January, the linear effect of PM_{10} in May and September, and the nonlinear effects of temperature and pressure. Using the combined list of covariates from the months composing each season, we used a stepwise variable selection technique to obtain a model without any measure of PM_{10}. Typically, this led to two or three meteorological covariates selected for each season to predict daily mortality. As a final step, we included the measure of PM_{10} and examined the direction and size of the corresponding coefficient.

To illustrate the importance of considering a season-by-season analysis, we also present results from an analysis combining the full year of observations for both Cook County and Salt Lake County. In this analysis, we fitted a yearly factor, a cubic time trend for each season, the meteorological covariates that were significant predictors of mortality in the season-by-season models, and seasonal interaction terms for selected meteorological covariates. We then compared the estimation of the PM_{10} effect from the models with and without PM_{10}-by-season interaction terms.

Results and Discussion

Empirical Evaluation in Cook County

There are several sets of results for Cook County. We first present full-year and season-by-season analyses using the Poisson regression model estimating daily death counts for individuals 65 and older (elderly mortality). Because daily death counts are high here, an ordinary (normal) regression model will give similar results. The linear predictors are detailed in Tables 5 and 6. As discussed in the previous section, the covariates other than the yearly factor and the PM_{10} variable were chosen using stepwise selection techniques based on the list of candidate covariates in Table 4. Other models and results for Cook County are summarized in Table 7.

In our full year analysis of Cook County, we conclude that it is necessary to estimate a separate PM_{10} effect for each season. Since the effect of meteorology differs by season (for example, increasing temperature acts as a stress factor in summer but decreasing temperature creates stress in winter), we began by considering models for the full year, which permitted separate estimates of the effect of weather within each season. Our final full-year model to predict elderly mortality from meteorology

includes separate seasonal terms for the yearly factors, the day-of-year effect, and temperature lagged 1 day. This permits the estimation of separate coefficients within each season for these terms. Other covariates whose effects do not vary significantly by season for Cook County include specific humidity for the concurrent day, 2-day lagged specific humidity, and station pressure for the concurrent day and previous day. We added the 3-day mean PM_{10} variable and compared the results from fitting a single estimate for the entire year with fitting separate estimates by season. The estimate for the single PM_{10} effect is 0.00054 with a standard error of 0.00020. Hence, an increase of 10 $\mu g/m^3$ of PM_{10} corresponds to approximately 0.54% more deaths, given constant levels of all other covariates. When the season-by-PM_{10} interaction term is added, the PM_{10} effect remains significant only in the spring and fall (Table 5). The estimated effects for the winter and summer are essentially zero. The chi-square test for the difference in deviance caused by inclusion of separate seasonal estimates for PM_{10} supports this inclusion with a *p*-value of approximately 0.001. To compare the overall effect of PM_{10} from this model, we calculated the predicted increase in the number of deaths in each season if PM_{10} were increased by 10 units. Specifically, we added 10 units to each of the observed values of PM_{10} and calculated the total number of predicted deaths. The overall predicted increase in mortality is 0.63%. A similar calculation, based on independent analyses of each month using the semi-parametric model, produces a 0.41% increase.

A finer tuned season-by-season analysis is obtained by fitting a separate model for each season. Here, we used the variables suggested by the semi-parametric models for the corresponding months to choose a parsimonious model predicting mortality from meteorology. The results for the separate seasonal analyses are presented in Table 6. The covariates included in the seasonal models vary significantly between seasons, suggesting that a separate model for each season may be more realistic than one full-year model. The PM_{10} coefficients and standard errors, however, are similar to the full-year analysis with the season-by-PM_{10} interaction terms. There is a significant effect in spring and fall, and no significant effect in the winter and summer.

The reported standard errors are calculated assuming independent observations. To check this assumption, we examined the autocorrelation structure of the standardized residuals for the full-year analysis. We computed the first seven lagged autocorrelations and found no correlations greater than 0.03. These values are all less than the approximate critical value of $2/(N)^{1/2} = 0.045$. Furthermore, the autocorrelations were neither persistently positive nor negative. We conclude that there is no evidence of significant serial correlation. Other diagnostic plots of the residuals confirm that the modeling assumptions are reasonable.

To investigate the consistency of the PM_{10} effect for different populations, we modeled daily death counts from several subgroups within Cook County and for different measures of PM_{10}, like a 5-day mean instead of a 3-day mean. Because the largest estimated PM_{10} effect for elderly mortality is in the fall, we restricted attention to this season. These analyses included total mortality (nonaccidental deaths, all ages), elderly males and females, elderly blacks and non-blacks, and total mortality classified by disease categories, including circulatory disease, respiratory disease, and cancer. For each group, we refitted the semi-parametric model by month to obtain the list of candidate covariates for the Poisson regression analysis. Table 7 shows the results from the final models selected.

To address concern over potential weekday versus weekend effects in both PM_{10} and mortality, we refitted the model for elderly mortality in the fall season, detailed in Table 6, to subsets of the data determined by day of week. We first extracted observations falling on Wednesdays, Thursdays, and Fridays, because the 3-day PM_{10} variable for these days is unaffected by the decline in PM_{10} over the weekend. The resulting 3-day PM_{10} coefficient is given in Table 7; it is approximately one-half of the size of the coefficient when all the data are used. We

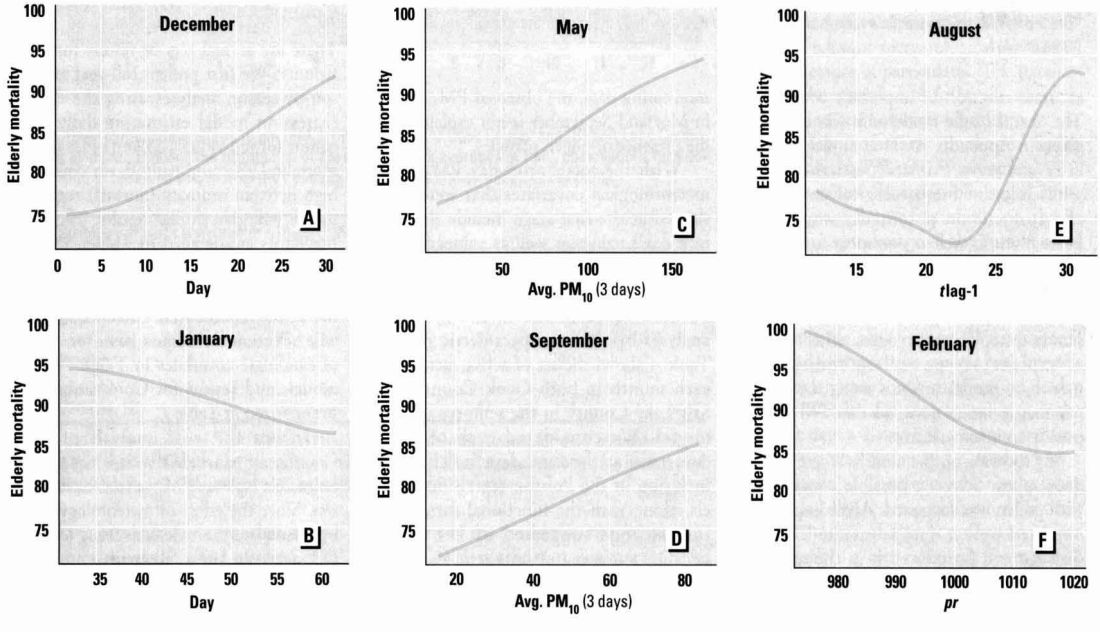

Figure 2. Some of the estimated effects for Cook County from the semi-parametric model. Predictions of elderly mortality holding all other variables constant at their median levels. (A,B) The day-of-month effect for December and January, highlighting the peak in the number of deaths around January 1; (C,D) the relationship between PM_{10} and mortality; (E,F) the potentially nonlinear dependence of mortality on meteorology. PM_{10}, particulate matter ≤10 μm; *t*lag-1, average temperature from 1 day before; *pr*, average daily station pressure from hourly observations.

Table 5. Full-year Poisson regression models: elderly mortality

Linear predictor log(EY)[a]		PM_{10} coefficient[b] (SE)
Cook County		
season * [year+poly(day,3)+poly($t$lag-1,2)]+q+$q$lag-2+pr+poly(prlag-1,2)+3-day PM_{10}		0.00054 (0.00020)
season * [year+poly(day,3)+poly($t$lag-1,2)+3-day PM_{10}]+q+$q$lag-2+pr+poly(prlag-1,2)	Winter	-0.00001 (0.00047)
	Spring	0.00083 (0.00034)
	Summer	-0.00028 (0.00036)
	Fall	0.00195 (0.00047)
Salt Lake County		
Model 1		
season * [year+poly(day,3)+pr+poly($q$lag-1,2)]+t_{mean}+3-day PM_{10}		-0.00025 (0.00043)
Model 2		
season * [year+poly(day,3)+poly ($q$lag-1,2)]+t_{mean}+3-day PM_{10}		0.00008 (0.00041)

PM_{10}, particulate matter ≤10 μm.
[a]The left-hand side shows the models fit to predict daily mortality, where brackets indicate the interaction terms included and poly(variable, n) indicates a polynomial term for the given variable of order n. Specification of an interaction implies inclusion of all lower-order terms.
[b]The right-hand side shows the estimated effects of the PM_{10} variable, along with estimated standard errors.

Table 6. Seasonal Poisson regression models: elderly mortality

Linear predictor log(EY)[a]		PM_{10} coefficient[b] (SE)
Cook County		
Winter	year+day+Jan+Feb+pr+poly(prlag-1,2)+3-day PM_{10}	0.00024 (0.00046)
Spring	year+$q$lag-2+3-day PM_{10}	0.00088 (0.00030)
Summer	year+poly(day,2)+poly($t$lag-1,2)+pr+prlag+3-day PM_{10}	-0.00024 (0.00035)
Fall	year+$q$lag-2+3-day PM_{10}	0.00138 (0.00040)
Salt Lake County		
With station pressure		
Winter	year+day+Jan+Feb+$t$lag-1+pr+3-day PM_{10}	0.00021 (0.00057)
Spring	year+3-day PM_{10}	0.00032 (0.00091)
Summer	year+poly(day,2)+3-day PM_{10}	-0.00027 (0.00124)
Fall	year+day+Oct+pr+Nov+3-day PM_{10}	-0.00131 (0.00094)
Without station pressure		
Winter	year+day+Jan+Feb+$t$lag-1+3-day PM_{10}	0.00056 (0.00054)
Fall	year+day+Oct+Nov+3-day PM_{10}	-0.00113 (0.00093)

PM_{10}, particulate matter ≤10 μm.
[a]Models for mortality estimated separately within each season are listed on the left-hand side.
[b]Estimated coefficients and standard errors are shown on the right.

Table 7. Summary of regression models, Cook County, fall season

Population[a]	Linear predictor log(EY)[b]	PM_{10} coefficient[c] (SE)
Total mortality	year+t_{mean}+$q$lag-2+poly(prlag-2,3)+3-day PM_{10}	0.00080 (0.00040)
Males 65+	year+poly($q$lag-2,2)+t_{mean}+3-day PM_{10}	0.00159 (0.00069)
Females 65+	year+$q$lag-2+3-day PM_{10}	0.00087 (0.00054)
Blacks 65+	year+poly($q$lag-2,3)+3-day PM_{10}	0.00166 (0.00089)
Whites, others 65+	year+$q$lag2+3-day PM_{10}	0.00134 (0.00045)
Circulatory deaths	year+poly($q$lag-2,2)+poly(prlag-2,3)+3-day PM_{10}	0.00064 (0.00052)
Respiratory deaths	year[$t$lag-2+poly(q_{mean},2)]+3-day PM_{10}	0.00220 (0.00125)
Cancer deaths	year+poly(q_{mean},3)+poly($t$lag-2,2)+3-day PM_{10}	0.00162 (0.00071)
Elderly mortality	year+poly($q$lag-2,3)+5-day PM_{10}	0.00158 (0.00047)
Wed, Thurs, Fri	year+$q$lag-2+3-day PM_{10}	0.00075 (0.00061)

PM_{10}, particulate matter ≤10 μm.
[a]The population subgroups for each analysis are listed in the left-hand column.
[b]The final models are indicated in the middle column.
[c]The corresponding coefficients and standard errors for the PM_{10} variable are listed in the right-hand column.

also analyzed each day of the week individually. Although all of the 3-day PM_{10} coefficients were positive, only the coefficient based on the Sunday data was significantly different from zero. The average of the seven daily coefficients is 0.00135, comparable to the coefficient of 0.00138 obtained in our original Poisson regression analysis of elderly mortality for fall (Table 6). Similar effects were observed in the spring. We interpret these results as inconclusive, neither supporting nor denying a weekday effect.

Although there appear to be inconsistencies in Table 7 (for example, a significant effect of PM_{10} on males but not on females), the difference of the two effects may be insignificant. In our analyses, the coefficient for cancer deaths is greater than the coefficient for circulatory deaths. This ordering is reversed from the numbers reported for Philadelphia (*1*) but, again, the differences in the coefficients may not be significantly different from zero. The lack of significance for blacks is due to the greater standard error resulting from the smaller size of the black population in Cook County. The estimated coefficient for elderly blacks is actually larger than the estimated coefficient for the whites and others category. The distinction between using the 5-day PM_{10} rather than the 3-day PM_{10} is to reduce the size of the effect somewhat, from 0.00195 to 0.00158, but it remains significant.

Empirical Evaluation in Salt Lake County

The analyses for Salt Lake County were carried out in similar fashion to those carried out in Cook County. The semi-parametric model was used on transformed (square-root of) mortality to ameliorate the effect of non-normality and nonconstant variances in the presence of small counts. The analyses proceeded as before from the variables in Table 4 to the models in Table 6.

The semi-parametric model identified PM_{10} as active in June and July. An estimated effect plot for July indicated that the effect of PM_{10} in July was oscillatory (as in March in Cook County) rather than monotone as in June (or as in May and September in Cook County; see Fig. 3). The Poisson regression analysis, however, did not support evidence of a PM_{10} effect in the summer. In fact, for the full-year and seasonal models, PM_{10} was never a significant predictor of elderly mortality in Salt Lake County.

For the full-year analysis, the single estimate of the PM_{10} effect is -0.00025 with a standard error of 0.00043 (Table 5). The full-year model including the season-by-PM_{10} interaction term fails to indicate a significant PM_{10} effect in any single season. Furthermore, unlike Cook County, the chi-square test for the difference in residual deviance does not support the inclusion of a season-by-PM_{10} interaction term. To investigate whether a possible PM_{10} effect is being masked by the presence of station pressure in this model, we refit the full-year model without station pressure as one of the candidate covariates. The selected model is identical, except for the deletion of station pressure. In this model (Table 5), there is also no significant PM_{10} effect. Additionally, the interaction term between season and PM_{10} fails to indicate a significant PM_{10} effect within any single season.

We also fitted separate models for each

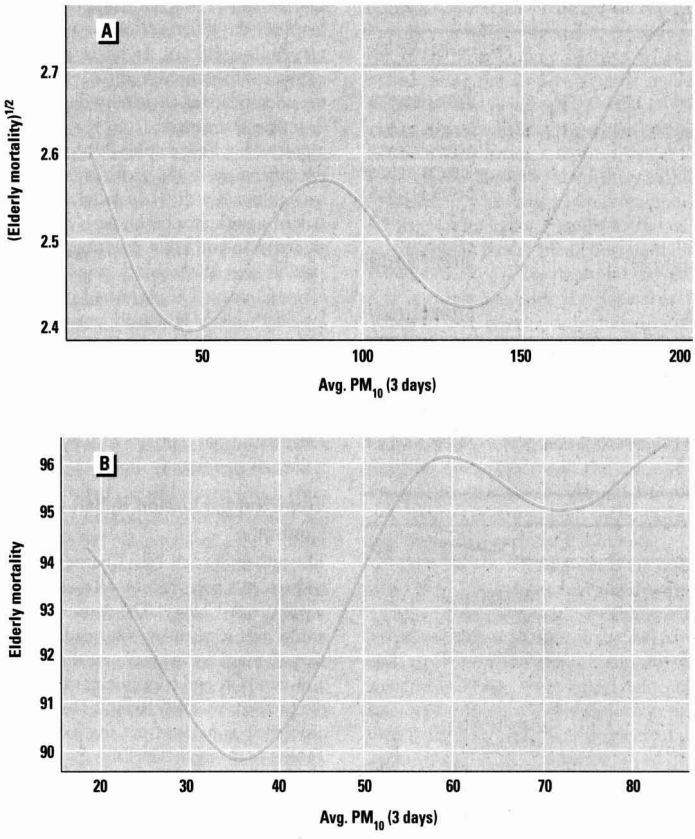

Figure 3. Estimated oscillatory effects from the semi-parametric model. In some months, particulate matter ≤10 μm (PM_{10}) appears as an active factor in the semi-parametric model, but the effect appears to be spurious.

season, as reported in Table 6. Here, we present results both with and without station pressure. Regardless of the inclusion of station pressure, PM_{10} never shows up as a significant predictor of mortality.

Summary

In summary, we analyzed data from Cook County, Illinois, and Salt Lake County, Utah, to assess the connections among mortality, particulates (PM_{10}), and weather. We found that season plays a strong role in Cook County. We found inconsistent results: no effect of PM_{10} was found in Salt Lake County in any season; no effect was found in Cook County in winter and summer; small, positive PM_{10} effects were found in Cook County in the spring and fall, and, more specifically, in the months of May and September.

One of the reasons for using multiple regression techniques is to remove the possible confounding effects of weather and possibly other pollutants. We demonstrate in Appendix B that weather conditions and airborne particulates are indeed associated in both Cook County and Salt Lake County. It is also generally accepted that weather conditions affect mortality rates. Under these circumstances, it is difficult to rule out the possibility that there is some common third cause of both elevated particulate levels and mortality. Perhaps more importantly, it makes it very difficult to understand the impact of having potentially large errors in the explanatory variables. Outdoor monitors, as well as airport weather data, are crude approximations of individual exposure levels. And any effort to include additional pollutants, like ozone, which is highly correlated with both particulates and weather, can also produce confusing results in the multiple regression setting. While we have not addressed all of these issues in detail, we have attempted to highlight some of the limitations of regression analysis in the discussion of our results.

We intentionally selected two counties with very different characteristics. Although our results were quite different depending on the location, we do not know whether this is due to differences in the populations, differences in the composition of PM_{10}, differences in weather that were not adequately modeled, or some other variable. To deduce causal relationships from the type of PM_{10} and mortality data available requires these kinds of considerations, which go beyond regression analysis. We have provided additional evidence with which to judge whether the association between particulate levels and mortality is consistent across settings. Our results do not show as much consistency as previously published analyses.

Appendix A. Semi-parametric Model

On day i in year j, with meteorological condition *met* and PM_{10} value *pm*, where *met* is a nine-dimensional vector of the meteorological variables listed in Table 3 and *pm* could be any of the PM_{10} measures used in the analyses, let $\mathbf{x} = (pm, met, i, j)$. The vector $\mathbf{x} = (\zeta_1, ..., \zeta_{12})$ is 12-dimensional. The response $y(\mathbf{x})$ (mortality) is assumed to be a realization of a stochastic process, $Y(\mathbf{x})$:

$$Y(\mathbf{x}) = \beta_j + Z(\mathbf{x}) + \varepsilon_{ij},$$

where β_j are constants, $j = 1,2, ...,6, Z(\mathbf{x})$ is a zero mean Gaussian process with covariance function $\mathrm{cov}[Z(\mathbf{x}), Z(\mathbf{x}')] = \sigma_Z^2 R(\mathbf{x},\mathbf{x}')$ to be specified later, and $\varepsilon_{ij} \sim N(0,\sigma_\varepsilon^2 I)$. For more discussion on the use of this technique for modeling response surfaces, see Sacks et al. (*10*), and the references cited therein.

Assume, as in Sacks et al. (*10*), that the covariance between $Z(\mathbf{x})$ and $Z(\mathbf{x}')$ is

$$\sigma_Z^2 R(\mathbf{x},\mathbf{x}') = \sigma_Z^2 \exp\left(-\sum_{k=1}^{12} \theta_k |\zeta_k - \zeta_k'|^{P_k}\right)$$

where $\mathbf{x} = (\zeta_1, ..., \zeta_{12})$, $\mathbf{x}' = (\zeta_1', ..., \zeta_{12}')$, $\theta_k \geq 0$; $k = 1, ..., 11$, $\theta_{12} = 0$ and $1 \leq p_k \leq 2$; $k = 1, ..., 12$; θ_{12} corresponds to the year variable. This class of stationary processes provides us with a wide range of functions.

Given the data $(\mathbf{x}_1, y_1)$, $(\mathbf{x}_2, y_2)$, ..., $(\mathbf{x}_n, y_n)$ for q consecutive years starting from year 1 (1985) with n_j data points in year j and $n_1 + ... + n_q = n$ and, provided σ_Z, σ_ε, and $R(\cdot,\cdot)$ are known, the best linear unbiased predictor $\hat{y}(\mathbf{x})$ at a new point $\mathbf{x}$ in year j can be written as

$$\hat{y}(\mathbf{x}) = \hat{\beta}_j + \hat{Z}(\mathbf{x}) = \hat{\beta}_j + \mathbf{r}'(\mathbf{x}) C^{-1}\left(\mathbf{y} - F\hat{\boldsymbol{\beta}}\right),$$

where $\mathbf{y} = (y_1, y_2, ..., y_n)$, $C = \mathrm{Corr}(y) = (\sigma_Z^2/\sigma^2) R + (\sigma_\varepsilon^2/\sigma^2) I$, where $\sigma^2 = \sigma_Z^2 + \sigma_\varepsilon^2$, and $R = \{R(\mathbf{x}_i, \mathbf{x}_j), 1 \leq i \leq n; 1 \leq j \leq n\}$, the $n \times n$ matrix of correlations among values of Z at the data points, $\mathbf{r}(\mathbf{x}) = (\sigma_Z^2/\sigma^2)[R(\mathbf{x}_1,\mathbf{x}),..., R(\mathbf{x}_n,\mathbf{x})]'$,

$$F = \begin{pmatrix} \vec{1}_{n_1} \times 1 & \vec{0} & \cdots & \vec{0} \\ \vec{0} & \vec{1}_{n_2} \times 1 & \cdots & \vec{0} \\ \vdots & \vdots & \ddots & \vdots \\ \vec{0} & \vec{0} & \cdots & \vec{1}_{n_q} \times 1 \end{pmatrix}_{n \times q},$$

and $\hat{\boldsymbol{\beta}}_1 = (\hat{\beta}_1, \ldots, \hat{\beta}_q)' = (F'C^{-1}F)^{-1} F'C^{-1}\mathbf{y}$, which is the usual generalized least-squares estimate of $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_q)'$.

The parameters σ_Z, σ_ε, θ, and p are fit by maximum likelihood. Cross-validation is used to assess variability of estimates. Values of p indicate smoothness of the response surface as a function of the corresponding variables. Larger values of θ usually indicate greater importance of the corresponding variables if the variables are on normalized scales. During the covariate selection procedure, those coefficients (θ) which are zero are the factors not included; the others are selected.

Appendix B. The Problem of Confounding

To examine the confounding relationship between PM_{10} and the meteorological variables, a forward-selection ordinary least-squares regression analysis was performed with log PM_{10} (the natural logarithm of today's PM_{10}) serving as the response variable and the meteorological variables serving as the covariates. The meteorological variables in the PM_{10} analysis were those included in the mortality analysis. The same seasonal structure was maintained for the PM_{10} analysis as for the mortality analyses.

Cook County. As mentioned earlier, PM_{10} levels were highest in the spring and summer while fall and winter levels were depressed. The R^2 values from the final models based on the forward-selection ordinary least-squares regression analyses ranged from a low of 20% in the winter to a high of 50% in the summer. Thus the relationship was strongest during the season with the highest PM_{10} levels. With the exception of the 2-day lag temperature term (*t*lag-2) in the fall, the regression coefficients for the various temperature terms were positive. Today's temperature (t_{mean}) showed up in all seasons with the exception of summer, while the square of today's temperature showed up in all seasons. All seasons except winter exhibited a strong rise in PM_{10} with increasing temperature. The coefficients on the specific humidity terms were negative. Yesterday's specific humidity (*q*lag-1) was important in all seasons, while today's specific humidity (q_{mean}) showed up in spring and fall. A quadratic term [(*q*lag-2)^2] showed up in the summer. These main-effect results are consistent in the sense that warmer, drier conditions contribute to increased levels of particulate matter. Interaction plots generally indicated that at low temperatures PM_{10} levels increased with increasing specific humidity, while the reverse was true at higher temperatures. Station pressure (2-day lagged variable, *pr*lag-2) showed up only in the fall and then was positive

Salt Lake County. The amount of variation in PM_{10} explained by the meteorological covariates ranged from 41% in fall to a high of 53% in winter (a time of high PM_{10} levels). In contrast to Cook County, station pressure was a significant variable in all seasons in addition to temperature and specific humidity. Station pressure lagged 1 day (*pr*lag-1) was the first variable to enter the forward selection process in fall and winter, where it added 25% and 42% to the R^2 value, respectively. The sign of the regression coefficient on the pressure terms was positive for all seasons. This strong association between pressure and particulate levels during fall and winter may have resulted from the occurrence of capping inversions which are associated with synoptic-scale high pressure systems. Given the nature of the landscape, these inversions would tend to trap pollutants near the earth's surface. In spring and summer, temperature terms were the first to enter the forward-selection process. The signs on the temperature terms varied with the season and within the season for different terms. Specific humidity terms entered all seasons in a negative manner except for winter. In spring and summer, PM_{10} levels generally increased as temperature increased; in winter PM_{10} levels decreased as temperatures rose. In fall an initial decrease in PM_{10} levels as temperatures rose turned to an increase in PM_{10} levels as temperatures moved above 7°C. In winter, summer, and fall PM_{10} levels initially increased with rising humidity levels and then began to drop as humidity continued to rise. In spring PM_{10} levels decreased as humidity increased. Results on fitting mortality to weather variables alone, without PM_{10}, indicated that temperature, humidity and pressure are all implicated (Tables 5 and 6).

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Consumption of PCB-Contaminated Sport Fish and Risk of Spontaneous Fetal Death

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Spontaneous fetal death has been observed among various mammalian species after exposure to polychlorinated biphenyls (PCBs). Our exposure-based cohort study assessed the relationship between consumption of PCB-contaminated Lake Ontario sport fish and spontaneous fetal death using 1820 multigravid fertile women from the 1990–1991 New York State Angler Cohort Study. Fish consumption data were obtained from food frequency questionnaires and history of spontaneous fetal death from live birth certificates. Analyses were stratified by number of prior pregnancies and controlled for smoking and maternal age. No significant increases in risk for fetal death were observed across four measures of exposure: a lifetime estimate of PCB exposure based on species-specific PCB levels; the number of years of fish consumption; kilograms of sport fish consumed in 1990–1991; and a lifetime estimate of kilograms eaten. A slight risk reduction was seen for women with two prior pregnancies at the highest level of PCB exposure (odds ratio = 0.36; 95% CI, 0.14–0.92) and for women with three or more prior pregnancies with increasing years of fish consumption (odds ratio = 0.97; 95% CI, 0.94–0.99). These findings suggest that consumption of PCB-contaminated sport fish does not increase the risk of spontaneous fetal death. *Key words*: fetal death, polychlorinated biphenyls (PCBs), reproductive toxicity, spontaneous abortion. *Environ Health Perspect* 103:498–502(1995)

Polychlorinated biphenyls (PCBs) are a group of thermal-resistant compounds that were widely used from the 1930s through the mid-1970s in the manufacture of dielectric fluids used in electrical transformers and capacitors. These industrial compounds are lipophilic and resist degradation. Low concentrations of PCBs in the environment can be magnified within the aquatic food chain and reach elevated levels in predatory sport fish (*1,2*). Consumption of contaminated fish has been shown to be an important source of human exposure to organochlorine compounds including PCBs (*2–5*).

Consumers of sport fish from the Great Lakes represent a population potentially at risk for adverse reproductive and perinatal outcomes related to environmental chemical exposures. Anglers and their families who eat sport fish are exposed to a complex mixture of chemicals including persistent lipophilic compounds such as PCBs, polychlorinated dibenzo-*p*-dioxin (PCDD), polychlorinated dibenzofurans (PCDFs), pesticides such as mirex and dichlorodiphenyl dichloroethene (DDE), and mercury (*6–8*). Sport fish consumption has been estimated to deliver a dose of PCBs which is 4300 times above background exposure from inhalation or drinking water (*9*). Estimates of chemical contamination levels in 1984 and 1985 suggest that Lake Ontario sport fish contain more than twice the concentration of PCBs found in fish from the other Great Lakes (*10*).

Several mammalian species have demonstrated a relationship between various levels of PCB exposure and fetotoxicity. Exposure to PCBs has been associated with spontaneous fetal death or resorption in rats (*11–13*), minks (*14–16*), rhesus monkeys (*17–19*), and guinea pigs (*20*). In addition, significantly smaller litter sizes have been demonstrated in rabbits (*21*) and swine (*22*) exposed to commercial PCBs compared to unexposed animals.

The potential mechanisms by which PCBs may impair human health and reproduction are numerous and poorly understood. Placental transport of PCBs and other organochlorine compounds has been shown, although fetal tissue and cord blood concentrations of PCBs are consistently lower than maternal levels (*23–25*). Placental tissue from women exposed to PCBs has been found to display markedly elevated induction of microsomal benzo[*a*]pyrene despite nondetectable concentrations of placental Ah receptors (*26*). PCBs and other organochlorine contaminants have been associated with endocrine disruption, neurotoxicity, and developmental delay in humans (*27*), and may be harmful to testicular function (*28*). Because PCBs can induce cytochrome P450, it has been suggested that the effect of PCBs on the reproductive system could be related to alterations in steroid hormones (*29*). Additionally, PCBs have been found to be mutagenic, with dose-related chromosome breakage in human white blood cell lines at low levels of exposure (*30*).

The relationship between PCB exposure and spontaneous fetal death in humans has received only limited investigation. In the few reports available, fetal loss was not the primary focus of the research, and the results are limited by small sample sizes (*31*). Follow-up studies of women exposed to PCB and PCDF-contaminated cooking oil in Taiwan reported the rate of fetal death among exposed women was nearly two times greater than in a group of control women (*32*). Among 11 women who were pregnant during a similar poisoning incident in Japan, 2 had stillborn infants (*33*). Exposed women in both of these studies were acutely poisoned and experienced other adverse health effects in addition to more fetal losses.

An investigation by Dar and associates (*34*) examined reproductive outcomes associated with consumption of sport fish from Lake Michigan and Green Bay. No consistent relationship was found between fish consumption and fetal death; women with the highest fish consumption had the lowest rate of fetal loss. However, the Green Bay women had substantially lower serum levels of PCBs when compared to occupationally exposed women (*35*) and when compared to a Lake Michigan fish-eating group (*36*). The Green Bay women also had a lower-than-expected rate of fetal loss compared to the general population of Wisconsin (*34*).

Despite advisory warnings, consumption of contaminated sport fish from the Great Lakes ranges from a few meals to subsistence levels. In the New York State Angler Cohort, comprising 11,431 anglers and their families, 9% eat a sport fish meal from Lake Ontario once a week or more (*37*). The question of reproductive and perinatal risks associated with sport fish consumption deserves concentrated attention. The present study addresses this concern, using a recently constructed exposure cohort to examine the relationship between sport fish consumption and spontaneous fetal death.

Methods

Data used in this investigation were collected as part of the New York State Angler Cohort Study. Briefly, this cohort is a population-based group of New York State anglers 18–40 years old who held fishing licenses for the 1990–91 season. Self-administered questionnaires were mailed to subjects and assessed sport fish consumption patterns, knowledge of fishing advisories, attitudes toward the safety of sport fish consumption, baseline health status, and reproductive information

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focused on children born from 1986 to 1991. Responses were received from 10,518 male anglers (39% response rate) and 913 female anglers (49% response rate); 6,651 wives/partners of male anglers also completed sections of the questionnaire on their own sport fish consumption, health status, and reproductive outcomes. Telephone interviews were conducted with a random sample of 100 nonrespondents. Nonrespondents were less likely to be married and had lower levels of education and lower income than respondents. However, sport fish consumption patterns were similar for respondents and nonrespondents. The exposure levels of nonrespondents were virtually identical to respondents.

Detailed information, including hospital of birth, was available for children born between June 1986 and June 1991. Computerized live-birth certificate information was available for 2529 cohort women from the New York State Health Department (91% of women with a self-reported live birth in 1986–1991 recorded on the questionnaire). Out-of-state delivery was the most common reason for not making a birth certificate match. Primigravidas (n = 609) and women with missing reproductive history information (n = 29) or missing exposure data (n = 71) were excluded from the study. All analyses were based on the remaining 1820 multigravid, fertile women with complete data. All women in the study were multigravid, having been pregnant at least twice, and fertile, having had at least one live birth. The excluded primigravidas were, on average, younger than the study group (26.2 years compared to 28.8) and consumed Lake Ontario sport fish for an average of 1 less year (2.6 years compared to 3.5), but no differences were seen in current consumption of sport fish, maternal education, maternal smoking, or paternal age (data not shown).

Multigravid, fertile women were studied to assess the potential impact of exposure on prior history of fetal death using a computerized vital registry (live birth certificates). This rationale is supported by the animal literature previously cited (*11–22*), which generally suggests an association between exposure and increased risk of pregnancy loss rather than an inability to become pregnant. Most women who experience pregnancy losses will go on to have live births (*38*). In fact, spontaneous fetal death is a fairly common reproductive event. Approximately 11–15% of all clinically recognized pregnancies will spontaneously abort (*39*).

We used reproductive history ascertained from the most recent available New York State live-birth certificate to assess maternal history of previous spontaneous fetal death. Birth certificates for 1986 and 1987 have one field for "previous spontaneous fetal deaths" and those for 1988–1991 have two fields "previous spontaneous abortions–less than 20 weeks; –20 weeks or more." These fields are intended to collect information on all fetal deaths including stillbirths. For the purpose of the current study, prior history of spontaneous fetal death was dichotomized as any occurrence versus none. A separate reliability study of this method of identifying women with a prior spontaneous fetal death was conducted (*40*). The reliability of this method of ascertaining spontaneous fetal death proved to be excellent. As part of a telephone interview focused on reproductive events, women were asked, "Have you ever had a pregnancy end in a miscarriage, spontaneous abortion, or stillbirth?" Exact agreement on the number of prior losses between a telephone interview and the birth certificate was 90% (k = 0.83) and agreement on any prior loss versus none was 94% (k = 0.90). Parental age and education also were obtained from the live birth certificate. Smoking, alcohol and sport fish consumption were obtained from the questionnaire, as were data on paternal consumption of sport fish and other demographic variables.

We used species-specific food frequencies and sport fish consumption histories from the questionnaire to construct four measures of exposure: 1) a lifetime estimate of PCB exposure based on species-specific PCB levels; 2) the number of years of sport fish consumption; 3) kilograms of sport fish consumed in the 1990–1991 season; and 4) a lifetime estimate of kilograms of sport fish eaten. Lifetime estimates of PCB exposure were calculated using the following formula:

$$\text{Estimated exposure} = \text{years} \times \Sigma \text{ species (frequency} \times \text{meal amount} \times \text{specific chemical concentration)}$$

where years = total number of years fish was consumed from 1955 to 1991; species = 0, not eaten or 1, eaten for each species consumed in 1990–1991; frequency = number of species-specific fish meals in the 1990–1991 season; meal amount = usual grams of fish eaten per meal; specific chemical concentration = milligrams of PCB by species as estimated by the New York Department of Environmental Conservation/Ontario Ministry of the Environment database, 1980–1990 (*41,42*).

The value calculated for estimated lifetime exposure to milligrams of PCBs represents a static cumulative model which assumes no elimination or degradation. Current consumers of sport fish were categorized into tertiles of exposure: low (≤ 1 mg), moderate (1.01–7 mg), and high (> 7 mg). Women who did not eat sport fish during the 1990–1991 season were not asked to complete species-specific consumption questions on the questionnaire and were categorized as past consumers. Past consumers were exposed but have an unquantified level of exposure. Women who had never eaten Lake Ontario sport fish were the reference group.

The total number of years sport fish was eaten were counted from 1955 to 1991. The number of years is essentially a measure of duration of exposure and is independent of the current amount of sport fish consumed. Kilograms of fish eaten during the 1990–1991 season were calculated by multiplying the reported number of fish meals, regardless of species, by the usual cooked portion size. Lifetime estimates reflect the kilograms of fish eaten in 1990–1991 multiplied by the number of years fish was eaten from 1955 to 1991. Current consumers were categorized by tertile of lifetime consumption: low (≤ 9.48 kg), moderate (9.49–36.7 kg), and high (> 36.7 kg). Past consumers were analyzed as a separate category, similar to lifetime PCB estimates.

We used various descriptive and analytical techniques. Relative risks and 95% confidence intervals were calculated in the bivariate analysis to identify potential confounders. Unconditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals for multivariable analyses. Preliminary testing for interactions revealed a significant interaction between the number of prior pregnancies and maternal age (β = -0.0377, p = 0.02, data not shown). No other statistically significant interactions were observed during model construction. Final analyses were stratified by the number of prior pregnancies into three levels: one, two, and three or more. We chose stratification, rather than leaving an interaction term in the model, in order to better describe the relationship between maternal age and spontaneous fetal death at different levels of prior gravidity. Gravidity is also a strong predictor of fetal death because pregnancy loss is a fairly common occurrence and each prior pregnancy represents an additional opportunity for a fetal death.

Full regression models included maternal age, smoking at some time in life, and female angler status. The bivariate analysis did not reflect an association between history of prior spontaneous fetal death and marital status, race, income, husand's or partner's fish consumption, maternal consumption of alcohol, sport or store-bought fish, canned fish, restaurant fish, non-New York State sport fish, or wild duck or turtle meals during pregnancy with the youngest

child. The potential for effect modification was also evaluated using stratified analyses. Gestational age at the time of loss (available from 1988–1991 certificates), maternal smoking, and levels of paternal sport fish consumption did not modify the relationship between exposure and outcome (data not shown). Only estimates from adjusted models are presented, given their similarity to the unadjusted models for all four exposure estimates.

Results

Women in the study group were characterized with respect to outcome, exposure, demographic characteristics, and other relevant variables (Table 1). Twenty-six percent of women (n = 471) in the study had a history of spontaneous fetal death recorded on the live birth certificate. Most of these women (81%; n = 383) had only one prior spontaneous fetal death. More than half of the women (54%) had never eaten Lake Ontario sport fish, and 24% were current sport fish consumers. Among women who consumed sport fish, half did so for more than 4 years. Women who reported current consumption ate an average of 4.9 kg (SD = 8.1) in 1990-1991, and the estimate of mean lifetime sport fish consumption was 57.4 kg (SD = 133.6) for those women.

Table 1. Description of the study sample of multigravid, fertile women from the New York State Angler Cohort Study with a live birth recorded in New York state from 1986 to 1991

Characteristic	n (%)
Prevalence of spontaneous fetal death	
None	1349 (74)
Any occurrence	471 (26)
PCB exposure categories	
None ever	979 (54)
Past consumer	408 (22)
Low (≤ 1 mg)	143 (8)
Moderate (1.01–7 mg)	142 (8)
High (> 7 mg)	148 (8)
Lifetime sport fish consumption	
None ever	979 (54)
Past consumer	408 (22)
Low (≤ 9.48 kg)	140 (8)
Moderate (9.49–36.7 kg)	144 (8)
High (> 36.7 kg)	149 (8)
Number of prior pregnancies	
One	883 (49)
Two	546 (30)
Three or more	391 (21)
Smoked cigarettes at some time in life	942 (52)
	Mean (SD)
Maternal age (years)	28.8 (3.8)
Maternal education (years)	13.4 (1.8)
Consumption of sport fish	
All women (years)	3.5 (6.5)
Current consumers (years)	7.6 (7.7)
All women (kg eaten, 1990–91)	1.2 (4.6)
Current consumers (kg eaten, 1990–91)	4.9 (8.1)

Table 2 shows the adjusted regression model for each of the four exposure measures. The highest level of estimated lifetime PCB exposure was associated with a significant risk reduction for women with two prior pregnancies (OR = 0.36; 95% CI, 0.14–0.92). For the low-exposure group with one prior pregnancy and three or more prior pregnancies, the moderate-exposure group with two prior pregnancies, and for past consumers with two and three prior pregnancies, ORs > 1 were observed, but none was statistically significant. The highest level of exposure was associated with ORs < 1 at all levels of gravidity, ranging from 0.36 to 0.71, but only the group with two prior pregnancies reached significance.

The number of years of sport fish consumption was entered into logistic models as a continuous variable and analyzed in relation to history of spontaneous fetal death. All of the ORs were close to 1. A significant risk reduction was seen in the group with three or more prior pregnancies (p = 0.03). This indicates that for each year of fish consumption, among women with three or more prior pregnancies, there was a 3% reduction in the risk of spontaneous fetal death.

Current sport fish consumption in the 1990–1991 season displayed a similar relationship to spontaneous fetal death as the number of years of consumption. In both sets of analyses, the ORs were close to 1 (range, 0.95–0.98). However, the risk reduction seen in the group with three or more prior pregnancies for current sport fish consumption is of borderline significance (p = 0.06).

The results for lifetime estimate of sport fish consumption were similar to those seen for lifetime PCB level and history of spontaneous fetal death. No statistically significant relationships were seen between spontaneous fetal death and category of lifetime fish consumption at any level of gravidity. As with PCB level, ORs were > 1 for the low-exposure group with one prior pregnancy and with three or more prior pregnancies, and for the moderate-exposure group with two prior pregnancies. The past-consumer category had ORs > 1 with the exception of the group with one prior pregnancy. The highest level of lifetime fish consumption had ORs ranging from 0.51 to 0.68, suggesting a reduced risk at all levels of gravidity. All of the confidence intervals, however, included 1.

Overall, the four measures of exposure do not indicate any consistent relationship between sport fish consumption and/or PCB exposure with spontaneous fetal death. The continuous measures of exposure (number of years of consumption and kilograms of fish consumed in 1990–1991) tend to show a slight reduction in risk. The categorical exposure variables (lifetime estimates of PCB exposure and lifetime kilograms of fish consumed) show an inconsistent pattern with ORs > 1 at low or moderate levels of exposure and < 1 for high exposure.

Discussion

No consistent relationship was seen between a history of spontaneous fetal death and the four measures of PCB exposure and sport fish consumption used in

Table 2. Adjusted odds ratios (ORs) based on Lake Ontario sport fish consumption among multigravid, fertile women from the New York State Angler Cohort Study with a live birth recorded in New York State from 1986 to 1991[a]

	1 Prior pregnancy (n = 883)		2 Prior pregnancies (n = 546)		3 Prior pregnancies (n = 391)	
Exposure measures	OR	95% CI	OR	95% CI	OR	95% CI
Lifetime PCB level						
None ever	1.00	reference	1.00	reference	1.00	reference
Past consumer	0.95	0.55–1.66	1.07	0.69–1.68	1.09	0.64–1.85
Low (≤ 1mg)	1.26	0.57–2.81	0.90	0.45–1.80	1.40	0.65–2.99
Moderate (1.01–7 mg)	0.53	0.18–1.51	1.06	0.52–2.16	0.69	0.33–1.42
High (> 7 mg)	0.51	0.18–1.48	0.36	0.14–0.92	0.71	0.35–1.41
Number of years						
Each year	0.98	0.94–1.02	0.98	0.96–1.02	0.97	0.94–0.99
Number of kg eaten, 1990–91						
Each kg	0.98	0.91–1.05	0.96	0.90–1.02	0.95	0.90–1.00
Lifetime sport fish consumption						
None ever	1.00	reference	1.00	reference	1.00	reference
Past consumer	0.95	0.90–1.01	1.08	0.69–1.68	1.08	0.64–1.84
Low (≤ 9.48 kg)	1.41	0.65–3.03	0.69	0.34–1.44	1.67	0.72–3.86
Moderate (9.49–36.7 kg)	0.28	0.07–1.17	1.17	0.57–2.39	0.85	0.44–1.64
High (> 36.7 kg)	0.62	0.23–1.62	0.51	0.22–1.15	0.52	0.25–1.09

[a]ORs are stratified by maternal gravidity, calculated by logistic regression for any history of spontaneous fetal death with lifetime estimate of PCB exposure, number of years consumption, kilograms of Lake Ontario sport fish consumed in 1990–1991, and lifetime estimate of Lake Ontario sport fish consumed. ORs are adjusted for maternal age, smoking at some time in life, and female angler status.

the current study. Although the four measures are interrelated and derived from a self-administered questionnaire, the consistency of the findings across exposure estimates lends greater confidence to the results. Lake Ontario sport fish represent a complex exposure to a variety of contaminants including PCBs. No increased risk was seen with either recent or lifetime fish consumption (complex exposure), estimated PCB exposure from sport fish, or duration of exposure. The present study findings are also consistent with those reported by Dar (*34*), which failed to show an association between spontaneous fetal death and PCB exposure from sport fish consumption.

The lack of an association between spontaneous fetal death and PCB exposure and sport fish consumption could be the result of many factors. Recently, there have been reports linking consumption of marine fish (not fresh-water fish) with prolonged gestation and increased fetal weight (*43,44*). It is possible that despite high levels of chemical contamination, the benefits of fresh-water fish from the Great Lakes may offset the potential adverse effects. It is also possible that PCBs have an impact on human reproduction that does not result in recognized fetal deaths. Another explanation for the current findings may be that women at the highest level of exposure have suppressed fertility and encounter longer times to conception or more frequent unrecognized pregnancy loss. It may be that at the highest level of exposure to these contaminants, the impact on pregnancy is a very early "all-or-nothing" effect which appears in this study as a protective effect of exposure. In order to be at risk for recognized fetal death, fertilization must occur and the conceptus must survive to clinical recognition of pregnancy (*45*). By design, this study focused only on clinically recognized fetal deaths. Studies of chemically detected pregnancies and early pregnancy loss are needed to better understand the relationship between exposure and outcome.

The current study had sufficient power to find an overall significant increase in risk of 1.16 ($\alpha = 0.05$, $\beta = 0.20$). Power was limited somewhat in the stratified analyses with the ability to detect a significant increased OR of 1.41 for past consumers compared to unexposed women and 1.69 for any tertile of exposed women compared to unexposed women ($\alpha = 0.05$, $\beta = 0.20$). Nevertheless, it does not appear that the lack of association is primarily due to a lack of statistical power.

Use of the reproductive history data on birth certificates for a study of spontaneous fetal death has limitations. Although the reliability of the data was good, reproductive toxicity risk can be assessed at only one point in the spectrum of human reproduction. Still, this methodology has tremendous benefits for conducting studies to examine the relationship between environmental exposures and fetal death quickly with a modest expenditure of resources. A particular strength of this study is that it represents a novel approach for assessing reproductive toxicity related to a low-level environmental exposure. While spontaneous fetal death is considered a sensitive outcome for the assessment of environmental reproductive toxicity, fetal death registration is often quite poor. Many states, for example, require death registration only after 20 weeks of gestation, or over a certain weight limit, such as 350–500 g (*46*). In contrast, vital registration of live births is generally quite good, and research opportunities using the live birth certificate have been encouraged (*47*).

The potential for error in the exposure measures is more problematic. A validation study is currently underway for the New York State Angler Cohort study. A static model, without any direct assumption of degradation of PCBs, was used to estimate exposure. However, PCB levels in Lake Ontario sport fish were substantially higher during the 1970s (*48*). It may be that the particular years sport fish were eaten is more important than the total number of years. However, all four measures of exposure had similar findings, including years of fish consumption, which was not dependent on current consumption.

Occupational data, an important confounder in studies of environmental exposure, are also unavailable. Although current occupation for both parents is characterized on the live birth certificates, this information is not included in registry data files. In any case, current occupation at the time of the last birth cannot be expected to reflect lifetime occupational PCB exposure, and considerable error has also been described in the recording of occupation on birth certificates (*49*). Similarly, no data were available to characterize other potential dietary or environmental sources of PCB exposure.

A final and important limitation of this investigation is that both the outcome and exposure are self-reported. Although there is concern about misclassification related to the self-reported nature of the data, ascertainment of outcome and exposure was made independently. Any bias present in outcome assessment should be nondifferential and would bias results toward the null hypothesis. The reproductive history reports come from birth certificates filed before the receipt of the angler questionnaire. The level of sport fish consumption should have no relation to the reported reproductive history on the birth certificate.

The lack of any consistent increase in risk for spontaneous fetal death associated with estimated PCB exposure or sport fish consumption in the study cohort suggests the absence of any strong association in this population. Careful interpretation of these findings is called for given the limitations of the study. Lake Ontario sport fish are contaminated with a variety of organochlorines and other persistent toxic compounds and heavy metals. The human health effects of exposure to these contaminants are not well understood, and the potential long-term effects are unknown. Further investigation of the relationship between these exposures and pregnancy loss are needed, particularly given the animal literature on PCB and fetotoxicity (*50*).

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Meeting Announcement

Engineering Solutions to Indoor Air Quality Problems

July 24–26, 1995
Sheraton Imperial Hotel and Conference Center
Research Triangle Park, NC

This international Symposium is cosponsored by the Air & Waste Management Association (A&WMA) and the U.S. Environmental Protection Agency's Air and Energy Engineering Research Laboratory. Participating organizations include the Consumer Product Safety Commission and the National Research Council Canada. The Symposium will provide a forum for the technical exchange of information on on-going research on characterizing sources of indoor air emissions and mitigating and preventing indoor air quality problems. Attendees will include researchers from the government, private sector, industry, and academia. The 2 1/2 day Symposium will include a general session, a poster session, continuing education courses, and an exhibition of related products and services.

Planned Program

Monday, July 24
a.m. - Source Characterization
p.m. - Source Management & Pollution Prevention Reception/
Exhibition/Poster Viewing

Tuesday, July 25
a.m. - Ventilation & Modeling
p.m. - Indoor Air Laboratory Tours

Wednesday, July 26
a.m. - Biocontaminant Control
p.m. - Indoor Air Laboratory Tours

For registration information or to receive a copy of the preliminary program, contact the A&WMA Registrar at 412-232-3444, extension 3142; fax 412-232-3450. Hotel reservations should be made directly with the Sheraton Imperial at 800-325-3535 or 919-941-5050. To ensure availability and rate ($70 single and double occupancy, plus applicable taxes), make your reservations by June 29. Be sure to mention the symposium to receive this rate.

For information on the technical program, contact:
Kelly Leovic
U.S. EPA, MD-54
Research Triangle Park, NC 27711
phone 919 541-7717
fax 919-541-2157

For information on the exhibition contact:
Roy Neulicht at 919-677-0249, ext, 5126
fax 919-677-0065.

Molecular Mechanisms of Environmental Carcinogenesis

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Over 250 people participated in a 2-day conference, "Molecular Mechanisms of Environmental Carcinogenesis," at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina, 19–20 September 1994. The purpose of the conference was to bring together scientists to discuss recent advances in basic cancer research, with an emphasis on the contribution of environmental factors to neoplasia. The conference was initiated with a brief welcoming address by NIEHS Director Kenneth Olden, and included 17 platform talks as well as a collection of poster presentations.

The conference was divided into four sessions. The first session focused on cell cycle control and cancer. Normal cells carefully monitor cell cycle events such as DNA replication and cell division to maintain a stable genome. Failure to regulate the cell cycle appropriately is a fundamental characteristic of cancer cells. Elucidation of the molecular events involved in cell cycle transitions, genetic instability, and responses to DNA damage is critical for understanding the impact of the environment on carcinogenesis.

The fission yeast, *Schizosaccharomyces pombe*, has provided an important model system for the identification of checkpoint genes. Mutants of *S. pombe* that fail to undergo cell cycle arrest when DNA synthesis is inhibited by hydroxyurea have recently been identified. These mutants proceed through mitosis and cell division without completing DNA replication. Because the molecules that control cell cycle transitions in yeast have been conserved through evolution, it will be of interest to elucidate the function of these new genes to ascertain their roles, if any, in mammalian cell checkpoint control.

The molecular details of how oncogenes and tumor-suppressor genes function in growth control are becoming clearer from studies of the retinoblastoma susceptibility gene product (pRB) and the product of the c-*abl* tyrosine kinase proto-oncogene, $p170^{Abl}$. Dominant-negative mutations in *Rb* disrupt the interactions between pRb and $p170^{Abl}$, resulting in an inhibition of the growth suppression function of pRb. Recently, mutations have been generated in *Rb* that prevent this growth-suppression function from being blocked by phosphorylation. These and other results have been used to suggest that $p170^{Abl}$ can regulate pRb complexes that in turn regulate entry into and exit from the cell cycle, as well as progression through DNA synthesis.

The role of the p53 tumor-suppressor gene product in cancer is of particular interest because p53 is the most commonly mutated gene in human cancers characterized to date. Cells that lack a functional p53 cannot undergo cell cycle arrest in response to DNA damage and will enter DNA synthesis with unrepaired DNA. The molecular dynamics of the cellular response pathways that involve p53 in response to DNA damage are currently under intense scrutiny. DNA strand breaks, induced by either ionizing radiation or microinjection of a restriction endonuclease, have been shown to lead to an increase in p53. This increase requires the currently undefined gene product(s) that are defective in ataxia-telangiectasia, a cancer-prone inherited disease. The induction of p53 results in either cell cycle delay or initiation of programmed cell death (apoptosis), depending on the cell type. A practical application of a better understanding of this pathway might be the specific induction of apoptosis in tumor cells after exposure to therapeutic agents.

Cytoskeletal alterations and genomic instability in cells transformed by the *mos* oncogene were also discussed in the first session. Murine fibroblasts infected with a *mos* virus have elevated levels of mitogen-activated protein (MAP) kinase activity and displaced spindles that are abnormally attached to the cell membrane during mitosis. The alteration in cytoskeletal components in *mos*-transformed cells, as well as inappropriate expression of certain mitotic phenotypes in interphase cells, could contribute to genomic instability in these cells, thus providing a model system for the further study of genomic instability in tumors.

The second session focused on cancer susceptibility genes. For many years, it has been clear that certain individuals and their offspring are prone to develop specific types of cancers at an earlier age or with an increased frequency compared to the general population. With recent improvements in DNA mapping strategies, along with advances in molecular biological techniques, scientists now can identify defects in specific genes that are responsible for these familial cancers. Among the relevant topics addressed at this conference were epidemiological studies of cancer prone families, characterization of a recently identified breast cancer gene, the role of heritable differences in xenobiotic metabolism in cancer susceptibility, and mouse models for the identification of new cancer susceptibility genes.

Data from kindreds of patients who develop soft tissue sarcomas early in life revealed strong evidence for a dominantly inherited cancer gene. Some of the patients were characterized as having Li-Fraumeni syndrome; their disease could be linked to mutations in the p53 tumor-suppressor gene. Recent studies have suggested an earlier age of cancer onset in consecutive generations of families carrying p53 mutations. This interesting observation could be due to improved screening and detection methods, an increase in environmental insults, or genetic instability associated with mutations in p53. Better monitoring and early detection of tumors will be critical for families with mutations predisposing them to cancer and should provide valuable insight into environmental carcinogenesis. Two presentations focused on the highly publicized breast cancer gene, *BRCA1*. One provided a historical context of the identification of the *BRCA1* gene and its role in the development of breast and ovarian cancers. *BRCA1* is thought to account for at least 85% of families with increased incidence of both early onset breast cancer and ovarian cancer. However, less than half the families with site-specific breast cancer are linked to *BRCA1*. Several of the site-specific breast cancer families that are not associated with *BRCA1* are linked to a second breast cancer susceptibility gene, *BRCA2*, which has recently been localized to chromosome 13q. A second presentation described work performed by scientists at NIEHS in collaboration with scientists at the University of Utah and Myriad Genetics on the molecular cloning of *BRCA1* and the characterization of mutations in the gene. The *BRCA1* gene encodes a relatively large protein of 1863

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amino acids with a RING finger motif in its amino-terminal region. Characterization of *BRCA1* may provide valuable insights into breast cancer biology.

The interaction of pro-carcinogens and genetic variability was stressed in several presentations. These included a discussion of allelic differences in the activation of chemical carcinogens by human cytochromes P450 (CYP450) and glutathione *S*-transferases with regard to their role in cancer susceptibility. Individuals with certain CYP450 alleles may be more susceptible to metabolic activation of carcinogens. The combination of genetic variation and environmental exposure represents one example of the complexity evident in carcinogenesis, from initial exposures to environmental pro-carcinogens to the establishment of genetically unstable tumors with highly malignant phenotypes. Identification of polymorphisms in xenobiotic metabolism alleles associated with increased incidence of cancer may enable researchers to evaluate individual exposure risks. One approach to unraveling these complex interactions is to use animal models in which the combination of genetic background and environmental exposure can be controlled. Mouse models have also been used to dissect tumor-susceptibility genes involved in hepatocarcinogenesis. For example, mice treated with the mutagen *N,N*-diethylnitrosamine showed a 100-fold difference in tumor multiplicity depending on which inbred strain was used. Such a strategy provides an experimental approach for identifying multiple genetic loci controlling the susceptibility to liver tumors. At the meeting, it was proposed that the promotion phase of hepatocarcinogenesis can be divided into a conversion and a proliferation step. The use of genetic studies to identify genes crucial for the development of tumors should improve our understanding of environmental carcinogenesis.

The third session introduced the importance of hormones in carcinogenesis, with an emphasis on estrogens. It is now clear that estrogens cause cell proliferation in certain *in vitro* systems and enhance tumor formation in carcinogen-exposed animals. However, estrogen effects in humans vary by tissue type, exposure pattern, and subject group. The relative risks of endometrial and breast cancer after estrogen exposure was a topic of great interest. Many women are now exposed to estrogens, through oral contraceptives and estrogen replacement therapy, in a variety of doses and admixtures, throughout their lives. This long-term exposure makes the assessment of relative risk for any single exposure much more difficult. Furthermore, it was pointed out that the baseline cancer rate in women changes with age, and it is critical to take such changes into account when judging the significance of any apparent increase in relative risk.

Molecular Mechanisms of Environmental Carcinogenesis

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The pathway by which estrogen increases cancer risk was also addressed. Important advances have been made in defining the genetic alterations that characterize estrogen-associated cancers, focusing on endometrial carcinoma and clear-cell adenocarcinoma of the vagina and cervix resulting from exposure to diethylstilbestrol *in utero*. In addition to DNA sequencing of tumor-suppressor genes, a search for loss of heterozygosity (LOH) has been used to identify critical genetic elements. Clinical data have indicated that LOH for human chromosome 14q is closely associated with a poor prognosis in patients with endometrial carcinoma. One hope is that positional cloning will help narrow the search for the genes involved. Another set of genes now thought to be critical to the regulation of genome stability are those involved in DNA mismatch repair. Microsatellite instability, observed in a variety of tumor cells, also appears to be present in as much as 10–20% of human breast carcinomas. An analysis of human mismatch repair genes, such as *MSH2*, is underway to see if inactivation of key repair proteins is responsible for genetic instability in various neoplasms.

Recent research has also explored estrogen-mediated changes in the control of proliferation by developing a series of variants of the human breast cell line, MCF7. A factor in serum, called estrocolyone-1, has been identified that specifically inhibits the proliferation of estrogen-sensitive cells. Variants of MCF7 have been generated that are no longer inhibited by serum, but are inhibited by estradiol. One of the implications of this work for therapy is that the selective manipulation of a patient's endocrine milieu can be important for regulating growth of estrogen-sensitive tumors.

The recognition of prostate cancer as a health issue for men has increased greatly in the last decade: current estimates are that 90% of men at age 80 will have some level of hyperplastic prostate disease. Research is in progress on the genetics and cell biology of prostatic tumors, with the goal of developing a set of tumor markers that can be used reliably to diagnose the severity of the disease. A model was proposed in which a set of proteins involved in cell–cell contact is inactivated, leading to a loss of adhesion and increased metastasis. These proteins include E-cadherin, α-catenin, and ß-catenin. Consistent with this model, the introduction of chromosome 5 into a prostatic tumor cell line, with a consequent expression of α-catenin, led to an increase in cell–cell contact. An analysis of families manifesting higher incidences of prostatic cancer, combined with an analysis of metastasis-suppressor genes in animal models, should enhance the ability to identify critical genes and to predict the potential severity of disease discovered in the early stages.

The final session of the meeting focused on tumor-suppressor genes and their biochemical functions. Studies of pRB and its interactions with the E1A protein of adenovirus have provided clues to the functions of these proteins in viral transformation. The E1A protein has been found to bind pRB and displace the E2F transcription factor that is usually bound by pRB. E2F DNA binding sites have been identified in several genes known to be involved in growth control. Thus, we can now postulate mechanisms for how environmentally induced mutations or viral infection can lead to a loss of growth control through the disruption of specific pro-

tein–protein interactions. Furthermore, the cloning of E2F homologues from *Drosophila melanogaster* has allowed an extensive analysis of E2F protein structure and expression during embryogenesis and may provide a useful marker for cells that have recently undergone cell division.

It is clear that animal models will continue to be important tools for studying the initiation and progression of cancers. For example, a simple base change that leads to a murine mutation, *min* (multiple intestinal neoplasia), predisposes mice to intestinal and mammary tumors. However, the genetic background of the mouse in which *min* is studied significantly alters the expression of neoplasia. Genetic loci termed *mom*, for modifier of min, have been identified and mapped to mouse distal chromosome 4. The influence of carcinogens on the incidence of neoplasia in strains with different genetic backgrounds is underway and should allow a more complete understanding of the interplay between genetic predisposition and environmental exposure.

Mutational spectra of tumor-suppressor genes are being studied to reveal the underlying patterns of spontaneous mutation in these genes and the biological relevance of specific mutations. Studies of a large number of mutations in the *Rb* and p53 genes indicated that the vast majority of *Rb* mutations were nonsense errors, whereas p53 mutations were diverse and varied according to the tissue of origin. One class of p53 G-to-T transversion mutations was overrepresented and was postulated to be the result of environmental mutagen exposure. However, phenotypic selection for relevant mutations may vary in different organs, and methodological biases must be accounted for before these spectra can be used to shed light on the role of specific mutations in the etiology of cancer.

The importance of repair processes was reiterated in a discussion of human mutators hMSH2 and hMLH1. The presence of multiple mutated genes in tumor cells has led to the question of how cancer cells arise given the usual low mutation rates in eukaryotic cells. A number of proposals have been made as to which kinds of replication and repair functions might be inactivated to generate mutator phenotypes. hMSH2 and hMLH1 belong to highly conserved families of mismatch repair proteins. Defects in these genes lead to increases in mutation frequencies of up to 1000-fold and enhanced rates of recombination. In some tumors, including the hereditary nonpolyposis colon cancer syndrome, mutator phenotypes due to aberrant repair may explain the observed increases in microsatellite instability. Alterations in other mutator genes may also play a critical role in tumor development.

In summary, this conference provided a strong reminder of the complexity of cancer, a disease with both environmental and genetic risk factors. The excitement generated by the discovery of new genes linked to familial disease was tempered by the realization that any single gene may be directly involved in a small percentage of cancers. However, it may be expected that the molecular and biochemical analysis of such genes will provide insights into the pathways by which processes such as cell growth and cell–cell contact are disrupted. Such an understanding should allow researchers to seek out, in a logical fashion, other candidate genes as well as environmental agents that influence these pathways. Finally, a more complete description of how these pathways are disrupted in cancer cells may provide the knowledge to develop effective preventive and therapeutic strategies, based on clear biochemical mechanisms and, ultimately, an improvement in our ability to successfully treat patients with cancer.

The Humane Society of the United States

Solicits Nominations for the

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The Russell and Burch Award is given annually to a scientist who has made an outstanding contribution to the advancement of alternative methods in the areas of biomedical research, testing, or higher education. Alternative methods are those that can replace or reduce the use of animals in specific procedures, or refine procedures so animals experience less pain or suffering. The award, which carries a monetary prize, is named in honor of William M. Russell and Rex L. Burch, British scientists who first articulated the 3Rs approach of replacement, reduction, and refinement.

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Individuals who have questions about their suitability for the award or the suitability of someone they wish to nominate should contact The HSUS.

Send nominations by June 1, 1995, to Philip Mendoza, Laboratory Animal Programs, The HSUS, at the address below, or call 301-258-3042, fax: 301-258-3082. No special forms are necessary. Persons nominating themselves or others should submit a cover letter explaining the person's suitability for the award and supporting documents such as a curriculum vitae and relevant publications. Winners are selected with the aid of a scientific advisory panel and are announced in the fall. The HSUS encourages applications from (and nominations of) individuals whose work falls in the areas of refinement and research (as distinct from testing and education), two areas underrepresented among previous years' candidates.

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Karl W. Böer, ed.
Boulder, CO: American Solar Energy Society, 1995, 476 pp. ISSN: 0731-8618, $125.

Africa and the Environment; Joint Hearing Before the Subcommittee on Economic Policy, Trade, and Environment of Africa and the Committee on Foreign Affairs
House of Representatives, 103rd Congress
Washington, DC: U.S. GPO, 1994, ISBN: 0160441056, no price available.

Biohazards Management Handbook
Daniel F. Liberman
New York: Marcel Dekker, 1995, 568 pp. ISBN: 0824789954, $175.

The Campo Indian Landfill War; The Fight for Gold in California's Garbage
Dan McGovern
Norman, OK: University of Oklahoma Press, 1995. ISBN: 0806127554 (acid-free paper), no price available.

Contaminants in Terrestrial Environments
Otto Franzle
London: Springer-Verlag, 1994, 450 pp. ISBN: 0387552774, $149.

1995 Edition of Carroll's Environmental Directory
Washington, DC: Carroll Publishing, 1995, ISSN: 1067-7208 $185.

E.C. Treaty and Environmental Law
Ludwig Krämer
London: Sweet and Maxwell, 1995, 178 pp. ISBN: 0421508906, no price available.

Environment
Peter H. Raven, Linda R. Berg, George B. Johnson
Fort Worth, TX: Saunders College Publishing, 1995. ISBN: 0030105889, $58.25.

Environmental Protection and Justice; Readings and Commentary on Environmental Law and Practice
Kenneth A. Manaster
Cincinnati, OH: Anderson Publishing Company, 1995. ISBN: 0870842536, no price available.

Environmental Protection Legal Framework
Frank F. Skillern, Daniel H. Benson, Charles P. Bubany
Colarado Springs, CO: Shepard's/McGraw-Hill, 1995, 412 pp. ISBN: 0071725210, $100.

Environmental Science; A Global Concern
William P. Cunningham, Barbara Woodworth Saigo
Dubuque, IA: William C. Brown Publishers, 1995, 624 pp. ISBN: 0697158934, $62.25.

Environmental Studies: Earth as a Living Planet
Daniel B. Botkin, Edward A. Keller
New York: Wiley, 1995, 627 pp. ISBN: 0471545481, $67.95.

EPA-Speak; The Interpharm Glossary of EPA Acronyms and Regulatory Terms
Dean E. Snyder
Buffalo Grove, IL: Interpharm Press, 1993, 640 pp. ISBN: 0935184465, $89.

Essential Health and Safety for Managers; A Guide to Good Practice in the European Union
Ron Akass
Brookfield, VT: Gower Publishers, 1994, 288 pp. ISBN: 0566073323, $54.95.

Fundamentals of Aquatic Toxicology; Effects, Environment Fate, and Risk Assessment
Gary M. Rand, ed.
Washington, DC: Taylor and Francis, 1995, ISBN: 1560320907 (cloth), $99.50. ISBN: 1560320915 (paper), $49.50.

Hydrology; An Environmental Approach
Ian Watson, Alister Burnett
Boca Raton, FL: Lewis Publishers, 1994, 702 pp. ISBN: 1566700876, $49.95.

Methods in Immunotoxicology
Gary R. Burleson, Jack H. Dean, Albert E. Munson, eds.
New York: Wiley-Liss, 1995. ISBN: 0471305979, $180.

New-Stream Restoration Handbook
Izaak Walton League of America
Gaithersburg, MD: Izaak Walton League of America, 1995, 111 pp. $15.

The OECD Green Model; An Updated Overview
Hiro Lee, Joaquim Oliviera-Martins, Dominique van der Mensbrugghe
Paris: Organisation for Economic Cooperation and Development, 1994, 58 pp. Technical paper no. 97. No charge.

Science and the New Zealand Environment
M.J. Taylor, J.E. Hay, S. J. de Mora, eds.
Palmerston North, NZ: Dunmore Press, 1992, 149 pp. ISBN: 0864691521, $30.

Toxic Struggles; the Theory and Practice of Environmental Justice
Richard Hofrichter, ed.
Philadelphia, PA: New Society Publishers, 1994, 256 pp. ISBN: 0865712697 (cloth), $39.95. 0865712700 (paper), $16.95.

The War Against the Greens; The Wise-Use Movement, the New Right and Anti-Environmental Violence
David Helvarg
San Francisco, CA: Sierra Club Books, 1995. ISBN: 0871564599, $25.

Wilderness Medicine; Management of Wilderness and Environment Emergencies
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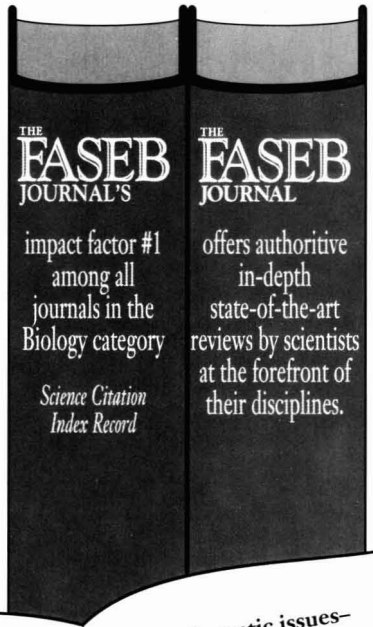

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Environment, Work and Health in the New Central and Eastern European Democracies
June 5–10, Mon–Sat
Constanza, Romania
Information: Mary Firestone JSI Center for Environmental Health Studies,
210 Lincoln Street,
Boston, MA 02111
(617) 482-9485
FAX: (617) 482-0617
E-mail: jsi@igc.apc.org

Cancer Prognosis Markers
June 7–8, Wed–Thu
Crystal City Marriott Hotel, Arlington, Virginia
Information: Ben Keddy, Cambridge Healthtech Institute, Bay Colony Corporate Center, 1000 Winter Street, Suite 3700, Waltham, MA 02154
(617) 487-7989
FAX (617) 487-7937

Technical Conference on Energy and the Environmnt in thePulp and Paper Industry
June 7–9, Wed–Fri
Thunder Bay, Ontario
Information: Jared Fein, E.B. Eddy Forest Products Ltd., 1047 Yonge Street, Toronto, Ontario M4W 2L2
(416) 922-4318

Society for Conservation Biology 1995 Annual Meeting
June 7–11, Wed–Sun
Information: Richard L. Knight Department of Fishery and Wildlife Biology, Colorado State University, Fort Collins, CO 80523
(303) 491-6714

14th Annual International Symposium of The Society of Toxicologic Pathologists
June 12–14, Mon–Wed
San Diego Marriott Hotel & Marina, San Diego, California
Information: Society of Toxicologic Pathologists, 875 Kings Highway, Suite 200,
Woodbury, NJ 08096-3172
(609) 845-1720

Second International Conference on Arsenic Exposure and Health Effects
June 12–14, Mon–Wed
Holiday Inn on The Bay at Embarcadero, San Diego, California
Information: Willard R. Chappell, CB 136,University of Colorado at Denver, PO Box 173364
Denver, CO 80217-3364
(303) 556-4520
FAX (303) 556-4292

International Benzene Conference
June 17–20, Sat–Tue
Rutgers University Campus, New Brunswick, New Jersey
Information: Jill Braun, Environmental and Occupational Health Sciences Institute,
681 Frelinghuysen Road,
PO Box 1179,
Piscataway, NJ 08855-1179
(908) 932-9271
FAX (908) 932-8726

Joint International Congress on Minimally Invasive Techniques in Neurosurgery and Otolaryngology
June 17–20, Sat–Tue
David L. Lawrence Convention Center, Pittsburgh, Pennsylvania
Information: Allegheny General Hospital Continuing Medical Education, 320 East North Avenue, Pittsburgh, PA 15212
(412) 359-4952
FAX (412) 359-8218

First Interdisciplinary Conference on the Environment
June 21–25, Wed–Sun
Park Plaza Hotel and Towers, Boston, Massachusetts
Information: Demetri Kantarelis, IEA, Economics/Foreign Affairs Department, Assumption College, 500 Salisbury Street, Worcester, MA 01615-0005
(508) 752-5615 ext 557
FAX (508) 799-4502

Cytokines and Adhesion Molecules in Lung Inflammation
June 22–23, Thu–Fri
Institut Pasteur, Paris, France
Information: Unité de Pharmacologie Cellulaire, Unité Associée IP/INSERM no. 285, Institut Pasteur, 25 Rue du Dr. Roux 75015 Paris, France
(33-1) 45.68.86.82
(33-1) 45.68.87.03

Indoor Air Quality, Immunity and Health
June 22–23, Thu–Fri
McKimmon Center, North Carolina State University, Raleigh, North Carolina
Information: Rodney Dietert
213 Rice Hall,
Cornell University,
Ithaca, NY 14853-5601
(607) 255-7789

SETAC-Europe 1995 Congress: Environmental Science and Vulnerable Ecosystems
June 25–28, Sun–Wed
Copenhagen, Denmark
Information: DIS Congress Service
DK-2730 Herlev, Denmark
45-4492-4492
FAX 45-4492-5050

Risk Assessment of Polycyclic Aromatic Hydrocarbons in the Environment
June 26–28, Mon–Wed
Hyatt Regency Airport Hotel, San Francisco, California
Information: Alex Taylor, JACA Corporation
550 Pinetown Road
Fort Washington, PA 19034
(215) 643-5466
FAX (215) 643-2772

Evaluations of Butadiene and Isoprene Health Risks
June 27–29, Tue–Thu
Inn at Semi-Ah-Moo Blaine, Washington
Information: The International Institute of Synthetic Rubber Producers, Inc.,
2077 South Gessner, Suite 133,
Houston, Texas 77063
FAX: (713) 783-7253

International Symposium on Peroxisomes: Biology and Role in Toxicology and Disease
June 28–July 2, Wed–Sun
The Aspen Institute, Aspen, Colorado
Information: Nancy Starks, Department of Pathology, W127, Northwestern University Medical School, Ward Building, Room 6-204, 303 East Chicago Avenue, Chicago, IL 606011-3008
(312) 503-8144
FAX (312) 503-8240

July

VII International Congress of Toxicology—Horizons in Toxicology: Preparing for the 21st Century
July 2–6, Sun–Thu
Seattle, Washington
Information: ICT–VII Management Support Staff, The Sterling Group, 9393 W. 110th Street, Suite 253, Overland Park, KS 66210
(913) 345-2228
FAX (913) 345-0893

Modulators of Immune Response; Hiking up the Evolutionary Trail
July 8–15, Sat–Sat
Beaver Run Resort and Conference Center, Breckenridge, Colorado
Information: Joanne Stolen, SOS Publications,
43 DeNormandie Avenue,
Fair Haven, NJ 07704-3303
(908) 530-3199
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Eighth International Conference of the International Federation of Science Editors
July 9–12, Sun–Wed
Barcelona, Spain
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Mid-Atlantic Industrial and Hazardous Waste Conference
July 9–12, Sun–Wed
Lehigh University, Bethlehem, Pennsylvania
Information: Arup K. Sengupta, Office of National Media Relations, 436 Brodhead Avenue, Bethlehem, PA 18015
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The Use of Trout and Zebrafish in Biomedical Toxicology
July 10–11, Mon–Tue
Oregon State University, Corvallis, Oregon
Information: Sandy Ernst Marine/Freshwater Biomedical Center, 232 Wiegand Hall, Oregon State University, Corvallis, OR 97331

Vth COMTOX Symposium on Toxicology and Clinical Chemistry of Metals
July 10–13, Mon–Thu
Vancouver, BC, Canada
Information: Secretariat, F. William Sunderman Jr., Departments of Laboratory Medicine and Pharmacology, University of Connecticut Medical School, PO Box 1292, Farmington, CT 06034-1292
(203) 679-2328
FAX (203) 679-2154

The Ninth International Congress of Immunology
July 23–29, Sun–Sat
San Francisco, California
Information: FASEB Office of Scientific Meetings and Conferences, 9650 Rockville Pike, Bethesda, MD 20814-3998

Engineering Solutions to Indoor Air Quality Problems; An International Symposium
July 24–26, 1995, Mon–Wed
Sheraton Imperial Hotel, Raleigh, North Carolina
Information: Kelly W. Leovic U.S. Environmental Protection Agency,
(919) 541-7717
FAX (919) 541-2147 or
Air and Waste Management Association
(412) 232-3444
FAX (412) 232-3450

August

American Chemical Society Meeting
August 20–25, Sun–Fri
McCormick Place Convention Center, Chicago, Illinois
Information: ACS Meetings, American Chemical Society, 1155 16th Street, NW
Washington, DC 20036
(202) 872-6059
FAX (202) 872-6128

Second International Conference on Environmental Mutagens in Human Populations
August 20–25, Sun–Fri
Prague, Czech Republic
Information: Radim J. Sram, Laboratory of Genetic Ecotoxicology, Prague Institute of Advanced Studies, University of Michelskeho lesa 366 140 00 Prague, Czech Republic
(422) 472-4756
FAX (422) 472-4757

Fourth International ISSX Meeting: Xenobiotic Interactions
August 27–31, Sun–Thu
The Westin Hotel,
Seattle, Washington
Information: ISSX Meeting/Convention Services Northwest, 1809-7th Avenue, Suite 1414
Seattle, WA 98101
(206) 292-9198
FAX (206) 292-0559

33rd International Congress on Forensic (TIAFT) and 1st Congress on Environmental Toxicology: Gretox 1995
August 27–31, Sun–Thu
Thessaloniki-Macedonia-Greece
Information: Anastasios Kovatsis, Laboratory of Biochemistry, Aristotelian University of Thessaloniki,
540 06 Thessaloniki, Greece
(30) 31-999851
FAX (30)-31-999851, -200392, or -206138

September

International Symposium on Tumor Markers
September 1–3, Fri–Sun
Guest Hotel, Bei-Di-He,
He Bei Provence, China
Information: Mei Yuan, General Secretary BRTIMB 1995, Cancer Research Laboratory, General Hospital of PLA, Beijing 100853, China
FAX 861-821-7073

Fifth International Congress on Hormones and Cancer
September 17–20, Sun–Wed
Quebec City, Quebec, Canada
Information: Fifth International Congress on Hormones and Cancer, Laval University Medical Center, 2705 Laurier Boulevard, Sainte-Foy, Quebec, GIV 4G2 Canada
1 (418) 654-2244
FAX (418) 654-2714

October

European Conference on Combination Toxicology
October 11–13, Wed–Sun
Congress Centre Koningship
Veldhoven, The Netherlands
Information: Secretariat Flora de Vrijer TNO Toxicology,
PO Box 360, 370 AJ Zeist The Netherlands
31 3404 44218
FAX: 31 3404 52224
E-mail: vrijer@voeding.tno.nl

Arkansas Toxicology Symposium: New Horizons in Chemical-Induced Liver Injury
October 19–20, Thu–Fri
The Doubletree Hotel,
Little Rock, Arkansas
Information: Jack A. Hinson, Director, Division of Toxicology University of Arkansas for Medical Sciences,
Little Rock, AR 72205
(501) 686-5766
FAX (501) 686-8970

Eighth International Conference of the Society for Human Ecology: "Livelihood and Liveability"
October 19–22, Thu–Sun
Lake Tahoe,
Tahoe City, California
Information: Nancy L. Markee, University of Nevada Reno,
MS 199,
Reno, NV 89557
(702) 784-1674
FAX (702) 784-1142

Mechanisms and Prevention of Environmentally Caused Cancers
October 21–25, Sat–Wed,
Santa Fe, New Mexico
Information: Alice M. Hannon, The Lovelace Institutes, 2425 Ridgecrest Drive S.E.,
Albuquerque, NM 87108-5127
(505) 262-7255
FAX (505) 262-7043

Fifth International Conference on the Chemistry and Biology of Mineralized Tissues
October 22–27, Sun–Fri
Kohler, Wisconsin
Information: L. Keller,
The University of Texas, Health Sciences Center at San Antonio,
7703 Floyd Curl Drive,
San Antonio, TX 78284-7823

Thirteenth International Neurotoxicology Conference
October 29–November 1, Sun–Wed
Hot Springs, Arkansas
Information: Joan Spyker Cranmer Professor and Conference Chairman, Department of Pediatrics, UAMS #512, Arkansas Children's Hospital,
1120 Marshall Street, Room 207,
Little Rock, AR 72202-3591
(501) 320-2986
FAX (501) 320-3947

The XVIII Symposium of the International Association for Comparative Research on Leukemia and Related Diseases
October 29–November 3, Sun–Fri
Kyoto International Conference Hall, Kyoto, Japan
Information: Secretariat, The XVII Symposium of IACRLRD, Laboratory of Molecular Oncology, The Institute of Physical and Chemical Research (RIKEN),
2-1 Hirosawa, Wako,
Saitama 351-01, Japan
81-48-462-1111 ext. 3161
FAX 81-48-462-4686

November

Living in a Chemical World–The Second Decennial Symposium
November 3–5, Fri–Sun
Hotel Omni-Shoreham,
Washington, DC
Information: David Rall,
5302 Reno Road,
Washington, DC 20015
(202) 244-5380
FAX (202) 966-3093

International Symposium: 66 Years of Surfactant Research
November 5–10, Sun–Fri
Vienna, Austria and Budapest Hungary, with poster sessions on board ship from Passau, Germany
Information: B. Lachmann Department of Anesthesiology, Erasmus University
Post Bos 1738,
3000 DR Rotterdam, The Netherlands
31 10 4087312
FAX 31 10 4367870

Susceptibility and Risk: The Third Annual Symposium of the Health Effects Research Laboratory
November 6–9, Mon–Thu
Raleigh, North Carolina
Information: 1995 HERL Symposium Susceptibility and Risk, c/o RSD Conference

Cordinator, Health Effects Research Laboratory, U.S. Environmental, Protection Agency Mail Drop 70, Research Triangle Park, NC 27711

Eighth Annual Incinerator Ash Conference Tracks Renewed Interest in Waste-to-Energy
November 14–15, Tue–Wed
Stouffer Renaissance Hotel, Crystal City, Arlington, Virginia
Information: Richard Will, The Coordinate Group, Inc., Box 3356, Warrenton, VA 22186-1956
(800) 627-8913 or
(703) 347-4500
FAX (703) 349-4540

Third Congress of Toxicology in Developing Countries
November 19–23, Sun–Thu
Cairo, Egypt
Information: Sameeh A. Mansour (V-P & SG/3rd CTOX-DC), National Research Centre, Dokki, Cairo, Egypt
(202)701211/701362/701433/701499
FAX (202)-700931

December

International Conference on Food Factors: Chemistry and Cancer Prevention
December 10–15, Sun–Thu
Act City Hamamatsu, Hamamatsu, Japan
Information: ICoFF Secretariat, Japan Institute for the Control of Aging, Nikken Foods Co. Ltd., 723-1, Haruoka, Fukuroi, Shizuoka 437-01, Japan
81 538 49 0125
FAX 81 538 49 1267

International Symposium on Environmental Biomonitoring and Specimen Banking
December 17–22, Sat–Fri
Honolulu, Hawaii
Information: K.S. Subramanian, Environmental Health Directorate, Health Canada, Tunney's Pasture, Ottawa, Ontario CK1A OL2 Canada
(613) 957-1874
FAX (613) 941-4545

1996

May

Fourth International Symposium on Metal Ions in Biology and Medicine
May 19–22, Fri–Mon
Tarragona/Barcelona Catalonia, Spain
Information:Mercedes Gómez, Laboratory of Toxicology and Biochemistry, School of Medicine, c/San Lorenzo 21, 43201 REUS, Spain
34 77 759 376
FAX 34 77 759 322

September

Biological Monitoring in Occupational Environmental Health
September 11–13, Wed–Fri,
Espoo, Finland
Information: Biological Monitoring, c/o Finnish Institute of Occupational Health Symposium Secretariat, Topeliuksenkatu 41 a A FIN-00250 Helsinki, Finland
358-0-47-471
FAX 35804747548

Fellowships, Grants & Awards

Postdoctoral Fellowships in Toxicology/Epidemiology

Postdoctoral fellowships are available in a unique NIH-sponsored training program in toxicology/epidemiology of respiratory tract disease caused by environmental agents. Conducted jointly by the Inhalation Toxicology Research Institute (ITRI) and the Department of Medicine, University of New Mexico (UNM), the program provides training focus in either laboratory or epidemiology-based research with cross-training in the other discipline. The program develops research skills for investigative careers, incorporating interdisciplinary laboratory-human extrapolation. ITRI-based participants will undertake postdoctoral laboratory research and receive lecture and field cross-training in epidemiology and toxicology jointly with UNM-based fellows in epidemiology. Programs are tailored to individuals. Laboratory research or pathogenesis of disease can focus on one of several disciplinary areas, including cell biology, molecular biology, biochemistry, immunology, pathology, physiology, toxicology, radiobiology, aerosol science, or mathematics modeling, depending on interests and qualifications. Annual stipend of $30,800 plus health insurance, tuition and travel costs.

Contact:
Dr. David E. Bice
Education Coordinator
Inhalation Toxicology Research Institute
PO Box 5890
Albuquerque, NM 87185
or call (505) 845-1257 for application materials.
We are an Equal Opportunity Employer.

European Cancer Centre Two-Year Fellowships for Oncologists

The European Cancer Centre was founded in Amsterdam in 1991. Its major goal is to improve oncologic care by developing an international research network through collaborative research. The ECC focuses on organizing early clinical research, placing emphasis on translating basic laboratory research into clinical phase I and phase II studies.

The ECC invites young clinical specialists with a proven interest in research to apply for the ECC Fellowship Programme, which is funded by trade and industry. A substantial part of this two-year fellowship will be spent in the laboratory, performing basic research. The fellows work in the Amsterdam oncologic centres participating in the European Cancer Centre under the supervision of the principal investigator of the study.

Eligibility Criteria: Candidates must meet the following conditions:
- Maximum age 35 years
- Medical degree with specialization in oncology
- Proven research skills
- At least two publications with first authorship in the international peer reviewed literature
- Guaranteed position in home institute after completion of the fellowship.

It is recommended to support an application with letters of reference from present and former supervisors and/or mentors.

Application Procedures: The Research Groups of the European Cancer Centre submit their research proposals and request for a fellow. The ECC Scientific Board, chaired by Professor H.M. Pinedo, MD, PhD, evaluates the proposal on scientific value and innovative importance. After approval of the project, fellowship candidates can be recommended by members of an ECC Research Group. Those interested can also request information about available projects and send in their application.

To apply, candidates must submit: 1) a letter of application with the completed ECC Fellowship Programme Application Form, 2) a short curriculum vitae listing at least three specialists/scientists willing to supply a reference, 3) no more than five relevant full publications,
4) a letter stating a guaranteed permanent position at the home institute upon return.

Selection Procedure: Twice a year, on March 1 and September 1, the applications are reviewed by a selection committee, considering the aforementioned criteria. Selected fellows are then informed of the available research projects best suiting their curriculum and are introduced to the principal investigators.

They will also be invited for interviews with the selection committee and to give a presentation of their work. After the second deliberation round, the selected fellows will be invited to start their two-year fellowship in Amsterdam within a foreseeable time.

Salary and Stipend: A salary and stipend are provided which include all costs of housing and living. The Board encourages the home institute to provide additional funding.

For more information contact:
European Cancer Centre
PO Box 7057
NL-1007 MB Amsterdam
The Netherlands
31 20 644 4500/4550
FAX 31 20 644 4551

Solar Processes and Hazardous Chemicals

The National Renewable Energy Laboratory (NREL) seeks the participation of U.S. educational institutions in a program of research and development on solar processes for the destruction or removal of hazardous chemicals from air or water. This program seeks to identify new processes or improve already known processes (photochemical, photothermal, photocatalytic).

Areas of interest include but are not limited to: 1) photochemical reactor engineering; 2) process chemistry; 3) catalyst improvements; and 4) physical and chemical mechanisms. Up to six awards are anticipated. For solicitation copy, write to:
NREL, Subcontracts Section
M/S 6320-17/2
1617 Cole Boulevard
Golden, CO 80401-3393,
Attn: Kendra K. Ecton
Or FAX request to (303) 231-1444. Telephone for more information only: Paulette Fontaine-Westhart at (303) 231-7807. Reference: Synopsis No. 4-298.

Earthwatch Field Grants

The Center for Field Research invites field biologists to apply for an Earthwatch field grant. The Center for Field Research encourages and evaluates proposals for support by its international affiliate Earthwatch. Earthwatch is a private, nonprofit organization established in 1971 to fund field research, pro-

mote communication between scholars and the public, improve science education, and enhance public understanding of pressing environmental and social problems.

Through its system of participant funding, Earthwatch supports both basic and applied research. Proposals are welcome for field studies on almost any life science topic, in any country, by advanced scholars of any nationality. The research must have scientific merit and feasibly and constructively involve nonspecialist Earthwatch volunteers in the research tasks.

Earthwatch field grants average $20,000. These funds are derived from the contributions of Earthwatch members who enlist for the opportunity to join scientists in the field and assist with data collection and other tasks. On average, each volunteer contributes $600–900 towards the field grant and spends 12–16 days in the field. A typical Earthwatch project employs 4–8 volunteers each on 3–5 sequential teams. To be economically feasible for Earthwatch, the total number of Earthwatch volunteers participating on a project in one year is usually at least 20.

Earthwatch field grants cover the costs of maintaining volunteers and principal researchers in the field. They also help with other project expenses, except principal investigator salaries, capital equipment, overhead, and preparation of results for publications. Applying for grants is a two-stage process. Preliminary proposals are submitted to The Center for Field Research at least 13 months in advance of anticipated field dates. Full proposals are invited upon review of preliminary materials. Proposals are accepted and reviewed year round. For more information, contact:

Dee Robbins,
Life Sciences Program Director,
The Center for Field Research,
680 Mt. Auburn Street,
Watertown, MA 02172
(617) 926-8200
FAX (617) 926-8532

Great Lakes Protection Fund Call for Preproposals

In order to assist potential applicants in planning and coordinating grant requests, the Great Lakes Protection Fund announces adoption of two fixed dates for submission of preproposals–January 2 and July 1. These annual deadlines for general calls for preproposals will apply in 1995 and future years. The fund may also issue a limited call for preproposals to target a specific topic or topics within one of the fund's four goals.

Eligibility: The Fund's priority applicants are nonprofit agencies; however, individuals and proprietary entities may apply if a clear public benefit can be demonstrated and if financial benefits stemming from the proposed work accrue to the public good. Successful applicants must maintain open access to project data, records and financial information. Results must be disseminated so that they are readily accessible to others.

Preproposal Application and Evaluation Process: The two-page preproposal is the first of two steps in the fund's proposal review process. The second step is an invitation to submit a full proposal based upon favorable evaluation of the preproposal.

Preproposals are evaluated strictly against the fund's mission and must address one of the fund's four goals. Proposed projects must be appropriately collaborative among the private, public and independent sectors. The fund seeks to support projects which are supplemental and non-duplicative of other efforts. For multi-year projects, the fund may issue challenge grants to encourage supplemental contributions.

Staff reviews the preproposals and makes recommendations to the fund's grant making committee of the Board of Directors. Preproposals are not sent to outside technical reviewers. Full proposals, however, are sent to at least three independent technical reviewers.

Preproposal Deadline: Preproposals must be received in the office by 5:00 pm Central Time, January 2, 1995. Preproposals received after that date will be considered with preproposals submitted for the July 1, 1995 deadline. *There are no exceptions to these deadlines.*

The fund also supports efforts to promote collaboration, coordination and regional action through planning and discretionary travel grants. For more information on these grants, please contact the fund:

Preproposal Application
Great Lakes Protection Fund
35 East Wacker Drive, Suite 1880
Chicago, IL 60601

Position Announcements

Public Health Scientist
The Natural Resources Defense Council, a national nonprofit public interest organization, seeks a Senior Scientist to bring scientific analysis and knowledge to advocacy in various forums for the prevention of adverse health and ecological effects of toxic chemical pollution. A PhD or MD/MDH is required, with several years of experience in environmental or public health, or a related field. Candidates should be knowledgeable about cutting-edge toxics issues such as disproportionately impacted subpopulations, endocrine disruption, and other non cancer endpoints, and emerging issues regarding carcinogenesis. The position requires the established ability to keep abreast of scientific advances and work with the public health and academic communities. The ability to conduct outreach activities to build bridges with persons affected by toxics problems is also very important. The salary is $60,000 to $70,000, commensurate with experience. Send resume to: Public Health Program, NRDC, 1350 New York Avenue, NW, Suite 300, Washington, DC 20005. Equal Opportunity Employer.

Open Rank Faculty Position Announcement—Occupational and Environmental Exposure Assessment
University of Michigan invites applications for an open rank, tenure-track faculty position in Occupational and Environmental Exposure Assessment. The primary appointment will be in the School of Public Health, Department of Environmental and Industrial Health and will be at a rank and salary commensurate with experience.

Desired candidates will hold wither a PhD in industrial hygiene, epidemiology, environmental health, molecular genetics or other relevant disciplines or an MD with experience in such disciplines. Candidates should have an active interest in innovative and interdisciplinary solutions to theoretical and applied problems in exposure assessment in environmental and occupational settings. Examples of areas of interest include the application of environmental and occupational exposure assessment to exposure-response modeling and risk estimation, and the integration of measures of target organ dose in exposure modeling. Successful candidates will have a demonstrated ability to attract competitive external funding, to publish original research in the peer reviewed literature, and to teach at the graduate level including doctoral level students or medical students.

The University of Michigan actively encourages interest from women and minorities and is an Equal Opportunity/Affirmative Action Employer.

Letters of application, accompanied by a curriculum vitae, statement of research and teaching interest, and the names and addresses of three references should be sent to: Thomas Robins, MD, MPH, Associate Professor,
The University of Michigan School of Public Health,
Department of Environmental and Industrial Health,
1420 Washington Heights,
Ann Arbor, Michigan 48109-2029
e-mail: trobins@umich.edu
FAX (313) 763-8095.

Postdoctoral Research Opportunities at the National Institute of Environmental Health Sciences
Listed below are outstanding opportunities to conduct research with leading scientists in Research Triangle Park, North Carolina.

To apply, please send a cover letter, curriculum vitae, bibliography, and names of three references to the hiring scientist at the maildrop and laboratory listed using the following address: NIEHS, PO Box 12233, Research Triangle Park, North Carolina 27709. In your cover letter, list the position title and the HNV number.

Minorities, women and handicapped individuals are encouraged to apply. All applicants receive consideration without regard to race, religion, color, national origin, sex, physical or mental handicap, political affiliation, age (with statutory exceptions) or any other nonmerit factor. Positions are open until filled.

Molecular Mechanisms of DNA Repair (HNV88)
Miriam Sander
(919) 541-2799
Laboratory of Molecular Genetics,
Maildrop D3-04
Mechanisms of DNA repair in Drosophila are being investigated with focus on the *in vivo* and *in vitro* functions of Rrp1 (recombination repair protein 1). This protein is potentially important in DNA repair and homologous recombination. Future studies will include enzymatic, physical, and genetic characterization of Rrp1.

Mammalian Molecular/ Developmental Genetics (HNV89)
Steven S. L. Li
(919) 541-4253
Laboratory of Genetics,
Maildrop D3-05
The organization and developmental regulation of mammalian genes, including neurogenic genes, are being investigated. Applicants should have a strong background in genetics, biochemistry or molecular biology.

Effects of Melatonin on Cell Biology (HNV90)
Gloria Jahnke
(919) 541-3376
Laboratory of Molecular Carcinogenesis,
Maildrop C3-03
The effect of melatonin on the regulation of growth and survival of normal and neoplastic breast epithelial cells is being investigated. Emphasis is being placed on signal transduction pathways that may be affected by melatonin. Applicants should have training in toxicology, cell biology and biochemistry.

Molecular Neurobiology (HNV94)
J.S. Hong
(919) 541-2358
Laboratory of Environmental Neurosciences,
Maildrop E1-01
The signal transduction pathways regulating the expression of neuropeptide and cytokine genes in neural and glial systems are being investigated. Studies on the effects of neuropeptides on the biosynthesis and release of cytokines in microglial cells and potential roles of cytokines in neurodegeneration will be conducted. Applicants should have experience in neuropharmacology, neurochemistry or molecular biology.

Ion Homeostasis and Cell Injury (HNV95)

Elizabeth Murphy
(919) 541-3873
Laboratory of Molecular Biophysics, Maildrop 17-05
Changes in ion transport and homeostasis appear to be involved in apoptotic cell death. Studies focus on measuring changes in intracellular calcium, pH, sodium and magnesium in isolated cells using fluorescent indicators in cells stimulated to undergo apoptosis. Alterations in signal transduction pathways which are responsible for the ionic alternations are also under study. Applicants must have experience in ion measurements using fluorescent indicators or experience with cell culture or molecular biology.

Molecular Dosimetry and Epidemiology (HNV96)

George W. Lucier
(919) 541-3802
Laboratory of Biochemical Risk Analysis,
Maildrop A3-02
Knowledge and techniques in molecular biology are applied to investigations designed to determine effects of low-dose exposures to environmental agents. Animal models, cell systems and human samples are used. Studies encompass mutation analysis and signal transduction elements.

Molecular and Cellular Biology (HNV97)

Anton Jetten
(919) 541-2768
Laboratory of Pulmonary Pathobiology,
Maildrop D2-01
The action and function of several nuclear (orphan) receptors in the regulation of gene expression and differentiation are being investigated. Studies involve characterization of response elements, interaction with other transcriptional factors and gene knockouts. Applicants must have training in molecular biology techniques.

Mechanisms by Which Organisms Produce Mutations (HNV99)

Roel M. Schaaper
(919) 541-4250
Laboratory of Molecular Genetics,
Maildrop E3-01
Studies are aimed at understanding the mechanisms by which organisms produce mutations. Specific projects involve the isolation and molecular characterization of *antimutator* mutants in the bacterium *E. coli;* the genetic and biochemical analysis of DNA replication fidelity in this organism; and a structure-function analysis of the *dnaE* and *dnaQ* genes (encoding, respectively, the DNA polymerase and exonucleolytic proofreading activity).

Mechanisms of DNA Replication (HNV100)

William Copeland
(919) 541-4792
Laboratory of Molecular Genetics,
Maildrop E3-01
The regulation and mechanism of human DNA polymerases involved in the replication of nuclear and mitochondrial DNA is being investigated. Attention is on the mutation rate of the mitochondrial and nuclear genome by understanding the enzymology of the mitochondrial and nuclear DNA polymerases. Future studies will include the regulation of these essential enzymes in the cell.

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Editorial Policy

Environmental Health Perspectives is intended to be a forum for the discussion of issues in environmental health, and several formats have been devised for that purpose. In addition, several formats are available for the publication of scientific articles and scientific discussion. All scientific articles are subject to peer review. The primary criteria for publication are environmental significance and scientific quality.

Environmental science is made up of many fields, and therefore we are prepared to consider scientific progress in all of them. Cross-fertilization and serendipity have proven to be extremely important processes in the advance of science in general, and this must hold true for the science of environmental health. We will consider for publication articles ranging from the most basic molecular biology to environmental engineering. We particularly encourage those researchers concerned with mechanisms of toxic action and new approaches for detecting and/or remedying environmental damage.

Opinions and ideas based on scientific observation and argument are welcome. While the expression of opinions may lead to debate and disagreement, such reactions are healthy and can lead to new research and discoveries. Presentations of ideas and opinions will be promoted, but our policy will be to strive for objectivity and balance.

In addition to scientific articles and discussion, we publish news of the environment. We will consider factual articles about issues that affect the environment and human health. We summarize legislative and regulatory developments, grant information from NIEHS and other granting agencies, new research areas, environmental problems, technological advances, and information about the National Toxicology Program and other important programs. Presentations of news strives for objectivity and balance and is based on the strength of scientific evidence.

Our policy is to give the corresponding author of each published article 200 free reprints.

Scientific Research

Scientific articles are subject to rigorous peer review. Two formats are available for the publication of scientific articles:

Research Articles are original manuscripts reporting scientific research and discovery in the broad field of environmental health. Research articles may come from any field of scientific research, from the most basic molecular biology and biochemistry to atmospheric physics, ecology, and engineering. The criteria for publication are weighted toward scientific quality and environmental significance. The work will be assessed according to its originality, scientific merit, and experimental design; the manuscript will be evaluated based on its conciseness, clarity, and presentation. We also attempt to address certain ethical problems during the review process. We require assurances that all human and animal subjects have been treated humanely and with due regard for the alleviation of suffering. Manuscript review also considers scientific integrity as part of the process.

Research Advances are concise articles intended to address only the most recent developments in a scientific field. Lengthy historical perspectives are not appropriate in this category. Clarity of presentation is of primary importance because these articles are intended to be educational though targeted to the expert audience.

Opinions, Ideas, Perspectives

The journal is a forum for the expression of ideas and opinions. Opinions and ideas should be carefully considered and based on scientific principles. Several formats are offered:

Editorial statements are published by our editors, members of our editorial boards, and occasional guest editors. These statements are intended to focus attention on important or neglected areas of environmental health, offer opinions and ideas, and stimulate discussion.

Reviews & Commentaries are up-to-date, narrowly focused review articles that may present commentaries offering perspective and insight on a particular topic. Only recent developments in a field should be addressed.

Correspondence is encouraged. Opinions, perspectives, and insight are welcome. Comments on articles published in *Environmental Health Perspectives* are also welcome, but criticism will always be balanced by the opportunity for defense and clarification. Letters to the Editor cannot exceed 1200 words.

Meeting Reports are short summaries of conferences, symposia, or workshops in which the scientific objectives and achievements of a meeting are described.

Environews

The news section provides up-to-date information on important issues in environmental health covering a variety of areas including policy, legislative, and regulatory actions; innovative technological and conceptual research advances; conference and meeting summaries; and emerging environmental problems. The news section consists of several components:

Forum articles are brief reports on matters of potential environmental health significance such as chemical spills and contamination episodes. Brief reviews of recent scientific advances are also included.

NIEHS News summarizes significant activities or accomplishments at NIEHS and the National Toxicology Program.

Focus articles are substantive news items about important issues in environmental health. Examples include reports on risk assessment, risk management dilemmas, women's health initiatives, environmental equity, relevance of animal models to toxicity testing, and structure–activity approaches to toxicity evaluation.

Spheres of Influence is a legal/regulatory column that presents reports on significant events and decisions involving the executive branch, Congress, and regulatory agencies. Examples include new directions of White House policies, impact of Clean Air Act legislation, and coverage of congressional hearings on environmental health issues.

Innovations presents emerging opportunities in environmental health based on new discoveries or approaches in biology, chemistry, engineering, or information sciences. Examples include the use of transgenic animals in toxicity testing, new advances in molecular biology, development of more rapid and efficient methods for clean-up of hazardous wastes, and methods for early detection of environmental damage and environmentally mediated diseases.

Announcements includes a calendar of upcoming events such as conferences, workshops, and public hearings. Appropriate listings are made for industrial, academic, regulatory, and legal activities. This section also includes listings of fellowship and grant announcements and positions available.

Environmental Health Perspectives Supplements

During the last 20 years, we have focused on the development of a series of monographs that have generally arisen from symposium or conference proceedings. We continue to publish monographs, but they now appear as supplements to the main journal. Six to eight supplements are published per year. Four to six of these consist of conference, workshop, or symposium proceedings, and two issues are dedicated to the publication of solicited and unsolicited comprehensive reviews on environmental health. All articles published in the supplements, regardless of their source, are peer reviewed.

Each supplement resulting from a conference, symposium, or workshop should address a specific problem, an area of concern, a research problem, or a particular scientific issue. Supplements will, in general, be dedicated to scientific issues and not programmatic themes. It is intended that each collection of manuscripts form a landmark statement for a particular subject. Each supplement must be an up-to-date, balanced source of reference material for researchers, teachers, legislators, and the informed public. Publication of conference proceedings in *Environmental Health Perspectives Supplements* requires the submission of a proposal as described in Instructions to Authors.

Supplement Articles from conferences are generally the result of research investigations, reviews, or a combination of both; however, brief reports and commentaries are also appropriate.

Perspective Reviews are targeted to the one or two specific issues of *Environmental Health Perspectives Supplements* set aside for the publication of reviews in environmental health sciences. Perspective reviews are in-depth, comprehensive review articles that address developments in specific scientific areas. Perspective reviews must not be simply a compilation of the literature. Perspective reviews should be scholarly, landmark statements offering a complete and balanced perspective as well as insight into the environmental significance of the research.

Instructions to Authors

To ensure fairness, objectivity, and timeliness in the review process, we routinely request three reviews. Therefore, authors must submit four copies of each manuscript. All manuscripts must conform to the instructions to authors; those that do not will be returned without review.

All manuscripts must be typed, double-spaced, in English. Type the article on white paper, 216 ×279 mm (8.5 × 11 in) or ISO A4 (212 × 297 mm), with margins of at least 25 mm (1 in). Type only on one side of the paper. Number pages consecutively, beginning with the title page. If the manuscript is accepted for publication, a computer disk copy must be submitted along with two hard copies of the revised manuscript. Organizers of conference, symposium, or workshop proceedings will receive 25 free copies of the published supplement. Corresponding authors will receive 100 free reprints after publication.

Organization of Manuscripts

Research Articles are manuscripts reporting scientific research and discovery in the broad field of environmental health and may come from any field of scientific research. Criteria for publication are weighted toward quality and environmental significance.

Title Page: List title, authors (first or second names spelled out in full), full address of the institution where the work was done, and affiliation of each author. Indicate author to whom galley proofs and reprints should be sent (include complete address for express mail service, telephone and FAX numbers).

Second Page: Provide a short title (not to exceed 50 characters and spaces) that can be used as a running head. List 5–10 key words for indexing purposes. List and define all abbreviations. Nomenclature and symbols should conform to the recommendations of the American Chemical Society or the International Union of Pure and Applied Chemistry (IUPAC). Include acknowledgments and grant information.

Abstract: Place a double-spaced abstract on the third page. The abstract should not exceed 250 words. The abstract should state the purpose of the study, basic procedures, main findings, and the principal conclusions. Emphasize new and important aspects of the study or observations. The abstract should not include details of materials and methods or references.

Introduction: Begin the introduction on a new page. State the purpose of the research and give a brief overview of background information. Do not include data or conclusions from the work being reported.

Methods: Begin on a new page. Describe the materials used and their sources. Include enough detail to allow the work to be repeated by other researchers in the field or cite references that contain this information.

Results: Begin on a new page. Present your results in logical sequence in the text. Do not repeat materials and methods, and do not repeat data in tables or figures. Summarize only important observations. Results and Discussion may be combined if desired.

Discussion: Begin this section on a new page. Emphasize new and important aspects of the study and the conclusions that follow. Relate results to other relevant studies. Do not simply recapitulate data from the Results section.

References: Begin this section on new page. References are to be numbered in order of citation in the text and should be cited in the text by number in parentheses. The style for references is as follows:

Journal Article:

1. Canfield RE, O'Connor JF, Birken S, Kirchevsky A, Wilcox AJ. Development of an assay for a biomarker of pregnancy in early fetal loss. Environ Health Perspect 74:57–66 (1987).

Book Chapter:

2. Lohman AHM, Lammers AC. On the structure and fiber connections to olfactory centers in mammals. In: Progress in brain research: sensory mechanisms, vol 23 (Zotterman Y, ed). New York:Elsevier, 1967;65–82.

Book:

3. Harper R, Smith ECB, Jones DB. Odour description and classification. New York: Elsevier, 1968.

Editor as Author:

4. Doty RL, ed. Mammalian olfaction, reproductive processes, and behaviour. New York: Academic Press, 1976.

Conference Proceedings:

5. Ames B, Shigenaga MK, Gold LS. DNA lesions, inducible DNA repair, and cell division: three key factors in mutagenesis and carcinogenesis. In: Proceedings of the conference on cell proliferation, 14–16 May 1992, Research Triangle Park, NC. New York:Xavier, 1993; 35–44.

Government Report:

6. Melvin DM, Brooke MM. Laboratory procedures for the diagnosis of intestinal parasites. Report no. 75-8282. Atlanta, GA:Centers for Disease Control, 1974.
7. U.S. EPA. Status of pesticides in reregistration and special review. EPA 738-R-94-008. Washington, DC:Environmental Protection Agency, 1994.

Other Publications:

8. IARC. Arsenic and arsenic compounds. In: IARC monographs on the evaluation of carcinogenic risk of chemicals to man, vol 23. Some metals and metallic compounds. Lyon: International Agency for Research on Cancer, 1980;39–141.
9. Spiegelhalder B, Preussmann R. Nitrosamines and rubber. In: N-nitroso compounds: occurrence and biological effects (Bartsch H, O'Neill IK, Castegnaro M, Okada M, eds), IARC scientific publications no. 41. Lyon:International Agency for Research on Cancer, 1982;231–243.

Abbreviate journal names according to *Index Medicus* or *Serial Sources for the BIOSIS Previews Database*. List all authors; do not use et al. in the bibliography. Include the title of the journal article or book chapter and inclusive pagination. References to papers that have been accepted for publication but have not yet been published should be cited in the same manner as other references, with the name of the journal followed by "in press." Personal communications, unpublished observations, manuscripts in preparation, and submitted manuscripts should not be listed in the bibliography. They are to be inserted at appropriate places in the text, in parentheses, without a reference number.

Figures and Legends: Three sets of publication-quality figures are required. Graphs and figures should be submitted as original drawings in black India ink, laser-printed computer drawings, or as glossy photographs. Electronic versions of figures are encouraged, but should be submitted in addition to, not in lieu of, hardcopies of the figures. Dot matrix computer drawings are not acceptable as original art. The style of figures should be uniform throughout the paper. Letters, numbers, and symbols must be drawn to be at least 1.5 mm (6 points) high after reduction. Choose a scale so that each figure may be reduced to one-, two-, or three-column width. Identify all figures on the back with the authors' names and figure number; indicate TOP. Color figures will be considered for publication if the color facilitates data recognition and comprehension.

Figure legends should be typed on a separate page following the references. Legends should be numbered with Arabic numerals.

Tables: Each table must be on a separate page. Tables should be numbered with Arabic numerals. General footnotes to tables should be indicated by lowercase superscript letters beginning with a for each table. Footnotes indicating statistical significance should be identified by *, **, #, ##. Type footnotes directly after the table. Complex tables should be submitted as glossy photographs.

Computer Disks: Electronic copies of initially submitted manuscripts are not required. Revised manuscripts resubmitted after acceptance for publication must be sent in electronic form together with two hard copies.

Submit electronic formats on 3.5" disks suitable for reading on either PC or Macintosh platforms. Macintosh is the preferred platform, although PCs are acceptable. The file should contain all the parts of the manuscript in **ONE** file.

Label the outside of the disk with the title of the manuscript, the authors, and the number it has been assigned. Name the computer used (e.g., IBM, IBM compatible, Macintosh, etc.) and the operating system and version (e.g., DOS 3.3). Identify the word processing program and version. Microsoft Word format is preferred, and its use will greatly facilitate publication; however, we can convert other formats, including: Microsoft Word, WordPerfect, ASCII, Text Only.

Research Advances are concise articles intended to address only the most recent developments in a scientific field. Lengthy historical perspectives are not appropriate. Begin with the title

page and continue as described for research articles. References, abbreviations, figures, and tables should be handled as described for research articles. Clarity of presentation is of primary importance and the use of color figures is encouraged. Include a photograph (black and white or color) of the author together with a brief biography. If multiple authors or groups are involved, up to three biographies with photographs may be included.

INNOVATIONS are short articles that describe novel approaches to the study of environmental issues. Prepare initial pages as described for Research Advances. Maintain text in a clear and precise manner and wherever possible include color photographs to illustrate strategy and clarify conceptual problems. Some degree of speculation regarding the potential usefulness of a new technique or novel process in other areas of environmental health may be included. References should not be included, but a suggested reading list is required.

COMMENTARIES are short articles offering ideas, insight, or perspectives. Begin with a title page and second page as described for research articles. Include a brief abstract.

REVIEWS & COMMENTARIES are brief, up-to-date, narrowly focussed, review articles with commentaries offering perspective and insight. Begin with a title page and second page as described for Research Articles. Include an abstract and handle references, tables, figures, and abbreviations as described for Research Articles.

MEETING REPORTS should not exceed 2400 words in length. Begin with the title of the meeting and authorship of the report and start text on the next page. Detail when and where the meeting was held, how many people participated, who sponsored the meeting, and any special organizational arrangements. Meeting sponsors and principal participants, such as session chairs, may be listed on a separate page. The report should summarize the contributions of the meeting to scientific knowledge, insight, and perspective; this should not take the form of comments of participants or personalized perspectives. Space is limited, so only the highlights should be mentioned. Novel ideas, perspectives, and insights should be emphasized. Do not describe social aspects of the meeting. Send an electronic copy and four hard copies.

ENVIRONMENTAL HEALTH PERSPECTIVES SUPPLEMENTS

SUPPLEMENT MANUSCRIPTS result from conferences, symposia, or workshops and may take several forms. 1) Manuscripts reporting original research should be formatted as described for Research Articles, 2) opinions and discussion about a particular topic should be formatted as described for Commentaries, 3) manuscripts reviewing a topic or reporting a combination of review and original research should be formatted as described below for Perspective Reviews.

PERSPECTIVE REVIEWS are in-depth, comprehensive reviews of a specific area. They should begin with a title and second page as described for research articles. Introduction and presentation of information should be continuous with specific items and discussion indentified by using subheadings. Abstracts, references, abbreviations, figures, and tables should also be handled as described for research articles.

PROPOSALS for the publication of conference, symposium, and workshop proceedings will be considered; however, space is limited. We turn away many excellent proposals simply because we do not have space to publish them.

All proposals are reviewed and examined with a number of specific questions in mind. In developing a proposal, consider the following: Proposals are assessed according to their originality and scientific merit. Is the supplement needed? Is the subject matter timely and potentially useful to workers in the field? What is the environmental significance of the topic being addressed? Is the proposed supplement a complete representation of the field? Are there other aspects that should be included? Does the proposal contain sufficient information for evaluation? Is the presentation clear? Can the organizers integrate the participants into a cohesive unit? Are the contributors appropriate for the topic listed and do they have scientific credibility?

The source of funding is also considered. Scientific objectivity is extremely important, and it must be clear that organizers are not being used to present a bias favored by the funding body. Contributions from an interested party to a conference need not disqualify a proposal, but it is appropriate that the major source of funding be from a disinterested source or that organizational safeguards be set in place to minimize the intrusion of institutional bias.

All proposals must be submitted at least six months in advance of the conference. In the publication of conference proceedings, timeliness is essential. Because it takes at least six months to publication, no proposal will be considered after the conference has been held.

SUBMISSION OF MANUSCRIPTS AND PROPOSALS

Submit all manuscripts and proposals in quadruplicate to:

Editor-in-Chief
Environmental Health Perspectives
National Institute of Environmental Health Sciences
PO Box 12233
111 Alexander Drive
Research Triangle Park, NC 27709 USA

In your covering letter please provide assurances that the manuscript is not being considered for publication elsewhere and that all animals used in the research have been treated humanely according to institutional guidelines, with due consideration to the alleviation of distress and discomfort. If the research involved human subjects then a statement must be made to the effect that participation by those subjects did not occur until after informed consent was obtained.

Permission to reprint figures or tables from other publications must be obtained by the author prior to submission of the manuscript.

Finally, a statement must be made indicating that all authors have read the manuscript and are in agreement that the work is ready for submission to a journal and that they accept the responsibility for the manuscript's contents.

Inquiries may be made by calling (919) 541-3406 or by FAX at (919) 541-0273.

SUBMISSION OF NEWS INFORMATION

Environmental Health Perspectives welcomes items of interest for inclusion in the Environews, Calendar of Events, and Announcements sections of the journal. All items are published subject to the approval of the Editors-in-Chief. All submission for these sections should be sent to the attention of:

Associate News Editor
Environmental Health Perspectives
National Institute of Environmental Health Sciences
PO Box 12233
111 Alexander Drive
Research Triangle Park, NC 27709 USA

Items submitted for inclusion in the Forum section must not exceed 400 words. Items may be edited for style or content, and by-lines are not attached to these articles. If possible, items should be submitted on computer disk using WordPerfect or Microsoft Word, in straight text without formatting.

Items received for the Calendar of Events will be published in as timely a manner as possible, on a space-permitting basis. Submissions should include all relevant information about the subject, date, time, place, information contact, and sponsoring organization of the event.

Position announcements will be limited to scientific and environmental health positions and will be run on a space-permitting basis. Although we seek to publish all appropriate announcements, the timeliness of publication cannot be guaranteed.

Public information advertisements will be run free-of-cost as space becomes available. All ads are run subject to their appropriateness to the editorial format of the journal. Submissions of advertisements should include full-page, half-page, and quarter-page formats if available. Ads should be camera-ready, black and white positives.

Persons interested in free-lance writing opportunities with Environmental Health Perspectives should submit a cover letter, resume, and writing samples to the address above. For inquiries call the associate news editor at (919) 541-5377.

In This Issue

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National Institutes of Health
NIH Publication 95-218

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