HEI HEALTH EFFECTS INSTITUTE

update

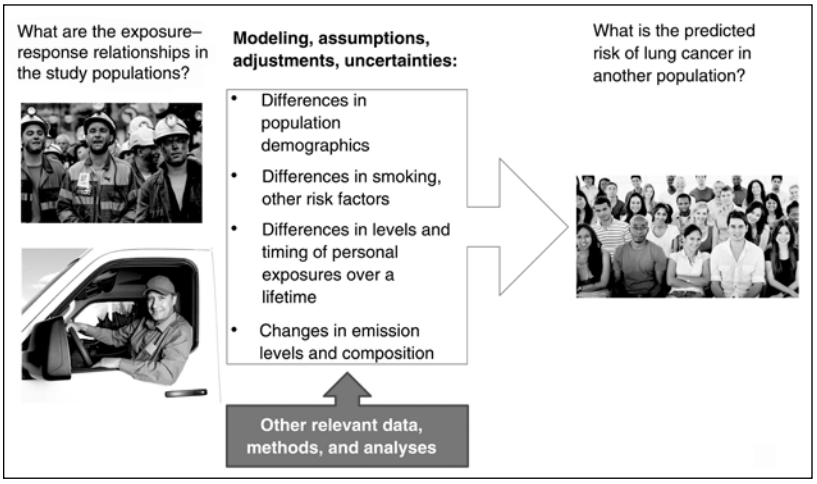
FALL 2015

New HEI Studies to Examine Potential Health Effects at Low-Level Pollution

The HEI Board of Directors has approved two new studies that will investigate the health effects of exposure to low levels of air pollution in large populations. These studies are being funded under a request for applications (RFA) that HEI issued in the fall of 2014; this RFA constitutes the first major activity under HEI's *Strategic Plan for Understanding the Health Effects of Air Pollution 2015–2020*. The RFA attracted 39 preliminary applications. The HEI Research Committee invited the eight candidates with the most promising applications to submit full proposals, from which the two funded studies were selected; a third potential study is still under consideration.

The selected teams are led by Francesca Dominici (Harvard University) and Michael Brauer (University of British Columbia). Their aim is to investigate health effects in millions of people exposed to low levels of air pollution in the United States and Canada, respectively. Their studies will rely on information from Medicaid and Medicare, and the Canadian census. They will use state-of-the-art hybrid exposure models including satellite data, chemical transport models, land use variables, and monitoring data. To evaluate health outcomes, the studies will include information on all-cause and cause-specific mortality and morbidity. They will also develop and apply new methods — related, for example, to errors in

Continued on page 5



This figure from Special Report 19 illustrates the important decisions that need to be made in translating worker health study data to estimation of risks in the general population.

TOP LEFT: © MATTHI/DREAMSTIME.COM; BOTTOM LEFT: © KURHAN/DREAMSTIME.COM; RIGHT: © RAWPIXELIMAGES/DREAMSTIME.COM

Panel Completes Review of Diesel Exhaust Studies

HEI has released Special Report 19, *Diesel Emissions and Lung Cancer: An Evaluation of Recent Epidemiological Evidence for Quantitative Risk Assessment*, the final report of the HEI Diesel Epidemiology Panel. In this new publication, the Panel evaluates two major 2012 studies examining the association between occupational exposure to diesel exhaust and lung-cancer mortality. In the wake of the decision in 2012 by the International Agency for Research on Cancer to recategorize diesel exhaust as a known human carcinogen, HEI had been asked by its sponsors to assess the two studies' potential for use in quantitative risk assessment, the process by which scientists use available evidence to estimate the risk of adverse health

Continued on page 5

Also in This Issue

Research Committee Welcomes Three New Members

Experts in air pollution science, biostatistics, and toxicology were recently appointed by the HEI Board of Directors as members of the HEI Research Committee, the multidisciplinary group that develops and oversees the institute's research program.

Jeffrey R. Brook is a senior scientist for the Canadian Ministry of the Environment's Air Quality Research Division. A leading expert on air quality, he has long been interested in air pollution science and policy as well as exposure and risk assessment. He has served on expert panels and committees advising the Canadian government, the California Air Resources Board, and the U.S. Environmental Protection Agency, along with HEI.

Jeffrey R. Brook.
PHOTO BY JAY MALLIN

Brook received his master's and doctoral degrees at the University of Michigan. In addition to his appointment at Environment Canada, he is a faculty member at the University of Toronto in the Dalla Lana School of Public Health and the Department of Chemical Engineering and Applied Chemistry. He also has a leading role at AllerGen, a Canadian government-sponsored, multi-university organization geared toward understanding, treating, and preventing asthma and allergy.

Brook has published and lectured widely and has led or co-led a range of epidemiological, toxicological, and clinical health effects studies. His research focuses on air pollution, its sources, its movement in the atmosphere, and its effects. Brook's team develops and deploys advanced mobile laboratories for measuring particulate and gaseous air pollutants and meteorological conditions. His recent studies have focused on regional- to local-scale interactions between air pollutants and meteorology, intra-urban pollutant patterns, assessment of air pollution from traffic, and near-road gas-particle processes. He is currently leading studies examining the impacts of oil and gas development on air pollutant levels and community exposure. This has led to a new and growing research program in partnership with Canadian Aboriginal communities.

Amy H. Herring is the Carol Remmer Angle Distinguished Professor of Children's Environmental Health and associate chair in the Department of Biostatistics, Gillings School of Global Public Health, at the University of North Carolina (UNC) at Chapel Hill. In addition, she is an elected faculty fellow at UNC's Carolina Population Center, where she conducts research using new statistical methods and innovative applications of statistics in public health and medicine. She is an elected fellow of the American Statistical Association (ASA), the new chair-elect of the ASA Biometrics Section, and a past president of the International Biometric Society's Eastern North American Region (ENAR). She currently serves as associate editor of the *Journal of the American Statistical Association* (Applications and Case Studies) and is on the editorial board of *Environmental Health Perspectives.* Herring has authored and coauthored more than 200 peer-reviewed publications related to statistical methodology, public health, and medicine and is currently the principal investigator of a 5-year project, funded by the National Institutes of Health, exploring Bayesian methods for high-dimensional epidemiological data. Her long-standing research interests include environmental health science, reproductive epidemiology, maternal and child health, neonatology, nutrition, and obesity. Herring is a former winner of the American Public Health Association's Mortimer Spiegelman Award for Outstanding Public Health Statistician and the Gertrude Cox Award conferred by the Research Triangle Institute (RTI International) and the Washington Statistical Society. Herring earned her doctor of science degree in biostatistics at Harvard University.

Amy H. Herring.

Ivan Rusyn is a professor in the Department of Veterinary Integrative Biosciences, College of Veterinary Medicine & Biomedical Sciences, at Texas A&M University. Previously he was a professor of environmental sciences and engineering at the University of North Carolina (UNC) at Chapel Hill, where he also served as an associate director of the Curriculum in Toxicology and deputy director of the UNC Superfund Research Program. His work focuses on the mechanisms of chemical toxicity, the genetic determinants of susceptibility to toxicant-induced disease, and computational toxicology. His studies on health effects of chemical agents have resulted in more than 160 peer-reviewed publications. He has served on many national scientific committees and is currently a member of the National Research Council's Standing Committee on Use of Emerging Science for Environmental Health Decisions, Committee on Toxicology, and its Committee on Incorporating 21st Century Science in Risk-Based Evaluations. Rusyn also served on several monograph working groups of the World Health Organization's International Agency for Research on Cancer. In addition, he is on the Board of the Scientific Counselors of the United States National Institute of Environmental Health Sciences and the Science Advisory Board for the North Carolina Department of Environment and Natural Resources.

Ivan Rusyn.
PHOTO BY JAY MALLIN

Rusyn received a doctor of medicine degree from Ukrainian State Medical University in Kiev and a Ph.D. in toxicology from UNC–Chapel Hill. He conducted postdoctoral research at the Massachusetts Institute of Technology and Heinrich Heine University in Düsseldorf, Germany, where he was a Deutscher Akademischer Austauschdienst (DAAD) fellow.

Mark Your Calendar! HEI Annual Conference

May 1–3, 2016 • Denver, Colorado

WHO Plans Update of Global Air Quality Guidelines

In September, HEI President Dan Greenbaum and HEI Principal Scientist Aaron Cohen participated in a three-day expert consultation at the World Health Organization's (WHO's) European Centre for Environment and Health in Bonn, Germany, to help advise the WHO as it plans an update of its Global Air Quality Guidelines. These guidelines provide critical benchmarks for health-based risk management and environmental policy around the world. At the meeting, attended by more than 40 scientific and technical experts from major WHO regions, along with representatives of organizations such as the U.S. Environmental Protection Agency and the European Commission, participants discussed the latest available evidence on health effects of ambient air pollution and the implications for the next update of the guidelines, and considered the scope and conduct of the update, which is expected to take three years to complete.

The WHO guidelines for air quality are presented in a set of several volumes, which propose recommendations for risk assessment and risk management of a variety of pollutants — including particulate matter (PM) and gaseous emissions — in both ambient and indoor air. For ambient air, the last update of the guidelines, released in 2005, specifies levels for five pollutants, $PM_{2.5}$, PM_{10}, ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2). If achieved, these levels "would be expected to result in significantly reduced rates of adverse health effects," as stated in WHO's *Air Quality Guidelines Global Update 2005*. Those current guidelines, developed by many of the world's leading scientific experts on air pollution, were based on the scientific evidence available at the time. In the intervening years the evidence has grown with the publication of many new epidemiological studies, including studies in previously underrepresented regions such as East and South Asia; the emergence of evidence on previously unstudied health outcomes, including neurological effects; and the development of a richer database of toxicological evidence in animals and humans. Recent estimates from the Global Burden of Disease collaboration and WHO indicate that air pollution is now among the leading risk factors for premature mortality worldwide, providing a strong basis for revisiting the current guidelines to ensure that they remain effective public health tools.

The United Nations tower in Bonn, Germany, houses the World Health Organization's European Centre for Environment and Health. MICHAEL SONDERMANN/BUNDESSTADT BONN

At the meeting in Bonn, the experts agreed that the new scientific evidence warrants an update of the current guidelines for PM, O_3, NO_2, and SO_2, and that earlier guidelines for carbon monoxide should be updated as well. In addition, they reviewed the evidence for more than 20 chemical air pollutants present in ambient air, for which WHO has developed guidelines in the past. Their review and discussions will inform the process for developing the next update of the guidelines, which will be based on systematic reviews of the scientific literature conducted by leading experts according to established WHO protocols.

HEI staff played key roles in the design and conduct of the 2005 Global Air Quality Guidelines, and HEI-funded research figured prominently in evidence informing the guidelines for PM and other pollutants. The institute will contribute to the new update through such efforts as the estimation of the global burden of disease due to ambient air pollution and its major sources, recent and ongoing HEI research, and HEI's "Accountability" program, which generates systematic reviews of research on the health impacts of actions taken to improve air quality.

For additional information on the WHO Global Air Quality Guidelines and the planned update, contact Aaron Cohen (acohen@healtheffects.org).

NEW HEI RESEARCH REPORT

A Closer Look at Exposure to $PM_{2.5}$ and Its Composition

Many epidemiological studies rely on outdoor concentrations of air pollutants recorded at one or a few central or fixed site monitors as a surrogate for human exposure. Yet people spend a majority of their time indoors. In addition, certain activities — such as driving, cooking, and smoking — can contribute substantially to each person's exposure. HEI's Relationships of Indoor, Outdoor, and Personal Air (RIOPA) study, published in two parts, in 2005 and 2007, addressed the challenge of understanding how different sources contribute to individual exposure to $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 µm or smaller) and its composition. Subsequently, HEI funded the posting of all of the RIOPA data on the Web for any investigator to use, and solicited and funded two HEI studies to apply new and innovative statistical methods to analyze this rich data set. The first study, led by Stuart Batterman from the University of Michigan–Ann Arbor, was published in 2014 (HEI Research Report 181). Results from the second study, by Patrick Ryan and colleagues from Cincinnati Children's Hospital, will appear in HEI Research Report 185, *Analysis of Personal and Home Characteristics Associated with the Elemental Composition of $PM_{2.5}$ in Indoor, Outdoor, and Personal Air in the RIOPA Study,* which HEI expects to release this December.

Ryan and his team analyzed RIOPA data to explore relationships among elemental concentrations of personal, indoor, and outdoor $PM_{2.5}$ samples. The investigators found that outdoor concentrations did not represent personal exposures well for elements other than the ones associated with long-range transport, such as sulfur and vanadium. The addition of indoor concentrations and personal and home characteristics did not improve the prediction of personal exposure for most elements.

In its independent review of the study, the HEI Review Committee concluded that the authors conducted an extensive set of analyses. However, they urged caution in interpretation of the results because important clustering in the data was not accounted for, the number of predictor variables in the models was large, and the influence of outlier values was not tested. Studies such as RIOPA remain useful for quantifying exposure measurement error, the committee said, and ultimately should be taken into account in health analyses.

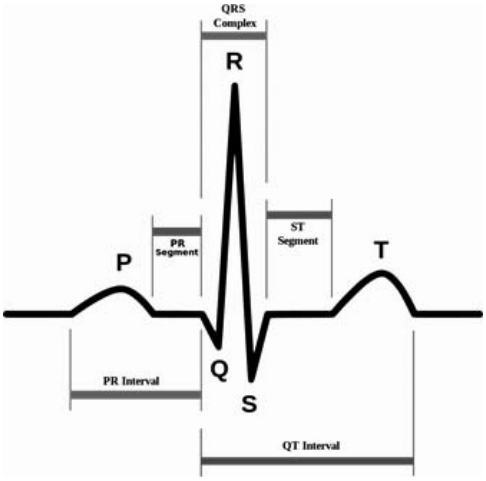
Research Report 185 will soon be available for downloading, free of charge, at http://pubs.healtheffects.org; printed copies can be purchased from HEI. For more information, contact Hanna Boogaard, jboogaard@healtheffects.org. The RIOPA Database is available at https://riopa.aer.com/login.php.

NEW HEI RESEARCH REPORT

Study Evaluates Rapid Heart Rhythm Changes After PM Exposure

A number of epidemiological studies have reported that exposure to airborne particulate matter (PM) is associated with higher rates of cardiovascular mortality and hospitalization in older adults and in people whose health is compromised, such as those with lung or heart disease. Research aimed at identifying the mechanisms of the observed associations has shown that short-term exposures to PM and other pollutants can cause changes in cardiac rhythm, which can be readily and non-invasively measured by recording an electrocardiogram (ECG) and examining features such as beat-to-beat fluctuations in heart rate, referred to as heart rate variability (HRV).

In a soon-to-be-released HEI report, David Q. Rich of the University of Rochester School of Medicine and Dentistry, Annette Peters of Helmholtz Zentrum München–German Research Center for Environmental Health, and their colleagues set out to evaluate how soon after exposure to PM the changes in heart rhythm can be observed. Specifically, they analyzed the ECGs of more than 200 individuals in relation to exposure to ultrafine particles (UFPs) and fine particles ($PM_{2.5}$, or PM with an aerodynamic diameter ≤ 2.5 µm) in the previous 6 hours. They focused on three ECG variables: standard deviation of normal-to-normal beat intervals (SDNN), a marker of total HRV; root mean square of the successive differences (RMSSD), a marker of parasympathetic regulation; and T-wave complexity, a marker of cardiac repolarization. They reanalyzed existing ECGs from four previous studies conducted by their teams:



This figure, which appears in the report's Critique, shows the "waves" typically observed in a single heart beat in a healthy adult. WIKIMEDIA COMMONS

- a panel study of individuals with diabetes or impaired glucose tolerance and individuals with a genetic susceptibility to oxidative stress, conducted in Augsburg, Germany;
- a panel study of patients with a history of acute coronary artery disease, conducted in Rochester, New York; and
- two controlled ultrafine exposure studies of healthy volunteers and volunteers with diabetes.

The results will appear in HEI Research Report 186, *Ambient and Controlled Particle Exposures in Association with Rapid ECG Changes.*

Rich, Peters, and their colleagues found that increased exposure to fine PM during the previous 2 to 5 hours was associated with changes in SDNN and RMSSD but not with T wave complexity; increased exposure to ultrafine PM in the same period was associated with changes in SDNN but not with the other two markers. However, very recent exposures (occurring less than one hour before observation) were not associated with any ECG changes.

In its independent assessment of the study, the Review Committee concluded that it was carefully conducted and made efficient use of existing data to address important questions regarding the associations between markers of cardiac function and recent exposure to fine and ultrafine PM. While noting some limitations in the study, the committee also noted that the observed associations, although not likely to be of clinical significance, provide evidence of particle-related subclinical physiological changes. Whereas the study provides evidence of effects on some cardiac markers following exposure to both fine and ultrafine PM, it remains unclear whether the effects of ultrafine PM are independent from those of fine PM. The committee also said that the results of this study increase its confidence in the use of HRV parameters as intermediate markers for the association between air pollution and cardiovascular outcomes. HEI

HEI Research Report 186 will soon be available for downloading, free of charge, at http://pubs.healtheffects.org; printed copies can be purchased from HEI. For more information, contact Maria Costantini (mcostantini@healtheffects.org).

New Look for HEI Web Site

Watch for HEI's redesigned Web site in 2016, user-friendly and aimed to more effectively engage and inform our online visitors. New features include topics pages to guide you to specific research programs — such as those on ozone, technology, accountability, and oil and gas — and quick links to specific documents and other important information. The renovated site will also be adapted for mobile platforms and will provide easy links to social media. HEI

Health Effects Institute

101 Federal Street, Suite 500
Boston, MA 02110-1817, USA
Phone: +1-617-488-2300
Fax: +1-617-488-2335
www.healtheffects.org

Richard F. Celeste, *Chair, Board of Directors*
Daniel S. Greenbaum, *President*

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 all published HEI reports are available for downloading, free of charge, from the Web site.

Production Staff for *Update:*

Hilary Selby Polk, *Managing Editor*
Hope Green, *Editor*
Annemoon M.M. van Erp, *Webmaster*
Sarah Benckart, *Web Assistant*
Ruth E. Shaw, Cameographics, *Layout and Composition*

DIESEL EXHAUST *(Continued from page 1)*

effects or other outcomes that might result when people are exposed to different concentrations of an agent.

On the whole, the Panel found the epidemiological information generated from both studies to be relevant and informative for quantitative risk assessments, even though each study has limitations that need to be carefully considered as part of that process.

For this project, the institute appointed the nine-member Diesel Epidemiology Panel (see *HEI Update*, Spring 2013), chaired by Daniel Krewski, a professor of epidemiology at the University of Ottawa and an internationally recognized authority in risk assessment. The first study the Panel looked at, the Diesel Exhaust in Miners Study (DEMS), was conducted by the National Cancer Institute (NCI) and the National Institute for Occupational Safety and Health (NIOSH) and involved a cohort of more than 12,000 U.S. nonmetal miners. It was led by Debra Silverman of NCI and Michael Attfield of ERS Inc. (formerly of NIOSH) in Morgantown, West Virginia. The second, conducted by Eric Garshick of the U.S. Department of Veterans Affairs Boston Healthcare System and Harvard University and his colleagues, was a retrospective cohort study among about 50,000 male workers employed in the unionized U.S. trucking industry. To reach its conclusions, the Panel carefully evaluated the studies, reviewed various critiques of their findings, and conducted new analyses of the DEMS data. HEI held a public meeting to discuss the studies and to hear presentations by the original investigators, by other scientists with relevant expertise in risk assessment, and by investigators who had conducted additional analyses in the DEMS data sets with funding from an industry consortium coordinated by the Engine Manufacturers Association (EMA).

The Panel concluded that both studies were well designed and conducted, with attributes considered important for quantitative risk assessment. More specifically, where diesel exhaust is concerned, the two studies were designed to address most, if not all, of the major limitations of previous epidemiological studies of diesel exhaust and lung cancer. These limitations related to the quality and specificity of exposure measurements for diesel exhaust, the lack of quantitative estimates of personal exposure with which to estimate the exposure–response relationship, and the inability of the prior studies to account for exposures that might otherwise explain the relationship observed between diesel exhaust and lung cancer, particularly individual smoking habits.

The Panel also recognized a number of limitations, or sources of uncertainty, in each of the 2012 studies that warrant consideration in their use for quantitative risk assessment. For example, given the need to reconstruct historical exposures to workers in both studies, the actual exposures experienced cannot be known with absolute certainty. In the truckers cohort study, information on individual smoking habits was not available as it was in the DEMS case-control study. The limitations, in the Panel's view, do not undermine the basic integrity of the studies and their findings. What matters is that the studies and their data allow for exploration and communication of the nature and magnitude of the potential uncertainties in evaluating exposures to diesel exhaust.

Although the Panel considered the evidence generated by these studies to be informative for estimating the risk of human lung cancer in relation to exposure to diesel exhaust, it recognized that they are only part of a more comprehensive quantitative risk assessment process. It is unrealistic, the Panel said, to expect that individual findings from these studies would be universally applicable or could have anticipated all the issues involved in extrapolating the results of the studies to other populations, time periods, and exposure conditions, including different diesel-exhaust technologies. A more comprehensive process would probably include other scientific evidence, as well as other analyses to understand how to translate risk estimates from these predominantly male, white workers, exposed during a working lifetime, to different patterns of exposure to diesel exhaust in the general population. The Panel said that future risk assessment would also need to take into account the changing levels and characteristics of diesel exhaust that have occurred in response to a long history of regulations of diesel engines, and that may, therefore, differ notably from those in the miners and truckers studies, which cover the past several decades.

The Panel's report underwent extensive peer review by scientists not involved in the studies and reflects comments received from the original investigators of both studies, as well as from the EMA analysts. The Panel also acknowledged many useful comments it received following its presentation of the main conclusions at the HEI Annual Conference last May. HEI

HEI Special Report 19 is available for downloading, free of charge, at *http://pubs.healtheffects.org*; printed copies can be purchased from HEI. For more information, contact Katherine Walker (*kwalker@healtheffects.org*).

HEI in Beijing

HEI President Dan Greenbaum presented the first results of HEI's Global Burden of Disease from Major Air Pollution Sources project (GBD MAPS; see *HEI Update*, Fall 2014) to 250 science and policy leaders at the International Workshop on China Coal Cap Strategy, held in Beijing on November 4.

COURTESY OF NATURAL RESOURCES DEFENSE COUNCIL

LOW-LEVEL POLLUTION *(Continued from page 1)*

measuring exposure — and apply direct and indirect approaches to correct risk estimates for the effects of important potential confounding variables, such as smoking. The Dominici team will also develop and apply methods to examine causality of associations.

To ensure the highest standards in soliciting and selecting the studies, HEI established a panel of outside experts, chaired by Jonathan Samet of the University of Southern California, to evaluate the proposals for these studies and advise the Research Committee, which is responsible for selecting projects for institute funding, on their scientific merits. Members of HEI's standing scientific committees who might be among those who applied did not participate in any stage of the RFA writing or study selection process. The independent review panel and the Research Committee met in the early fall and conducted detailed reviews of all the submitted proposals, leading to the selection of the Brauer and Dominici teams and a possible third.

Health Effects Institute

101 Federal Street, Suite 500
Boston, MA 02110-1817

HEI Announces Recipient of 2015 Walter A. Rosenblith New Investigator Award

Kymberly Gowdy, assistant professor in the Brody School of Medicine, East Carolina University, Greenville, North Carolina, has been selected as the recipient of HEI's 2015 Walter A. Rosenblith New Investigator Award for her proposal "Scavenger Receptor B1 Regulates Oxidized Lipid Driven Pulmonary and Vascular Inflammation After Ozone Exposure." Gowdy received a Ph.D. in immunology and toxicology from North Carolina State University and subsequently conducted postdoctoral research at Duke University and the National Institute of Environmental Health Sciences. She joined the faculty of the Department of Pharmacology and Toxicology at East Carolina University in 2014. Gowdy was recognized earlier this year by the American Association of Immunologists with both a Young Investigator Award and a Travel for Techniques Award.

Gowdy's research focuses on how exposure to agents in the environment, such as air pollutants, affects responses in the lung and elsewhere in the body and how it may increase susceptibility to chronic diseases. The objective of her Rosenblith Award study is to address the role of scavenger receptor-B1 (SR-B1) in ozone-induced lung injury and in subsequent development of cardiovascular disease. SR-B1 is a receptor for high-density lipoprotein cholesterol (HDL) and mediates cholesterol transfer to and from HDL. SR-B1 also binds oxidized phospholipids, which are formed in response to reactive oxygen species under many conditions, including atherosclerosis.

Kymberly Gowdy.

Gowdy hypothesizes that the clearance of oxidized phospholipids in the lung during ozone exposure is mediated by SR-B1. She further hypothesizes that the lack of clearance of these oxidized phospholipids will lead to their translocation through the bloodstream, resulting in vascular inflammation and ultimately cardiovascular disease. The studies will be performed by exposing normal mice, as well as mice lacking the SR-B1 gene (SR-B1 knockout mice), to ozone in inhalation chambers and measuring levels of oxidized phospholipids along with multiple markers of pulmonary and vascular function. This study could shed new light on the mechanisms by which exposure to ozone may induce injury, both in the lung and in the circulatory system.

Named for the first chair of the HEI Research Committee, the Rosenblith award supports the work of a promising scientist early in his or her career. In selecting award recipients, the committee considers each applicant's potential for a productive research career in examining air pollution and its effects on health, the support provided by the applicant's institution, and the scientific merit of the research project and its relevance to HEI's mission. The committee also felt that Gowdy had an excellent group of mentors, both inside and outside her institution, who would make a valuable contribution to her training — a further key component of the award decision process. Gowdy is the 21st scientist to receive the Rosenblith Award since the inception of the program in 1999 (see the list of awardees at *www.healtheffects.org/rosenblith.htm*).