HEI HEALTH EFFECTS INSTITUTE

update

WINTER 2011–2012

Effects of Diesel Exhaust Particles on People with Asthma and Allergies

A series of studies that began in the 1990s showed that exposure to diesel exhaust particles (DEP) increased allergic-type and inflammatory responses in the upper airways of healthy and allergic individuals. After exposure to whole diesel exhaust (DE) emissions, could such responses be found in the lower airways of people with both asthma and allergies? HEI Research Report 165, *Allergic Inflammation in the Human Lower Respiratory Tract Affected by Exposure to Diesel Exhaust Particles*, addresses this issue.

Marc Riedl of the University of California–Los Angeles and colleagues set out to determine whether exposure to DE in asthmatic and allergic individuals enhanced inflammatory and allergic immunologic responses in the lower airways and blood. Riedl's collaborators at Los Amigos Research Institute in Downey, California, built a facility with a human exposure chamber and characterized the exhaust generated by a 1999-model light-duty diesel truck.

The study was conducted in two phases, focusing on exposure to inhaled pollutants in the absence of or after an allergen challenge. In both phases, 15 allergic volunteers (nonsmokers 18 to 50 years old) with mild forms of asthma were exposed in random order, while intermittently exercising, for two hours to DE at 100 μg/m^3 particle concentration, nitrogen

Continued on page 4

The Chicago skyline rises above Oak Street Beach. PHOTO BY CESAR RUSS

Register Now for Annual Conference

This year's Annual Conference will be held April 15 through 17 at the stately Drake Hotel in Chicago, Illinois, where HEI held its successful 2007 conference. Presentations will cover the latest, most critical research findings on air pollution and health. Technical sessions include the following:

HEI's National Particle Component Toxicity (NPACT) initiative. Are some particulate matter components more harmful to health than others? HEI's four-year NPACT initiative, designed to address this important question, is drawing to a close. NPACT includes integrated toxicologic and epidemiologic studies of cardiovascular outcomes in U.S. cities with different compositions of particulate and gaseous copollutants. This session will provide a forum to discuss new insights from this work.

Diesel Emissions and Cancer: What Is the Evidence? With the recent introduction of innovative aftertreatment technologies, emissions from new diesel engines are decreasing dramatically, raising opportunities to substantially reduce human exposure. The Advanced

Continued on page 4

Also in This Issue

ACES Reaches Important Milestones

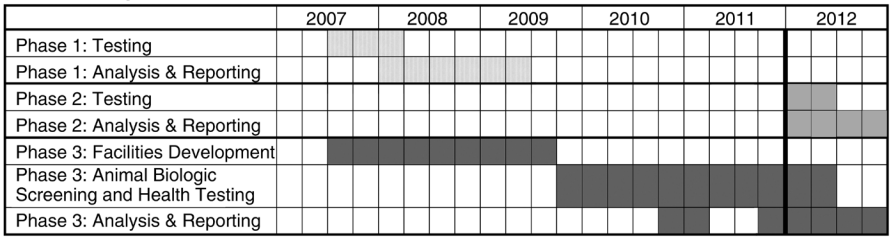
Since 2006, investigators for the Advanced Collaborative Emissions Study (ACES) have been testing diesel engine systems and fuels designed to reduce harmful air pollutants to levels that comply with the latest U.S. air quality regulations. This year ACES — a multistage program cosponsored by government agencies, industry, and the Coordinating Research Council (CRC) and carried out by HEI and the CRC — will reach several important landmarks.

First, scientists will complete the phase 2 characterization of emissions from 2010-compliant heavy-duty diesel engines. These engines have been designed to meet strict federal standards for emissions of nitrogen oxides (NO_x), in addition to the recent tighter standard for particulate matter emissions that was implemented in 2007. (Previously, four 2007-compliant engines were tested in ACES phase 1; these results have been published by the CRC and in the broader scientific literature.)

Emissions characterization of three 2010-compliant engines (from the participating manufacturers Cummins, Detroit Diesel, and Volvo) is being performed at Southwest Research Institute in San Antonio, Texas, using the same protocol as in phase 1, with minor modifications. A report from this stage of testing is expected to be available early in 2013.

Second, in April HEI will publish the first reports from the animal bioassays (phase 3B). These studies, which are currently undergoing HEI's rigorous peer review process, focus on the results of 1- and 3-month exposures in mice and rats, including the effects of inhaling diesel exhaust on overall organ toxicity, lung inflammation, cardiovascular effects, and genotoxicity. HEI's ACES Review Panel will prepare a Commentary for this publication. The reports will be submitted to the International Agency for Research on Cancer, which is scheduled to meet in June to evaluate the carcinogenicity of diesel exhaust and other types of emissions. Preliminary results of the 3-month mouse and rat studies were presented at the Directions in Engine-Efficiency and Emissions Research conference in Detroit, Michigan, in October.

Overall Project Timeline



Third, early this year HEI will publish Communication 17, containing results from characterization of exposure atmospheres at the Lovelace Respiratory Research Institute (LRRI) in Albuquerque, New Mexico, during phase 3A, which occurred before animal exposure and toxicity testing. A new system for exhaust generation and dilution had to be set up to accommodate the heavy-duty engine, and a new test cycle was developed. Investigators at LRRI made considerable efforts to ensure that the system performed optimally and target pollutant concentrations in the inhalation chambers were achieved and were stable over time. These careful early efforts have paid off, and the animal exposures have progressed satisfactorily during the first 15 months of exposure.

In June, this animal bioassay study will reach another milestone when the rats will have been exposed for 24 months. If the animals are healthy and mortality rates are low, the exposure period may be extended to 30 months. Reports of the final evaluation of the effects of exposures on biologic outcomes will then be prepared and reviewed by the HEI review panel, and results will be published in 2013. HEI

For more information on ACES, contact Maria Costantini (*mcostantini@healtheffects.org*), or Annemoon van Erp (*avanerp@healtheffects.org*).

Eaton Elected to Institute of Medicine

David Eaton, chair of the HEI Research Committee, has been elected a member of the prestigious Institute of Medicine (IOM). A renowned toxicologist, Eaton is the associate vice provost for research and director of the Center for Ecogenetics and Environmental Health at the University of Washington School of Public Health, Seattle. He is also a professor of environmental and occupational health sciences. His extensive work in environmental health has focused on toxicogenomics, which is concerned with understanding how genetic differences among individuals and species can result in potentially large differences in susceptibility to chemical carcinogens.

David Eaton.
PHOTO BY PAUL H. SCHNAITTACHER

Induction into the IOM — a part of the U.S. National Academies — is among the highest honors in health and medicine. Members are elected for their professional achievement in fields relevant to the IOM's mission, which is to provide decision makers and the public with unbiased, authoritative advice to improve health. Eaton has long been active at the Academies, where he has served as a member and chair of several committees and panels. HEI

Three New HEI Studies Launched

Recently approved by HEI's Board of Directors:

Ozone Exposure and Inflammatory Cells

Alison Fryer of the Oregon Health and Science University will evaluate the pathways by which exposure to ozone may affect the formation of blood cells in bone marrow — in particular, a type of white blood cells known as eosinophils — and thus lead to increased numbers of inflammatory cells in the blood and lungs. Previous research by Fryer using guinea pigs, an established animal model of ozone-related airway inflammation, has indicated that eosinophils activated by ozone inhalation initially promote airway hyperresponsiveness in the 24 hours after exposure, but that newly formed eosinophils may actually decrease hyperresponsiveness at about 72 hours after exposure. This effect may be modified in animals previously sensitized with the allergen ovalbumin. In the current two-year study, Fryer will determine the lowest effective ozone concentration that may induce the formation of eosinophils and other inflammatory cells in bone marrow in guinea pigs and evaluate whether this induction is reversible 14 days later. She will also study what signaling mechanisms may be involved in the communication between airway epithelium and bone marrow.

For more information, contact Annemoon van Erp (*avanerp@healtheffects.org*).

(Continued on page 3)

New Investigator Awards Announced

Juana Maria Delgado-Saborit, a research fellow at the University of Birmingham, United Kingdom, and Richard Peltier, an assistant professor at the University of Massachusetts–Amherst, have been selected as recipients of HEI's 2011 Walter A. Rosenblith New Investigator Award. Named for the first chair of the HEI Research Committee, the award supports the work of a promising scientist early in his or her career. In selecting recipients, the committee considers each applicant's potential for a productive scientific career in air pollution research, the support provided by the applicant's institution, and the scientific merit of the research project and its relevance to HEI's mission. Twelve other scientists have received this award since the inception of the program in 1999 (see list of recipients at *www.healtheffects.org/rosenblith.htm)*.

Juana Maria Delgado-Saborit.
PHOTO BY LYDIA REA

Delgado-Saborit received a doctorate in environmental sciences from the Universitat Jaume I in Spain in 2005. She has served as a temporary adviser to the World Health Organization on its indoor air quality guidelines and is the winner of the Cefic (European Chemical Industry Council) 2010 Long Range Initiative Innovative Science Award. Her long-term research goal is to help increase knowledge about environmental stressors to human health, potentially informing environmental policy decisions.

For her New Investigator project, Delgado-Saborit will conduct a panel study to improve methods of estimating human exposure to the air pollutant mixture (specifically ultrafine particulate matter [PM], fine PM, black carbon, and nitrogen dioxide). She plans to study people who live in homes near or far from traffic and with gas or electric stoves. Her aim is to assess the degree of misclassification associated with the use of surrogate measures of exposure — such as measurements made at central monitors — and to identify key activities and sources of these pollutants. The subjects will wear personal monitoring equipment for four consecutive days in winter and summer. A novel feature of this study is the use of sensors that can provide detailed data on pollutant concentrations over time and accelerometers to estimate subjects' physical activity level so that equivalent respiration rates and inhaled doses can be calculated.

Peltier received his doctorate in atmospheric chemistry from the Georgia Institute of Technology in Atlanta in 2007 and subsequently completed postdoctoral training at the New York University School of Medicine in Tuxedo. At the University of Massachusetts–Amherst, he is currently assistant professor in the Department of Public Health, Division of Environmental Health Science. His research interests are in aerosol chemistry and exposure science; his long-term goal is to build a productive research laboratory that focuses on identifying the chemical components of ambient air pollution that are most responsible for observed health effects.

Richard Peltier.
PHOTO BY J.R. PILSNER

With his New Investigator Award, Peltier will develop and characterize a new instrument that can quantify the formation of reactive oxygen species (ROS) caused by fine PM exposure. The method is based on a particle-into-liquid sampler that will be combined with acellular and cell-based approaches to measure ROS formation in solutions containing collected particles. The instruments will be characterized first in the laboratory and subsequently in two field locations, one rural and one urban. In the field, these instruments will be located next to aerosol chemical-speciation instruments to characterize the PM composition associated with ROS formation.

HEI expects to continue to award one or two New Investigator Awards each year, depending on available funding and the number and quality of applications. HEI

Apply Now for 2012 Rosenblith Awards

HEI is now accepting applications for the 2012 Walter A. Rosenblith New Investigator Award. This program provides three years of funding for a small project relevant to HEI's research interests to a new investigator with outstanding promise at the assistant professor or equivalent level. Letters of intent are due February 1; full applications are due March 1. For more information, visit *www.healtheffects.org/funding.htm* or contact Annemoon van Erp (*avanerp@healtheffects.org*).

NEW STUDIES *(Continued from page 2)*

PM Exposure and Heart Rhythm

David Rich of the University of Rochester, New York, and Annette Peters, Helmholtz Institute, Munich, Germany, will investigate whether exposure to fine or ultrafine particulate matter (PM) is associated with cardiac responses one hour or less after the exposure. In this two-year study, Rich, Peters, and colleagues will reanalyze existing electrocardiograms from four human studies — two panel studies and two involving controlled human exposures — for evidence of short-term effects of PM exposure on heart rhythm. The study is innovative because it will evaluate changes in heart rhythm very soon after exposure to PM and thus may provide valuable information, if effects are found, that could be useful in managing the care of potentially susceptible individuals. In addition, stored blood samples from earlier studies will be analyzed for total antioxidant capacity, to determine whether the oxidant status of the individual affects these immediate changes after exposure to PM.

For more information, contact Geoffrey Sunshine (*gsunshine@healtheffects.org*).

Impact of Exposure in Early Life

Fern Tablin of the University of California–Davis and colleagues will investigate the impact of exposure to PM from wildfires and ozone on the immune system at an early age. In particular, they will assess effects on immune responses mediated by a class of proteins known as toll-like receptors and effects on platelet activation and function in peripheral blood. The study will be conducted in two groups of young rhesus macaques maintained at UC–Davis since birth. One group was housed outdoors and thus exposed to ambient air pollution; the other group was housed indoors and is considered to be unexposed. In their two-year study, Tablin and colleagues plan to compare monkeys born before wildfires occurred in the area during July 2008 and the following year, when no major wildfires occurred. Preliminary data showed that PM concentrations in the air during the wildfire period in 2008 were substantially higher than those in the same period in 2009; the levels of ozone did not differ much between the two years. HEI

For more information, contact Maria Costantini (*mcostantini@healtheffects.org*).

CONFERENCE *(Continued from page 1)*

Collaborative Emissions Study (ACES; see related story) has documented improvements in such emissions, and the ACES investigators have recently completed analysis of the first health results (1-, 3- and 12-month exposures) from a comprehensive animal bioassay using exhaust from a new engine. Also, some new studies examining a potential association between human cancer and worker exposure from older diesel engines are becoming available, and new reviews of risk from diesel exposure are under way. This session will review these and other developments and put them into a broader scientific and regulatory context.

Ultrafine Particles: An HEI Perspective. Given continuing interest in the implications of exposure to ultrafine particles, last year HEI convened an expert panel to conduct a critical evaluation of what we know — and don't know — about their potential to harm human health. Their report will soon be published as part of the *HEI Perspectives* series. In this session, panelists will present primary conclusions from their assessment of the sources and factors that contribute to human exposure; the evidence from experimental studies in animals and in human volunteers; and the evidence from observational epidemiologic studies. They will then explore implications for future research.

Long-Term Exposure to Photochemical Oxidants and Chronic Disease. Setting regulatory limits on ambient levels of ozone and estimating the benefits to human health that might result from them pose important questions for both science and policy. Exposure to ozone has been associated with acute adverse health effects and irreversible changes in lung structure and function. When exposure to $PM_{2.5}$ is taken into account, cohort studies find some evidence of an effect of long-term exposure to ozone on mortality from respiratory disease, but little, if any, evidence of effects on cardiovascular mortality. This session will review current knowledge, exploring the strengths and weaknesses of studies of long-term exposure and of approaches for assessing human exposure to ozone and other photochemical oxidants.

Improving Methods for Assessing Exposure to Traffic-Related Pollutants. This session will explore ways for scientists conducting health studies to improve the assessment of exposure to traffic-related pollution. It is intended to build on the findings of HEI's major review of the literature on traffic-related air pollution, published in 2010 (Special Report 17), and lay the groundwork for upcoming deliberations on research needs in this area. Speakers will discuss lessons learned from near-road measurements, the role of local chemistry, and new tools and strategies for collecting exposure data for health studies.

An additional, brief session organized by HEI President Dan Greenbaum and Vice President Robert O'Keefe will inform attendees about regulatory developments in the United States, Europe, and elsewhere. HEI

Program updates and hotel registration information are available at *www.healtheffects.org/annual.htm.*

DIESEL EXHAUST *(Continued from page 1)*

dioxide (NO_2) at 0.35 ppm, or the control atmosphere, filtered air. NO_2 is a major gaseous component of DE, so its effects could be gauged in the absence of DEP. In phase 1, the participants had asthma and were allergic to at least one common aeroallergen. In phase 2, the participants had asthma and were allergic to cat allergen; their responses were evaluated after the administration of cat allergen one hour after the exposure. Several respiratory end points were evaluated, as were inflammatory end points (levels of cells and cytokines in induced sputum and blood) and characteristics of the allergic response (including levels of immunoglobulin E and cytokines such as interleukin 4 in sputum and blood).

Riedl and colleagues reported few associations between exposure to DE and the end points measured. Exposure to DE slightly increased airways' resistance in phase 1 and counts of polymorphonuclear cells and eosinophils in sputum in phase 2. These sparse positive findings suggest that the concentration and duration of exposure in this study may be at or near the lowest levels to cause airway inflammatory effects in people with mild asthma. Exposure to NO_2 resulted in few positive changes in phase 1 and none in phase 2.

The HEI Health Review Committee, in an independent review of the study, noted that it addressed an important issue — the effects of inhalation of DE, a major component of urban ambient air pollution. The committee agreed with the authors that the findings were predominantly negative and did not support the original hypothesis that exposure to DE would enhance inflammatory or allergic-type responses in the lower airways and blood of individuals with asthma. The committee also agreed that caution should be used in extrapolating the findings. For example, persons with more severe asthma, those exposed for longer periods or to higher DE concentrations, or those exposed to DE mixtures from other types of diesel engines or fuels might have different responses.

The committee noted that this lack of response was seen at relatively high levels of diesel emissions – 100 $\mu g/m^3$ – rarely encountered in the ambient air of industrialized countries, though such levels are frequently seen in developing countries. Moreover, the emissions tested came from a 1999 engine with no aftertreatment device. Although such engines are still in operation, their numbers are decreasing in industrialized countries as later-model diesel engines have been introduced that cut back emissions. In addition, starting with model year 2007, diesel engines have been outfitted with devices that reduce PM to very low levels. HEI

Research Report 165 will be available for downloading, free of charge, at *http://pubs.healtheffects.org*; printed copies can be purchased from HEI. For more information, contact Geoffrey Sunshine (*gsunshine@healtheffects.org*).

Health Effects Institute

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HEI is a nonprofit organization funded jointly by government and industry to research and evaluate the health effects of air pollution. An overview of HEI, information on its current research program, and a list of published HEI Research Reports are available on request or from the Web site.

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Some Improvements from Wood Stove Changeout Program

Over the past decade, HEI has funded several studies to evaluate whether actions intended to improve air quality have succeeded in reducing exposure to air pollution and thereby protecting public health; this area is known as "health outcomes" or "accountability" research.

A recent study resulting from this HEI program is described in Research Report 162, *Assessing the Impact of a Wood Stove Replacement Program on Air Quality and Children's Health*. Curtis Noonan of the University of Montana in Missoula and colleagues evaluated a relatively large-scale program to replace about 1200 older wood stoves with new, less polluting stoves in the rural mountain community of Libby, Montana, where residential wood combustion had been identified as a major source of fine particulate matter (PM) during the heating season. Exposure to wood smoke is associated with increased respiratory symptoms in children and adults, decreased lung function in children, and more emergency department visits and hospitalizations. In addition, wood smoke has been classified as "probably carcinogenic in humans" by the International Agency for Research on Cancer.

Noonan and colleagues collected air quality and health data during four consecutive winters starting in 2005, the first year of the changeout program. The majority of changeouts took place during the second and third winters; the fourth winter constituted the post-changeout phase. Additional data were collected retrospectively to cover two baseline winters before the start of the program.

The team measured PM with an aerodynamic diameter of 2.5 μg/m^3 or smaller ($PM_{2.5}$) and some of its components outdoors, inside schools, and in about 20 homes before and after the changeout. They focused on compounds believed to be specific markers for wood smoke, such as levoglucosan, abietic acid, and dehydroabietic acid, and evaluated whether these compounds could be used to track source-specific changes in air quality inside homes as well as in ambient air. In parallel, they tracked respiratory symptoms (as reported by parents) and illness-related school absences.

Ambient winter concentrations of $PM_{2.5}$ gradually declined over the study period and were 30% lower in the final winter after the changeout program than in the baseline years. By the end of the study period, Libby was no longer out of compliance with the National Ambient Air Quality Standard for $PM_{2.5}$. After stove changeout, indoor $PM_{2.5}$ concentrations were lower in a majority of the homes sampled, although there was substantial variability within and between homes. At the elementary and middle schools, indoor concentrations of markers for wood smoke and $PM_{2.5}$ were variable and not consistent with the timing of the changeout program.

Using data from about 1700 surveys filled out by parents of schoolchildren during the four years, Noonan and colleagues reported a significant reduction in childhood wheezing associated with lower winter ambient $PM_{2.5}$ concentrations. The most robust associations were observed for itchy or watery eyes, sore throat, bronchitis, influenza, and throat infection. There were no differences in health outcomes (notably, wheezing) between children from homes with wood stoves and children from homes with other types of heating. Analysis of school absence data showed that reductions in average ambient winter $PM_{2.5}$ concentrations were associated with fewer illness-related absences among older students, yet students in grades 1 through 4 had higher absence rates.

In its independent evaluation, the HEI Review Committee concluded that this study showed that wood stove changeout programs can contribute to community-level improvements in air quality. Generally, air quality inside homes also improves, but stoves remain relatively high emitters compared with oil or gas furnaces, and proper stove operation remains an important determinant of emissions. This study provided some evidence, based on parental surveys, that children's health improved in the community, with evidence for reduced reporting rates for wheezing, itchy or watery eyes, sore throat, bronchitis, influenza, and throat infection. Further research using hospital admission data or more direct outcomes, such as medication use, or biomarkers of exposure and effect would be useful. HEI

Research Report 162 is available for downloading, free of charge, at *http://pubs.healtheffects.org;* printed copies can be purchased from HEI. For more information, contact Annemoon van Erp (*avanerp@healtheffects.org*).

Symposium Sheds Light on Air Toxics Hot Spots

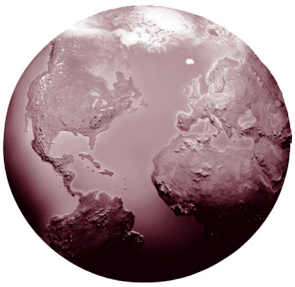
A symposium titled "Air Toxics Hot Spots: Searching for a Definition" was held at the 21st Annual Meeting of the International Society of Exposure Science in Baltimore, Maryland, in October. It was organized by HEI principal scientist Maria Costantini.

The term "hot spot" is generally applied to areas with elevated concentrations of pollutants resulting from nearby sources, including vehicular traffic. The idea for the symposium came from HEI's recently completed research program on air toxics hot spots, which aimed at identifying hot spots where health studies may be conducted in the future. Among the lessons learned from the HEI program is that hot spots should be defined very carefully because of spatial and temporal variation in pollutant levels. Characteristics of the control site (the less polluted site) with which the presumed hot spot is compared also need to be evaluated with caution.

The goal of the symposium was to shed light on characteristics that are important for hot spots. The studies presented were conducted in Camden, New Jersey; Pittsburgh, Pennsylvania; Las Vegas, Nevada; Tianjin, China; and southern California. They were selected because they have some features that were pertinent to the general theme of the symposium, even though they were not necessarily designed to identify hot spots. Discussion of these presentations highlighted some key points:

- there is no common, widely accepted definition of a hot spot;
- the assessment of whether an area is a hot spot depends on whether one is concerned about short- or long-term effects;
- the control, or background, location(s) for "comparison" should be as far as possible from major sources;
- it may be useful to include several background locations to capture the spatial variability of pollutants; and
- the target population at the hot spot should be explicitly identified, possibly with personal exposure measurements.

HEI is interested in understanding pollutant exposure in proximity to traffic hot spots and is planning a workshop for this spring to explore ways to improve the assessment of exposure to traffic-related pollution. HEI



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Workshop Brings Experts Together

Atmospheric Chemists and Health Effects Scientists Discuss Common Goals at HEI

Despite their many common scientific issues and concerns, investigators studying atmospheric science and those assessing the health impact of air pollution generally pursue isolated research programs and rarely collaborate. As a result, even basic knowledge is not always widely shared. In October, leading experts representing both areas met at HEI for a two-day workshop designed to explore the various and multidimensional interactions between their fields of inquiry.

Frank Dentener of the EC Joint Research Center, Ispra, Italy (left), and Ben Armstrong, HEI Review Committee. PHOTOS BY MORGAN YOUNKIN

The workshop was cosponsored by the United Nations World Meteorological Organization, the European Commission's (EC's) ACCENT program (European Network of Excellence on Atmospheric Composition Change), the international Commission on Atmospheric Chemistry and Global Pollution, International Global Atmospheric Chemistry, and HEI. Participants identified the main areas in which integrated research is needed and discussed the benefits for environmental and health policy that would accrue from dealing with air pollution and atmospheric chemistry in a more unified way.

Atmospheric scientists and health effects researchers, including some members of HEI's scientific committees and HEI-funded investigators, provided perspectives on the connections between atmospheric chemistry and health. They summarized recent findings on the role of atmospheric chemistry in epidemiology and toxicology and the health effects of individual and multiple components of the air pollution mixture; they also discussed the current status of and recent advances in atmospheric measurements and modeling most relevant to health effects research.

Representatives of the U.S. Environmental Protection Agency, the World Health Organization, and the EC reviewed ways in which atmospheric science and research on air pollution–related health effects currently inform policy making. They discussed the potential contributions of an integrated research program to address air pollution and issues related to climate change, including the health effects of diverse short-lived greenhouse pollutants such as black carbon, sulfate particles, and ozone.

Workshop participants plan to issue a report with copies of the presentations and prepare a summary of the major conclusions and recommendations for publication in a peer-reviewed journal. HEI

For further information on the workshop, contact Aaron Cohen (*acohen@healtheffects.org*).