



HEALTH  
EFFECTS  
INSTITUTE

December 2000

# Request for Applications

## Fall 2000 Research Agenda

**RFA 00-1 Effects of Diesel Exhaust and Other Particles on the Exacerbation of Asthma and Other Allergic Diseases**

**RFA 00-2 Walter A. Rosenblith New Investigator Award**

**RFPA 00-3 Health Effects of Air Pollution**





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# THE HEALTH EFFECTS – FALL 2000 RESEARCH AGENDA

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# INTRODUCTION

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## INTRODUCTION

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This booklet contains the Fall 2000 Research Agenda of the Health Effects Institute (HEI). We thank you for your interest in HEI and its research program. The areas of research for which the Institute is requesting applications at this time are described below.

**REQUEST FOR APPLICATIONS 00-1:  
EFFECTS OF DIESEL EXHAUST AND OTHER  
PARTICLES ON THE EXACERBATION OF ASTHMA  
AND OTHER ALLERGIC DISEASES**

Request for Application (RFA) 00-1 on pages 5-11, solicits applications for research to (1) investigate whether exposure to diesel exhaust particles (DEP) is associated with exacerbation of asthma and other allergic diseases; (2) determine whether particulate matter from other sources (for example gasoline engines, natural gas engines, power plants, crustal dust, etc.) has effects similar to those induced by DEP; and (3) investigate the mechanisms that may lead to the effects observed.

Letters of Intent for RFA 00-1 are due on February 14, 2001; applications are due on April 11, 2001.

**REQUEST FOR APPLICATIONS 00-2:  
WALTER A. ROSENBLITH NEW INVESTIGATOR  
AWARD**

The purpose of this award, on page 17, is to bring new, creative investigators into active research on the health effects of air pollution. It will provide 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. For information on HEI's current research priorities, applicants should consult Appendix A. HEI expects to provide one award from this RFA this year and to continue the award on an annual basis. The evaluation process for these applications will consider the qualifications and background of the applicant, the quality and relevance of the research proposal, and the research environment of the applicant.

Letters of Intent for RFA 00-2 are due on February 14, 2001; applications are due on April 11, 2001.

**REQUEST FOR PRELIMINARY APPLICATIONS 00-3:  
HEALTH EFFECTS OF AIR POLLUTION**

The Request for Preliminary Applications 00-3, on pages 23-24, provides an application mechanism for investigators whose area of interest falls outside the topics targeted in other current research requests, but is relevant to HEI's current priorities. For information on HEI's current priorities, applicants should consult Appendix A.

This year we have changed the Preliminary Application process in that the HEI Research Committee will be reviewing Preliminary Applications only once during the next year. The deadline for submission is August 31, 2001. The HEI Research Committee will review them at its fall 2001 meeting and request full applications for those considered most relevant to the needs of the Institute.

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## WHAT IS HEI?

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HEI is a public–private partnership established in 1980 to provide decision makers, scientists, and the public with high quality, impartial, and relevant scientific information that helps answer key questions about the health effects of emissions from motor vehicles and other sources in the environment. The idea for the Institute grew from the debate between the Environmental Protection Agency and the automotive industry concerning the certification requirements in the 1977 Clean Air Act Amendments. As a result, EPA and industry representatives cooperated to establish an independent institution to carry out the much-needed health-related research. The intent of the Health Effects Institute has been to develop the facts concerning health effects carefully and credibly so that controversy about the facts themselves will be removed from the adversarial agenda and the debates over clean air can instead focus on national policy issues.

HEI is an unusual model of government-industry collaboration in support of research. The Institute receives half of its core funds from the U.S. Environmental Protection Agency and half from twenty-eight manufacturers or marketers of motor vehicles or engines in the United States. HEI also periodically receives funding from other organizations, including the U.S. and European chemical and oil industries, the European Commission, and the California Air Resources Board to supplement its funding for some of its research programs. The Institute has developed consultation processes with its sponsors and others to help focus its research priorities. However, none of the contributors has control over the selection, conduct, or management of HEI studies, and HEI makes no recommendations on how to apply research to regulatory policy.

The Institute's autonomy is supported, even beyond the statements in its charter, by the integrity and commitment of both its scientific leadership and its Board of Directors. Subject to the approval of the Board of Directors, the work of the Institute is carried out by two external and independent Committees for research and review, each consisting of distinguished scientists knowledgeable about the scientific issues inherent to investigating the health effects of air pollutants. HEI's staff works with Committee members in carrying out the work of the Institute.

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## HOW DOES HEI WORK?

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After seeking advice from HEI's sponsors and others interested in its work, the HEI Research Committee determines the research priorities of the Institute. When an area of inquiry has been defined, the Institute announces to the scientific community that applications are being solicited on specific topics by issuing requests for applications such as those in this booklet. Applications are reviewed first for scientific quality by an ad hoc panel of appropriate experts. They are then reviewed by the HEI Research Committee both for quality and relevance to the goals of the research program.

Before a study is recommended for funding, there is often a negotiation period in which the investigators may be asked to address the reviewers' comments or modify the study design or budget. Studies recommended by the Research Committee undergo final approval by the Board of Directors, which also reviews the procedures, independence, and quality of the selection process. HEI's mechanism for providing funds to its investigators is a cost-reimbursement contract (Research Agreement) containing a Statement of Work, which is a description of the work to be performed in each contract year, and a budget. Because HEI is sensitive to the fact that research may generate unexpected results leading to a need for a change in the scope of work, HEI's contracts can be amended upon agreement by both parties.

During the course of each study, the Research Committee and scientific staff maintain close contact with HEI-funded investigators by means of progress reports, site visits, workshops, and the HEI Annual Conference. The ten-month progress report serves as the basis for contract renewal for multi-year projects. A site visit is conducted to many investigators' laboratories, not only to assess the conduct of the study, but also to provide an opportunity for discussion and exchange of ideas. At the annual conference, HEI investigators, Research Committee and Review Committee members, HEI staff, representatives of sponsor organizations, and invited guests meet to share information and develop new ties to strengthen the HEI community of scholars. A more detailed description of the relationship between HEI and investigators can be found on pages 29-32.

In order to fulfill its mission of providing timely, high-quality research results for decision makers, HEI has developed a rigorous review process to evaluate results of the research it funds. When a study is completed, the investigator is required to submit a comprehensive final

report. The HEI Review Committee, which has no role in the review of applications or in the selection of projects, assesses the scientific quality of each completed study and evaluates its contribution to unresolved scientific questions. The investigator's Final Report and the Commentary of the Review Committee are published together by HEI. Additionally, all HEI investigators are urged to publish the results of their work in the peer-reviewed literature. More information on the final report and review process can be found on page 31.

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## THE HEI RESEARCH PROGRAM

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The HEI research program has addressed many important questions about the health effects of a variety of pollutants, including carbon monoxide, methanol, diesel exhaust particles, nitrogen oxides, and ozone. The current research program focuses on air toxics and ambient particles. HEI has funded studies to understand the mechanisms of diseases, to develop better methods to assess health effects and determine exposure and dose, and to address issues common to many pollutants. The program has included theoretical, in vitro, animal, controlled human exposure, and epidemiologic studies. The choices of which pollutants to study or scientific questions to investigate have been made based on many considerations, including evaluation of issues raised by sponsors and analysis of the regulatory needs and uncertainties about health effects of specific pollutants. HEI has, on some occasions, produced special reports to evaluate the state of existing science in areas related to policy and to determine research needs in new areas.

In February 2000, after extensive consultation with sponsors, scientists, and other constituents, HEI issued a new five-year plan, the *HEI Strategic Plan for the Health Effects of Air Pollution 2000-2005*, which describes research priorities and plans for implementing them. This plan has an overarching theme of an international perspective for HEI's work, based on the increasingly global nature of industry and of environmental issues. HEI's plan lays out three key scientific areas for research and assessment: (1) the air pollution mixture, with a focus on three submixtures—particulate matter and gaseous pollutants, diesel exhaust, and air toxics; (2) health effects of emerging technologies; and (3) the impact of air quality regulations on public health (accountability). For more detailed information, please see Appendix A, pages 63-74, which provides sections from HEI's current strategic plan on research priorities and plans for implementing them.

The problems associated with the evaluation of the health effects of mobile source emissions are complicated, as researchers who have devoted their efforts to this field are well aware. The resolution of questions pertaining to the effect on health of relatively low levels of these complex mixtures is perhaps a more challenging area of scientific investigation than is often realized by industry, policymakers, or the general scientific community. HEI seeks to develop a community of scientists and scholars who can generate new collaborations and fresh approaches to the problems of air pollution. To this end, HEI has funded both established investigators and newcomers, attracting a number of scientists into this area who did not work in it before.

## REQUEST FOR APPLICATIONS 00-1

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### RFA 00-1: EFFECTS OF DIESEL EXHAUST AND OTHER PARTICLES ON THE EXACERBATION OF ASTHMA AND OTHER ALLERGIC DISEASES

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#### INTRODUCTION

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Over the last two decades, evidence has accumulated suggesting that short-term exposure to urban particulate matter (PM) pollution, which includes particles from different sources and with varying composition, may be associated with effects on the cardiovascular and respiratory systems (reviewed by Pope and Dockery 1999). One of the respiratory conditions believed to be affected by exposure to PM is asthma (Koren and Utell 1997).

Ambient particles tend to fall in a trimodal distribution of coarse (with a diameter greater than 1  $\mu\text{m}$ ), fine (with a diameter of 0.1 to 1  $\mu\text{m}$ ), and ultrafine (with a diameter less than 0.1  $\mu\text{m}$ ). Because of concerns about health effects, the ambient levels of both coarse and fine PM are regulated by the US EPA through the National Ambient Air Quality Standards for PM<sub>10</sub> (particles smaller than 10  $\mu\text{m}$ ) and PM<sub>2.5</sub> (smaller than 2.5  $\mu\text{m}$  in diameter) (Federal Register 1997). PM<sub>2.5</sub> (which includes fine and ultrafine particles) is dominated by emissions from combustion processes; PM<sub>10</sub> (which includes coarse, fine, and ultrafine particles) comprises a much higher proportion of particles generated by mechanical processes from a variety of noncombustion sources. It is currently not clear how much particles of different sizes and composition differ in their effects.

Diesel engines are an important part of the world's transportation and industrial infrastructure and are one of a number of contributors to the fine PM mass and to the ultrafine PM number in urban areas. Particles from diesel exhaust (DEP) are composed of a carbon core onto which sulfate, nitrate, metals, and organic compounds are adsorbed. Compared to gasoline engines, diesel engines are more efficient and emit less CO<sub>2</sub> (a greenhouse gas) per unit work done, but produce more oxides of nitrogen (NO<sub>x</sub>) and PM. Increasingly more stringent emission standards have resulted in decreasing levels of diesel engine particulate and gaseous mass emissions. However, levels of PM and NO<sub>x</sub> from diesel engines still remain a health concern.

To date, the primary focus of diesel health risk assessment has been the effects of long-term exposure to diesel exhaust on cancer. These effects have been extensively investigated and reviewed by HEI and others (US Environmental Protection Agency 1999; Cohen and

Nikula 1999; Office of Environmental Health Hazard Assessment 1998; Health Effects Institute 1995).

More recently, a number of studies have suggested that the effects of short-term exposure to diesel exhaust particles on the respiratory and immune system, particularly in individuals with asthma and other allergic diseases, may also be of concern. At the same time, some of these studies have suggested that other types of particles also contribute to these effects. The role of diesel exhaust and of other particles in these effects needs further investigation.

**The objective of this RFA is to better understand whether DEP and particles from other sources may contribute to the frequency and severity of asthma attacks and the exacerbation of allergic responses, especially in susceptible populations such as children, the elderly, or patients disabled by chronic diseases.**

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#### SCIENTIFIC BACKGROUND

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This section summarizes some of the research conducted to assess the effects of DEP and other PM, including DEP, on asthma morbidity and the possible role of PM in exacerbating allergic diseases. A brief overview of allergic airway diseases is provided as background to the studies discussed.

#### ASTHMA AND RHINITIS

Asthma is a chronic obstructive and inflammatory disease of the lower airways characterized by reversible airways obstruction, mucus hypersecretion, augmented bronchial hyperresponsiveness (with wheezing) to a variety of stimuli, and inflammation. The most prevalent form of asthma in children and young adults is referred to as "allergic asthma" (American Thoracic Society Workshop 1999) and is characterized by the production of cytokines (such as IL-4, IL-5, and IL-10) synthesized by the TH2 subset of CD4+ T lymphocytes, which trigger IgE production by B cells and recruitment of eosinophils. Allergic asthma is associated with more severe responses to allergens (hypersensitivity or atopy) and a tendency to airway hyperresponsiveness (increased non-specific responsiveness).

The prevalence and severity of asthma has increased worldwide in the last 20 years. In the United States

asthma morbidity and mortality are disproportionately high among minority children living in inner cities (Eggleston et al. 1999; Koren and Utell 1997). The reasons for this increase are not well understood, but are likely to involve the complex interplay of genetic, socio-economic, behavioral, and environmental factors. Some environmental factors believed to be associated with the exacerbation (and possibly the onset) of asthma are environmental tobacco smoke (Eggleston et al. 1999) and indoor allergens of dust mites, pollens, and cockroaches (Rosenstreich et al 1997; Malveaux and Fletcher-Vincent 1995; van der Heide 1994; Von Mutius et al. 1994; Sporik et al. 1990; Lau et al. 1989; Platts-Mills et al. 1989).

Exposure to air pollutants has also been associated with increased asthma morbidity either from a direct effect on the airways (such as non specific airway reactivity, inflammation, and bronchospasm discussed above) or from enhancement of the response to specific allergens (Eggleston et al. 1999, Koren and Utell 1997). A possible explanation for the increased susceptibility of asthmatic airways to air pollutants is that these airways produce more of specific types of inflammatory mediators (Devalia et al. 1999).

Allergic rhinitis (characterized by nasal obstruction) is another respiratory disease that has some features common to asthma in terms of pathogenesis, incidence, and prevalence, and is sometimes associated with asthma (American Thoracic Society Workshop 1999).

#### **EPIDEMIOLOGIC STUDIES OF THE EFFECTS OF TRAFFIC-RELATED AIR POLLUTION ON ASTHMA AND OTHER ALLERGIC DISEASES**

Several investigators have studied whether exposure to traffic-related air pollution may affect lung function (Brunekreef et al. 1997) and contribute to the exacerbation of asthma or allergic rhinitis (Wjst et al. 1993, Weiland et al. 1994, Edwards et al. 1994, vanVliet et al. 1997) in children. These studies were conducted in different locations using different approaches to estimating exposure. For example Wjst and colleagues used the traffic volume near schools in Munich, Germany, as an estimate of exposure and Edwards and colleagues considered the proximity of a child's residence to a high traffic area in Birmingham, United Kingdom. Weiland and colleagues estimated exposure using the truck density on the street of residence reported by the adolescent subjects in Bochum, Germany. Brunekreef and van Vliet, and their colleagues, measured the distance of the residence from a freeway, the volume of diesel traffic near the residence, and the levels of black smoke in the school for children

living in the Province of South Holland in the Netherlands.

All these studies reported an association between high traffic density and the outcome measures, which included wheezing, rhinitis, increased hospital admissions for asthma, or reduced lung function. The study by Edwards and coworkers also found that children admitted to a hospital for any cause were more likely to live within 200 meters of a main road; and children living in areas with high traffic flow were more likely to be admitted to the hospital for asthma. Investigators who measured truck traffic density (Brunekreef et al. 1997, van Vliet et al 1997) found a stronger association with health effects when the analysis was restricted to children living near motorways. Although these studies have generally been interpreted as showing an effect of mobile sources air pollution (in particular diesel exhaust) on the respiratory system in children, they have some limitations in that they used crude estimates of personal exposure, and often lacked information on other potential risk factors and confounding factors.

Two studies have investigated the association between road traffic and allergic symptoms and allergic sensitization in adults. In the late 1980's Ishizaki and colleagues (1987) reported an enhanced sensitization to cedar pollen and allergic symptoms among residents of the Nikko-Imaichi district, Japan, living near inner city roads with high traffic volume and with high levels of cedar tree pollen relative to residents in rural areas with comparable levels of pollen but less traffic. A recent study by Wyler and coworkers (2000), suggested a positive association between traffic exposure and sensitization to pollen, but not to other allergens such as molds or dust mites in adults living in Basel, Switzerland. Exposure estimates were based on the frequency of cars and trucks near the subjects' residences. Subjects living at locations with an intermediate or high traffic density were more likely to be sensitized to pollen than subjects living on roads with low traffic density. The association was more pronounced for subjects living in the same residence for at least 10 years. However, there was no association between traffic exposure and hay fever, allergic rhinitis, or asthma symptoms. In summary, although both the Ishizaki and Wyler studies suggest an association between exposure to road traffic level and pollen sensitization, they differ in their findings regarding the association between exposure to road traffic and allergic symptoms.

## EXPERIMENTAL STUDIES OF THE EFFECTS OF DEP AND OTHER PARTICLES ON ALLERGIC RESPONSE

Over the last decade a number of experimental studies have been conducted to examine the role of components of air pollution (primarily DEP and other particles) in the induction (sensitization) or exacerbation of an allergic response. In general, these experimental studies involved intranasal or intratracheal exposure to DEP or other particles and concomitant or sequential exposure to an allergen.

### Studies in humans

Experimental studies have shown that *in vivo* nasal challenge with 300 µg of DEP of both healthy and allergic subjects enhances the production of total IgE (but not of other Ig isotypes) in human upper airways by increasing the number of local IgE-secreting cells (Diaz Sanchez et al 1994). These investigators also showed that nasal challenge with 300 µg DEP increased production of both Th1- and Th2- type cytokines (including IL-4, IL-6, IL-13, and interferon) in the nasal mucosa (Diaz-Sanchez et al. 1995). In contrast, intranasal challenge with DEP plus ragweed allergen of human subjects allergic to ragweed markedly enhanced the production of ragweed-specific IgE (but not total IgE) relative to challenge with ragweed allergen or DEP alone. In addition, DEP in combination with ragweed challenge markedly increased the production of mRNA for Th2-type cytokines by cells in the nasal mucosa (Diaz-Sanchez et al. 1997).

In a recent study, adults with mild allergic asthma were exposed in a Stockholm tunnel for 30 minutes to the tunnel air (while sitting inside a car) and challenged 4 hours later with an allergen (Svantengren et al. 2000). Changes in pulmonary function and asthma symptoms were evaluated relative to components of tunnel air. Subjects exposed to NO<sub>2</sub> levels greater than, or equal to, 300 µg/m<sup>3</sup> or exposed to levels of PM<sub>2.5</sub> greater than, or equal to, 100 µg/m<sup>3</sup> had marginally greater early changes (increased airway resistance) and decreases in FEV1 in response to an allergen challenge at later times. In some subjects, late changes such as increased asthma symptoms were significantly correlated with NO<sub>2</sub> exposure, but not with PM<sub>2.5</sub> levels. Overall, however, there was no association between NO<sub>2</sub> or PM<sub>2.5</sub> exposure and any of the endpoints measured when all the exposed subjects were included in the analysis.

Some studies have investigated the effects of ozone on the early- or late-phase response to an allergen in allergic asthmatic subjects (Jörres et al. 1996; Peden et al. 1995;

Bascom et al. 1990). Despite some differences in results among the studies, they point to the need to control carefully for possible effects of other pollutants in epidemiologic studies.

### Studies in rodents

Takafuji and colleagues (1987) examined the ability of DEP to enhance an immune response (adjuvant activity) by administering ovalbumin (OVA) mixed with DEP in mice intranasally weekly on nine occasions or every 3 weeks on five occasions. They demonstrated an adjuvant effect of DEP on IgE antibody production in mice inoculated with the lowest concentration of OVA (0.25 µg) and 25 µg DEP after both exposure regimens. Lower doses of DEP (1 and 5 µg) were also effective. Takano and colleagues (1997) exposed mice by nasal instillation to 100 µg DEP once a week for 6 weeks and to OVA every 3 weeks for 6 weeks. DEP exposure aggravated OVA-induced airway inflammation compared to OVA or DEP alone, and markedly increased IL-5 levels in lung tissues and BAL and the expression of mRNA for IL-4, IL-2, and granulocyte macrophage-colony stimulating factor in lung tissues. In addition, DEP exhibited adjuvant activity for anti-OVA specific IgG (after 6 weeks) and IgE (after 9 weeks).

Fujimaki and colleagues (1997) also showed that mice exposed by inhalation to 3 and 6 mg/m<sup>3</sup> DEP for 6 weeks and intranasally sensitized with OVA (before, during, and after DEP inhalation) had higher anti-OVA IgE antibody titers than mice exposed to DEP or OVA alone. Similarly, footpad injection of 100 µg DEP in mice caused greater OVA-specific IgE responses than in mice exposed to OVA alone (Lovik et al 1997). A similar enhanced response was observed in mice exposed to OVA and carbon black, suggesting that particle composition may not be critical in inducing an adjuvant effect. This conclusion seems to be further supported by the study of Maejima and coworkers (1997) who found that various particles ranging in size from 0.3 µm to 5 µm (Kanto loam dust, fly ash, carbon black, DEP, and alum, each at a dose of 25 µg) had similar adjuvant effects on the production of Japanese cedar pollen-specific IgE and IgG in mice. A similar result was reported by Takafuji and coworkers (1989) using suspended ambient particles of two different sizes. More recently Lambert and co-workers (1999) showed that intratracheal instillation of 1000 µg residual oil fly ash in Brown Norway rats prior to sensitization with house dust mite allergen enhanced production of antigen-specific IgE and lymphocyte proliferation relative to animals exposed to dust mite alone. The investigators subsequently showed that some of these responses could be triggered by

instillation of metals present in the fly ash (namely nickel, vanadium, or iron) (Lambert et al. 2000).

## SUMMARY

Epidemiologic studies have raised questions as to whether various constituents of traffic air pollution (including DEP) may contribute to an increase in symptoms of asthma or rhinitis, or to an enhanced response to allergens. Some studies have suggested an association between sensitization to pollen and traffic-derived air pollution, but these studies did not measure the levels of individual pollutants. Studies with improved measures of exposure and outcomes as well as better control of potential confounders are needed to confirm some of the earlier findings.

The experimental studies using model particles, although hard to compare because of their different protocols, suggest that both DEP and other particles have the ability to enhance an immune response. However, the ability of these particles to specifically induce allergic-type immune responses remains to be established.

Lastly, there are questions about the relevance of the DEP doses used in the experimental studies to concentrations to which humans are exposed in ambient air. In the experimental studies the particles were resuspended and delivered in a bolus dose (usually to the nose), which is not a physiologically relevant method of exposure. The following calculations attempt to put the doses used in the experimental studies into an inhalation perspective. The maximum ambient concentration of DEP was estimated to be  $10 \mu\text{g}/\text{m}^3$  in Southern California (Cass and Gray 1995) and somewhat higher levels ( $14.9 \mu\text{g}/\text{m}^3$ ) of Black Smoke (a surrogate measure of elemental carbon) were described near a freeway in Delft, The Netherlands (van Vliet et al. 1997). The exposure duration necessary to deliver a dose equivalent to the bolus nasal dose ( $300 \mu\text{g}$ ) used in the human studies in a subject exposed to  $10 \mu\text{g}/\text{m}^3$  and breathing at a ventilation rate of  $1.5 \text{ m}^3/\text{hour}$  (assuming that 50% of the particles are deposited in the nose) is approximately 40 hours; the exposure duration for a similar study in mice (Maejima et al. 1997) using a dose of  $25 \mu\text{g}$  of DEP (assuming a ventilation rate of  $0.0026 \text{ m}^3/\text{hour}$ ) is approximately 2000 hours. More studies using a range of carefully established doses are needed to improve the ability to estimate dose-response relationships for use in extrapolation to effects at ambient levels.

There are data suggesting that some co-pollutants (e.g.,

ozone and  $\text{NO}_2$ ) also might increase the response to allergens in asthmatic subjects, possibly confounding the effects attributed to particulate matter. Thus, the role of co-pollutants in epidemiologic studies needs to be evaluated.

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## OBJECTIVES OF THE RFA

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Current studies raise questions about whether exposure to DEP and other particles may be associated with the exacerbation of asthma and other allergic diseases and may interact with other environmental factors to increase allergic responses. Further research to elucidate dose-response relationships extending to relevant exposure levels, and mechanisms is needed. In addition, studies should utilize individuals at risk and identify the types of particles that may be responsible for the effects in order to provide a stronger scientific basis for risk evaluation.

This RFA seeks epidemiologic and experimental research to address the following objectives:

- investigate whether exposure to DEP is associated with exacerbation of asthma and other allergic diseases and determine whether PM from other sources (for example gasoline engines, natural gas engines, power plants, crustal dust, etc.) has effects similar to those induced by DEP
- investigate the mechanisms that may lead to the effects observed
- evaluate particular subgroups of the general population that may be at increased risk of these responses.

Epidemiologic, human controlled exposure, and animal studies are of interest. Applicants proposing experimental studies should have experience in generating and characterizing the particles of interest or should involve scientists with such expertise. For both epidemiologic and experimental studies, careful characterization of both the exposure atmosphere and outcome is needed. Moreover, epidemiologic studies should strive to measure actual exposure levels and identify and correct for confounders (for example, exposure to other pollutants, housing characteristics, living conditions, and exposure to tobacco smoking).

Experimental studies should use inhalation as the route of exposure and a range of exposures including realistic levels of emissions. The use of routes of

exposure other than inhalation needs to be justified. Studies involving exhaust generated in the laboratory should use contemporary engines and fuels. Special attention should be paid to the operating conditions and the exhaust dilution conditions as these can affect the composition of the particles emitted. In the case of co-exposure to particles and gaseous components the role of the gases relative to that of the particles need to be assessed.

Applications will be evaluated with regard to the hypothesis to be tested, the experimental design (including number of animals or subjects and exposure groups), the statistical design and analytic plan, and the qualifications of the research team. Applicants are advised to seek biostatistical collaboration in the design, conduct, analysis, and interpretation stages of the proposed study.

HEI plans to have available about \$2.5 million for studies funded under this RFA. Studies can have a 3-year maximum period of performance (with rare and well justified exceptions).

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## **RFA 00-1: APPLICATION PROCESS AND DEADLINES**

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### LETTER OF INTENT

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Prospective applicants are asked to submit a one-page Letter of Intent, which should include a synopsis of the project indicating the specific goals, the general approach to be used, and a list of all participating institutions. Confidential or proprietary information on methodologic details should not be included in the Letter of Intent.

HEI requests Letters of Intent in order to organize the application review process. The Letter of Intent is not binding. In some instances, HEI may advise the applicant that the work described in the Letter of Intent does not appear to address the objectives of the RFA.

**Deadline for Letters of Intent:** The Letter of Intent should be received no later than **FEBRUARY 14, 2001**, at the following address (by mail, fax, or e-mail):

Ms. Teresa Fasulo  
Senior Administrative Assistant  
Health Effects Institute  
955 Massachusetts Avenue  
Cambridge, MA, 02139, USA  
Tel: +1-617-876-6700 (ext. 345)  
Fax: +1-617-876-6709  
email: [tfasulo@healtheffects.org](mailto:tfasulo@healtheffects.org)

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### FULL APPLICATION

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Full applications must be submitted on the forms found on pages F-1 to F-10. Investigators should consult Instructions for Completing the Application found on pages 33-36. Inquiries regarding application and evaluation procedures may be directed to Dr. Maria Costantini or Dr. Jane Warren at +1-617-876-6700 or by e-mail: [mcostantini@healtheffects.org](mailto:mcostantini@healtheffects.org) or [jwarren@healtheffects.org](mailto:jwarren@healtheffects.org). If two applications are interdependent or closely related, they should be appropriately cross-referenced in the project plan.

***Twenty-five copies of each application are needed by HEI for the review process.***

**Deadline for Applications:** Applications for RFA 00-1 must either reach the office of the Health Effects Institute by **APRIL 11, 2001 or be sent by air delivery service postmarked by that date**. Applications not meeting these conditions will not be considered. HEI will acknowledge receipt of the application in writing.

## **RFA 00-1: EVALUATION PROCESS**

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HEI is committed to facilitating research on the health effects of air pollutants from automotive emissions and other sources by encouraging applications from researchers with skills and methods in various disciplines, including those not conventionally associated with this field. Procedures and criteria for evaluation of applications have been designed with these goals in mind.

Applications received will be evaluated by HEI in a two-stage process: an external review followed by an internal review.

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### **EXTERNAL REVIEW**

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Applications undergo a competitive evaluation of their scientific merit by an ad hoc panel of scientists selected for their expertise in relevant areas. The panel will evaluate applications according to the following criteria.

- Relevance of the proposed research to the objectives of RFA
- Scientific merit of the research design, approaches, methodology, analytical methods, and statistical procedures
- Personnel and facilities, including:
  - \* Experience and competence of the principal investigator and scientific staff
  - \* Adequacy of effort on the project by scientific and technical staff
  - \* Adequacy of facilities
- Reasonableness of proposed cost

The applications ranked highly by the review panel may be additionally reviewed for evaluation of the experimental design and analytical methods by a statistician.

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### **INTERNAL REVIEW**

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The internal review is conducted by the HEI Research Committee and generally focuses on the applications ranked highly by the external review panel. The review is intended to ensure that the studies funded constitute a coherent program addressing the objectives of the Institute. The Research Committee makes recommendations regarding funding of studies to the Institute's Board of Directors, which makes the final decision.

## REQUEST FOR APPLICATIONS 00-2

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### WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD

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#### INTRODUCTION

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HEI has established the New Investigator Award to provide funding for outstanding investigators who are beginning independent research. By providing financial support for investigators at this point in their careers, HEI hopes to encourage highly qualified individuals to undertake research on the health effects of air pollution.

Each award will be up to \$75,000 per year in direct costs to support a research project for up to three years. The funds can be used to provide salary support for the investigator and supporting personnel as well as operating costs, including supplies and equipment. It is expected that the investigator will devote at least 50% of his or her time to this project or related research. HEI expects to provide one award from this RFA and to continue this award on an annual basis.

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#### HEI RESEARCH PROGRAM

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Since 1983, HEI's research program has addressed a broad range of questions about the health effects of air pollutants derived from motor vehicles emissions, including aldehydes, carbon monoxide, diesel particles and associated compounds, methanol, nitrogen oxides, and ozone. Several studies have addressed the effects of exposure to more than one pollutant. HEI's strategic plan, developed in 1994, designates three high priority research areas: air toxics, ambient particles, and oxygenated fuels and additives (such as MTBE). Since then HEI has initiated research programs in all of those areas as well as some research on oxidants.

In considering potential research topics, applicants should be aware of HEI's current areas of interest, as described in the *HEI Strategic Plan for the Health Effects of Air Pollution 2000-2005*. This plan emphasizes the "air pollution mixture" with a focus on (1) particulate matter and gaseous pollutants, (2) diesel exhaust, and (3) air toxics. Appendix A includes some sections of the Strategic Plan, which describe HEI's current research priorities and plans for implementing them. Appendix B

provides a listing of HEI studies and reports, which gives information on the pollutants and issues in which HEI has been interested over the years.

HEI studies have covered a wide range of designs: modeling, experiments with cell cultures, animal studies, controlled human exposure studies, and epidemiologic investigations. There are several cross-cutting issues that the Research Committee would like to emphasize in HEI-funded studies. One of these is to identify and evaluate effects in susceptible groups that may respond at lower levels of exposure than "normal subjects". Another important focus is to improve methods for understanding mechanisms by which toxic agents cause injury and disease and to measure the actual dose of a pollutant received by tissues, cells, and macromolecules. In all studies, accurate characterization of exposure is important. Studies that address the effects of multiple pollutants are also important in understanding health effects of ambient exposure. Finally, because the ultimate goal of HEI's research is understanding effects in people, human studies and studies to improve extrapolation from animals to humans are an important part of HEI's program.

The ultimate goal of research funded by HEI is to provide data that can inform regulatory decisions about air quality. HEI also encourages the development of new methods and technologies that could be used later to provide data useful for regulatory purposes. At the end of the project, the awardee must submit a comprehensive final report describing the project and results (see Section on *Project Negotiation, Project Management, and Investigator Commitments* on pages 29-32).

HEI encourages investigators to submit applications addressing the high priority research issues described above. However, HEI realizes that other areas of research may lead to results important to its mission. For this reason, we will also consider particularly innovative or high quality applications in other areas that speak to the overall goals of HEI's program.

## RFA 00-2: APPLICATION PROCESS AND DEADLINES

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### ELIGIBILITY REQUIREMENTS

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Scientists holding a PhD, ScD, MD, DVM, or DrPH degree or equivalent are eligible to apply. At the time of application the candidate should have one to six years of postdoctoral experience and must be in an entry-level position at an academic institution (generally assistant professor level) or its equivalent in a research institution. At the time of the appointment, HEI will require the candidate's institution to make a tangible commitment to helping the awardee become established as an independent investigator. Commitments can take many forms, such as providing laboratory space, financial support for a laboratory, or paying part of the awardee's salary.

Eligible candidates should be recognized by their peers to possess outstanding research potential. Evidence of this potential, in the form of written letters of support and publication is an essential part of the application materials.

Please note that an applicant who does not meet all eligibility requirements will not be considered for this award. HEI will not review applications from individuals with more than six years postdoctoral experience.

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### LETTER OF INTENT

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Although not required as part of the application process, applicants are encouraged to submit a one-page Letter of Intent summarizing the proposed project prior to submitting an application. The Letter of Intent should specify the research goals of the project and indicate the general approach to be used.

HEI requests Letters of Intent in order to organize the application review process. In some instances, HEI may advise the applicant that the work described does not appear to address HEI's research goals.

**Deadline for Letters of Intent:** The Letter of Intent should be received no later than February 14, 2001, at the following address:

Ms. Terésa Fasulo  
Senior Administrative Assistant  
Health Effects Institute  
955 Massachusetts Ave  
Cambridge, MA 02139, USA  
Tel: +1-617 876-6700 (ext. 345)  
Fax: +1-617 876-6709  
E-mail: [tfasulo@healtheffects.org](mailto:tfasulo@healtheffects.org)

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### FULL APPLICATION

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The full application consists of two parts: (1) a formal proposal for a research project of up to three years and associated materials; and (2) evidence of qualification. Inquiries regarding application and evaluation procedures may be directed to Dr. Annemoon van Erp or Dr. Jane Warren at (617) 876-6700 or by e-mail: [avanerp@healtheffects.org](mailto:avanerp@healtheffects.org) or [jwarren@healtheffects.org](mailto:jwarren@healtheffects.org)

The research proposal must be submitted on the forms found on pages F-1 to F-10. Investigators should consult *Instructions for Completing the Application* found on pages 33-36.

In addition to the materials required in the application, the following should also be submitted as evidence of qualification:

1. A cover letter describing the candidate's interest in the award and how this project fits with his or her career goals, including information concerning the long-term career plans of the applicant and how the HEI Award would contribute to these plans.
2. Two sealed letters of reference from well-established scientists familiar with the candidate's professional capabilities but who are not directly involved in the project. The letters should address the candidate's past contributions to scientific achievements, the candidate's potential to pursue and develop an independent research program, and how the HEI Award could contribute to this potential. Whenever possible, one of these letters should be from a postdoctoral research mentor.
3. A letter from an administrator such as a department chair, or other administrative official from the candidate's present institution, indicating tangible institutional commitment to the candidate.
4. Three recent publications.

**Fifteen copies of each application are needed by HEI for the review process.**

**Deadline for Applications:** Applications for RFA 00-2 must either reach the offices of the Health Effects Institute by **April 11, 2001, or be sent by overnight air delivery service postmarked by that date.** Applications not meeting these conditions will not be considered. Applications should be submitted to Ms. Terésa Fasulo at HEI.

## RFA 00-2: EVALUATION PROCESS

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Qualifications of the applicant, the quality and relevance of the proposed research, and the research environment will be considered in evaluating applications. Applications will be evaluated by HEI in a two-stage process: an external review followed by an internal review by HEI's Research Committee.

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### EXTERNAL REVIEW

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External scientists selected for their relevant expertise in the area of proposed research will evaluate the applications according to the following criteria:

- Scientific merit of the research design, approaches, methodology, analytical methods, and statistical procedures
- Adequacy of the facilities
- Appropriateness of the use of requested funds
- Consistency of the research plan with the candidate's career goals

Qualifications of the candidate will be reviewed according to the following criteria:

- Capacity to carry out independent research based on level of training, experience and competence commensurate with the purposes of this award
- Potential to make significant contributions to the field
- Appropriateness of the applicant's career development plan to HEI and the likelihood that the award will contribute substantially to the continued scientific development and productivity of the candidate

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### INTERNAL REVIEW

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The Research Committee will then review the full applications with consideration of the comments and recommendations of the external reviewers. The Research Committee makes final recommendations regarding funding of studies to the Institute's Board of Directors, which makes the final decision.

This award is named for Professor Walter A. Rosenblith, who served as the first Chair of HEI's Research Committee (from 1980 to 1989) and as a member of the HEI Board of Directors from 1990 to 1996. Professor Rosenblith's vision of science and standard of excellence enabled HEI to quickly develop a strong scientific program. At his urging, HEI developed a program that not only funds research that would contribute needed scientific information for regulation, but also research to strengthen the fundamental science related to environmental issues. Professor Rosenblith supported activities intended to attract people engaged in more basic scientific research so that they might bring new tools and new ideas to environmental questions.

## REQUEST FOR PRELIMINARY APPLICATIONS 00-3

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### RFPA 00-3: HEALTH EFFECTS OF AIR POLLUTION

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#### INTRODUCTION

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This Request for Preliminary Applications (RFPA) provides a mechanism for investigators whose area of interest falls outside of the current RFA, but is compatible with the HEI research program and mission, to apply for HEI funds. HEI is interested in receiving applications for research on novel and important aspects of the health effects of air pollutants, particularly those derived from motor vehicle emissions. Preliminary applications will be reviewed by the HEI Research Committee, which then will invite submission of full applications for the most promising preliminary applications. Full applications will be evaluated by several peer reviewers before consideration by the Research Committee.

A total of up to \$250,000 per year is available for studies funded this year through the preliminary application process. We encourage applications for small studies and pilot studies and suggest limiting the budgets to \$70,000 in direct costs per year.

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#### THE HEI RESEARCH PROGRAM AND RESEARCH PRIORITIES

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Since 1983, HEI's research program has addressed a broad range of questions about the health effects of air pollutants derived from motor vehicles emissions, including aldehydes, carbon monoxide, diesel particles and associated compounds, methanol, nitrogen oxides, and ozone. Several studies have addressed the effects of exposure to more than one pollutant. HEI's strategic plan, developed in 1994, designates three high priority research areas: air toxics, ambient particles, and oxygenated fuels and additives (such as MTBE). Since then HEI has initiated research programs in all of those areas as well as some research on oxidants.

In considering potential research topics, applicants should be aware of HEI's current areas of interest, as described in the *HEI Strategic Plan for the Health Effects of Air Pollution 2000-2005*. This plan emphasizes the "air pollution mixture" with a focus on (1) particulate matter and gaseous pollutants, (2) diesel exhaust, and (3) air toxics. Appendix A includes some sections of the

Strategic Plan, which describe HEI's current research priorities and plans for implementing them. Appendix B provides a listing of HEI studies and reports, which gives information on the pollutants and issues in which HEI has been interested over the years.

HEI studies have covered a wide range of designs: modeling, experiments with cell cultures, animal studies, controlled human exposure studies, and epidemiologic investigations. There are several cross-cutting issues that the Research Committee would like to emphasize in HEI-funded studies. One of these is to identify and evaluate effects in susceptible groups that may respond at lower levels of exposure than "normal subjects". Another important focus is to improve methods for understanding mechanisms by which toxic agents cause injury and disease and to measure the actual dose of a pollutant received by tissues, cells, and macromolecules. In all studies, accurate characterization of exposure is important. Studies that address the effects of multiple pollutants are also important in understanding health effects of ambient exposure. Finally, because the ultimate goal of HEI's research is understanding effects in people, human studies and studies to improve extrapolation from animals to humans are an important part of HEI's program.

The ultimate goal of research funded by HEI is to provide data that can be used in regulatory decisions or to provide better information for risk assessment. Sometimes the connection between HEI studies and these decisions is direct, but at other times new methods must be developed or biological mechanisms must be understood before studies of human health effects can be launched. Thus, HEI's research program is comprised of a variety of studies, which in either the near or the long term are important for obtaining better information on the human risks of exposure to air pollutants.

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#### OBJECTIVES

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While we feel that an understanding of HEI's research priorities is important for applicants to the preliminary application process, and would like in most cases to fund studies that are responsive to those, an important goal of this preliminary application process is to provide a means for investigators to suggest new areas of research. Thus,

applications will be considered not only on issues raised in the discussion above and in HEI's strategic plan, but also on other issues related to improving our understanding and assessment of the health risks of exposure to motor vehicle emissions and secondary pollutants derived from them, and the whole air pollution mixture to which they contribute.

In general, applications should include studies at concentrations that occur in the environment. Initial experiments using either new techniques or investigating mechanisms of health effects may need to start at pollutant concentrations higher than ambient levels, but will only be considered if there is a real likelihood that the effects studied will be relevant to understanding effects at

environmentally relevant concentrations. Although HEI is interested in both *in vivo* and *in vitro* methods, for the latter studies it is important to explain the relationship of the assay system to the *in vivo* situation being modeled. Methods using isolated tissues, cells, or subcellular fractions should be appropriate for the physical characteristics of the inhaled chemicals and the metabolic transformations that may occur *in vivo* before target tissues are exposed. The respiratory and central nervous systems are clearly important target sites, although other organ systems may also be appropriate for study if a strong rationale links them to possible toxic effects of air pollutants.

## **RFPA 00-3: APPLICATION PROCESS AND DEADLINES AND EVALUATION PROCESS**

The general preliminary application process consists of two stages. The first stage involves the submission of a preliminary application, which is reviewed by the Research Committee. If the Research Committee expresses interest in the study, then the investigator is asked to prepare a full application. In addition to the likelihood of high scientific merit, the preliminary applications will be reviewed in terms of relevance of the proposed research to the scientific problem being investigated and to the current objectives of HEI's research program. Investigators will be informed whether or not to submit a full application within one month of the Fall 2001 Research Committee meeting.

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### **PRELIMINARY APPLICATION**

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The preliminary application should contain two elements: a description of the project plan containing an outline of the intended experimental techniques and a rationale for the proposed study indicating its importance in light of current insights and knowledge about vehicle emissions. It is essential that both the scientific questions being addressed and the methodological approach be explained clearly. When critical, the experience of the investigators and the availability of any special equipment and facilities should be mentioned. The preliminary application must be no more than five pages in length.

In addition to the preliminary application, a brief curriculum vitae of the principal investigator and co-investigators should be provided. This information is not included in the 5 page limit outlined above. Detailed budgetary information is not desired in the preliminary application, but investigators should indicate the estimated scope of the project in terms of time and money.

**Five copies of the preliminary application are needed for our review process.**

### **Deadlines for Preliminary Applications**

Preliminary applications may be submitted at any time prior to **August 31, 2001**. In 2001, Preliminary Applications will be discussed at the Fall 2001 Research Committee meeting.

Questions regarding preliminary applications should be directed to Dr Debra Kaden or Dr Jane Warren at +1-617-876-6700 or by e-mail at [dkaden@healtheffects.org](mailto:dkaden@healtheffects.org) or [jwarren@healtheffects.org](mailto:jwarren@healtheffects.org).

Please send applications (by mail, fax, or e-mail) to:

Ms. Teresa Fasulo  
Senior Administrative Assistant  
Health Effects Institute  
955 Massachusetts Avenue  
Cambridge, MA 02139, USA  
Tel: +1-617-876-6700 (ext. 345)  
Fax: +1-617-876-6709  
email: [tfasulo@healtheffects.org](mailto:tfasulo@healtheffects.org)

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### **FULL APPLICATION**

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Full applications will be evaluated in a two-stage process. First, scientists selected for their relevant expertise will evaluate the applications according to the following criteria:

- Scientific merit of the research design, approaches, methodology, analytical methods, and statistical procedures;
- Personnel and facilities, including
  - \* Experience and competence of the principal investigator and scientific staff
  - \* Adequacy of effort on the project by scientific and technical staff
- Adequacy of facilities
- Reasonableness of the proposed cost

The Research Committee will then review full applications with consideration of the reviewers' comments and of the ways the proposed research could improve the understanding of the specific problem under investigation. The Research Committee makes final recommendations regarding funding of studies to the Institute's Board of Directors, which makes the final decision.

Investigators asked to prepare a full application should use the forms found on pages F-1 to F-10 and consult *Instructions for Completing the Application* found on pages 33-36. If a full application is requested, the deadline will be agreed upon between the investigator and HEI staff. *Five copies of each full application are needed by HEI for the review process.*

## **POLICY ON FOLLOW-ON APPLICATIONS**

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This section is addressed to HEI investigators who, when nearing completion of their projects, would like to apply to HEI for funding to continue their research. Its purpose is to describe guidelines and procedures HEI's Research Committee has adopted to evaluate requests for continuing support.

Approval of "follow-on" applications by the Research Committee will be on a highly selective basis. The Research Committee will recommend for funding only those applications most relevant to the current scientific objectives of the Institute, when evaluated against all other applications. Before submitting an application for further support, investigators are encouraged to contact the HEI staff to discuss both the technical and programmatic aspects of the study and the timing of submission. *The usual mechanism for a follow-on application is the preliminary application process described on pages 25.* If the Research Committee is interested in the additional work, then the investigator will be asked to submit a full application for the follow-on study.

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### **PROCESS AND TIMING FOR SUBMISSION**

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The follow-on (full) application should contain all of the elements for a full application to the Health Effects Institute as outlined in this booklet, including a budget, a project plan, and any additional submissions and should be prepared using the forms found on pages F-1 to F-10. In the project plan, investigators should provide a brief summary of results available to date and describe the relationship between these results and the future experiments described in the proposal. Furthermore, the

application should include a discussion of how anticipated results might apply to specific issues of potential health risks from exposure to mobile source emissions.

The Research Committee recognizes that a hiatus between projects can have an impact on experimental continuity and personnel adjustments in a laboratory. In order to minimize delay between project completion and the beginning of new research, investigators should submit their follow-on applications at least four months prior to the contract termination date. By timing a submission in this way, it is possible for the Research Committee to evaluate simultaneously the factors discussed above and to respond to the applicant before completion of the study. In some cases, however, the Research Committee may delay a decision until the Review Committee has evaluated the draft final report.

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### **CRITERIA FOR EVALUATION**

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Depending on the scope of the proposed research, follow-on applications may be subjected to outside peer-review prior to the Research Committee evaluation. The Research Committee's recommendation concerning approval of follow-on applications will depend on its appraisal of (1) the project just completed or underway, (2) the scientific quality of the new proposal, and (3) the ways the proposed research could improve the understanding of the specific problem under investigation. The Research Committee will also take into account performance, productivity, scientific results, and responsiveness to HEI contract obligations during the initial project period.

## HEI PROJECT NEGOTIATION, MANAGEMENT, AND INVESTIGATOR COMMITMENTS

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HEI has two main goals in funding research. One is to build a coherent research program for each set of related studies addressing questions in a more comprehensive way than would be possible with independent studies. Another is to provide timely, high-quality information to its sponsors and regulatory agencies for technological and regulatory decisions. In order to accomplish these goals, HEI works in a cooperative fashion with investigators and keeps in close contact with them through such means as progress reports, workshops, and its annual conference. The progress reports are reviewed by the HEI Research Committee and staff. In addition, HEI requires a comprehensive final report at the end of each study, which undergoes an in-depth review by the HEI Review Committee and additional experts.

The purpose of this section is to provide information to future HEI investigators about HEI's management of studies and about the process for review and publication of final reports from HEI-funded studies. Applicants should read this section carefully to ensure that they understand the commitments in conducting studies with HEI funding.

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### SCIENTIFIC NEGOTIATION OF PROJECT PLANS

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The Research Committee may request modifications in the project plan or budget before making a final funding recommendation to the HEI Board of Directors. For example, the Research Committee may request deletion of parts of the proposed project that are less relevant to HEI's objectives or overlap considerably with other studies; sometimes changes in the range of exposure concentrations of pollutants are recommended to make them more representative of ambient conditions. This approach enables HEI to mold diverse investigator-designed studies into a more coherent program and to generate data more relevant to regulatory needs. HEI staff scientists act as liaisons between the Research Committee and investigators in this scientific negotiation process. The end-product is a project plan that is acceptable to both the investigator and Research Committee.

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### RESEARCH AGREEMENT (CONTRACT)

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Upon satisfactory negotiation of the project plan and budget, a contract for the study is negotiated with the Principal Investigator's institution. HEI's Research Agreement is a cost-reimbursement contract rather than a grant. Investigators should be aware that because scientific and administrative contract negotiations may extend through a period of several months, and may result in changes in the scope or cost of the proposed study, certain portions of the applications may have to be updated prior to contract signing. In general, HEI requires that any significant changes in personnel, scope of work, and/or budget be reflected via submission of revised budgets, project plans, or other appropriate application materials prior to the signing of the contract. For human studies and major animal studies, a protocol and Standard Operating Procedures (SOPs) should be written before the study starts (see *Use of Human Subjects and Quality Assurance Program* below).

The contract contains a Statement of Work, which is an approved description of work to be performed in each contract year, and the budget. The scope of the research conducted should be consistent with the Statement of Work. If results suggest new directions for research, however, the contract can be amended to allow changes in the Statement of Work upon written agreement by the investigator's institution and HEI.

Contracts are usually issued for one year, although HEI expects to provide support for the number of years initially approved by the Research Committee if work is progressing satisfactorily. The Research Agreement has been designed to maximize the integrity of the scientific process while providing needed protections and meeting applicable federal regulations. Once a contract is signed by both parties, an Abstract and Statement of Work written by the principal investigator may be distributed to the Institute's sponsors. These also will be available to members of the public who request them.

No work should be started nor should any study costs be incurred prior to signing of the contract unless explicit written authorization is provided in advance by HEI's Director of Science or Director of Finance and Administration.

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## USE OF HUMAN SUBJECTS AND QUALITY ASSURANCE PROGRAM

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### HUMAN SUBJECTS

As mentioned in the section *Instructions for Completing the Application, Additional Submissions*, the applicant must submit, with the application, a written assurance for compliance with the guidelines established by the Department of Health and Human Services (DHHS) concerning protection of subjects (see pages 35-36). This is form HHS-596.

If HEI decides to fund a study involving human subjects, a detailed protocol and certification that an appropriate Institutional Review Board (IRB) has reviewed and approved the proposed study in accordance with the DHHS regulations are required before starting a study. In addition, investigators will be asked to comply with HEI's Special Quality Assurance (QA) procedures (see below). HEI is willing to provide some funds to support the investigator's time required to develop the protocol and the SOPs. In that case the applicant should indicate the period required for these activities and provide a separate budget. HEI also asks that the application to the IRB (including the informed consent) be provided to HEI at the time it is submitted to the IRB. HEI may propose modifications to the informed consent if it believes that the risks to the subjects are not properly represented.

Applicants utilizing data or samples from subjects recruited for another study need to provide the IRB approval and informed consent obtained for that study. If additional samples are collected for the HEI study, IRB approval for the HEI component will be required.

### QUALITY ASSURANCE

It is the policy of HEI to require that appropriate quality assurance (QA) procedures are in place for all approved research projects that may produce data of regulatory significance; these include all human exposure studies and certain animal studies. This policy assures our sponsors and the public that the data are acquired under well-defined conditions and are reliable and traceable. If HEI's Special QA procedures are to be applied to an approved animal study, the investigator will be informed by HEI's Staff Scientist overseeing the project. The QA procedures consist of five components that apply to different extent to different studies: a research protocol;

standard operating procedures; written records; documented data processing procedures; and data quality assessment procedures. A copy of the HEI document *Special QA Procedures* is available upon request.

The Principal Investigator has the primary responsibility for development and implementation of the procedures required by HEI for QA. A qualified individual selected by HEI will serve as a quality assurance officer to aid in HEI's assessment of QA activities in a study. The QA officer may conduct periodic audits to ascertain compliance with the study protocol or to examine records. He or she reports to HEI's Director of Science. The audit reports are confidential and are not released to persons not directly involved in management of the project.

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### PROGRESS REPORTS

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Progress reports are one of the ways by which HEI keeps informed of the progress of the studies that it supports. Investigators are required to submit progress reports at five and ten months of the first year of the study. In subsequent years, generally only a ten-month report is required. In the final year of the contract, the ten-month progress report is replaced by a comprehensive final report (see below).

The basic objective of the reports, particularly in the first year, is to indicate how much progress has been made in the development of experimental procedures, which objectives have been completed, and what problems, if any, have arisen. The ten-month report is actually a combined progress report and renewal application for the next year's funding. HEI's decision regarding renewal of the contract is based upon the information provided by the investigator in this report. The ten-month report should provide a detailed account of the experimental results obtained during the funding period, as well as a work plan, and a budget for the coming year. Progress reports are reviewed by the Research Committee and by HEI's scientific staff.

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### SITE VISITS

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HEI sometimes conducts site visits to the laboratories of its funded investigators during the course of their studies. The site visit team consists of members of the HEI Research Committee, HEI scientific staff, and outside consultants. The purpose of these visits is to evaluate the status of the project, to provide the investigator with expert technical

advice, and to provide an opportunity for an exchange of ideas between the investigator and other experts in the field.

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## ANNUAL CONFERENCE AND OTHER MEETINGS

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Each year HEI holds a conference that investigators are expected to attend. The Annual Conference provides an opportunity for HEI's sponsors to learn more about HEI studies, for HEI to receive feedback on its research program, and for informal interactions among investigators, Research and Review Committee members, sponsor representatives, and the HEI staff. For the past several years HEI has requested that each investigator submit an abstract and poster. Abstracts are published in the annual conference booklet. In addition to discussion of HEI program areas, the annual conference generally includes special symposia on broader issues of current interest.

Periodically, small workshops are organized for investigators working on projects in a particular research area. These meetings offer an opportunity for investigators doing related research to understand each other's research better and may open opportunities for coordination of studies or collaboration among investigators. In addition, critical gaps in HEI's program or ideas for new research may be identified.

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## INVESTIGATOR'S REPORT (FINAL REPORT)

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HEI has set as one of its goals to publish research reports of the highest scientific quality that will be of value to regulators, government officials, scientists, and the interested public. After a study is completed, each HEI-funded Principal Investigator prepares a comprehensive final report that describes the study and its findings. Because some of HEI's research projects are designed to provide information to be used in regulatory decisions, HEI places an emphasis on timeliness.

The HEI Review Committee, which has no role in either the selection of investigators for funding or the oversight of studies, evaluates the investigator's final report. The objectives of the HEI review process are to (1) evaluate the scientific quality and significance of the research, (2) point out the strengths and limitations of the study, (3) place the study into scientific and regulatory perspective, (4) identify future research opportunities, and (5) communicate all the findings (positive and negative) to the Institute's sponsors and the public.

Each draft final report is peer-reviewed by scientists with appropriate technical expertise, including a biostatistician. A compilation of the comments of the reviewers, together with the Review Committee's initial review, is sent to the investigator, who has an opportunity to respond to these comments and, if necessary, to revise the report. Occasionally, the Review Committee may request major changes such as additional analyses. Subsequently, the Review Committee prepares its commentary. The investigator is given an opportunity to comment on the commentary prior to publication. The contractual obligation to prepare a comprehensive final report and to participate in the HEI review process distinguishes HEI from most other funding agencies. Potential applicants should be aware of the effort associated with this responsibility.

The HEI Research Reports, which consist of the investigator's final report and the Review Committee's commentary, are the principal means by which the Institute communicates results of its research and review processes. They are distributed to the motor vehicle industry, the EPA, the scientific community, libraries that serve medical and scientific communities, and the general public. In addition, the HEI research reports are registered with the National Technical Information Services. Reports that have been published are indicated in Appendix B and are available on HEI's website [www.healtheffects.org](http://www.healtheffects.org).

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## PUBLICATIONS

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It is the policy of the Institute to encourage investigators to publish results of research conducted under HEI funding in the open scientific literature. HEI retains a non-exclusive license to publish material from work funded by HEI; it is the responsibility of the investigator and his/her institution to notify other publishers of HEI's rights.

A statement acknowledging HEI support and the following disclaimer must appear in all publications resulting from work funded by HEI: "Research described in this article is conducted under contract to the Health Effects Institute (HEI), an organization jointly funded by the United States Environmental Protection Agency (EPA) (Assistance Agreement R82811201) and automotive manufacturers. The contents of this article do not necessarily reflect the views of HEI, nor do they necessarily reflect the views and policies of EPA, or motor vehicle and engine manufacturers."

Copies of all journal articles, abstracts, and review articles describing HEI-funded research must be sent to the Institute at the time of their publication.

## INSTRUCTIONS FOR COMPLETING THE APPLICATION

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### GENERAL INFORMATION

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Applications must be submitted on the attached HEI Application for Research Agreement (forms F-1 to F-10). Applications should be typed single-spaced, within the margin limitations indicated on the forms.

Any contract awarded under this Request for Applications is expected to be funded in part by a grant from the U. S. Environmental Protection Agency. This award process will be subject to regulations contained in 40 CFR Subchapter B, and particularly Part 33 thereof. Neither the United States nor the U. S. Environmental Protection Agency is nor will be a party to this Request for Applications or to any resulting agreement.

HEI and its funded institutions are subject to the Office of Management and Budget and EPA accounting regulations.

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### BUDGET (APPLICATION FORMS F-4, F-5)

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**Cost or Pricing Data:** Provide adequate data and analysis to assure HEI that the proposed costs are reasonable and that adequate accounting procedures will be used. HEI has no specific limitation on the budgets of research proposals. Most of those funded to date have been within a range of \$70,000 to \$300,000 per year, including indirect costs. Projects requiring larger budgets or time periods longer than three years must have exceptional promise of developing important methods or information for understanding the health effects of automotive emissions. For applications responding to RFA 00-1 and RFA 00-2 the budget should be prepared assuming a project start date of October 1, 2001.

### PERSONNEL

List the names and positions of all applicant organization personnel involved in the project, both professional and nonprofessional, whether or not salaries are requested. Estimate the percentage of time or effort, or hours per week, on the project for professional personnel in relation to the total professional activity commitment to the applicant organization; estimate the hours per week on the project for nonprofessional personnel. List the dollar amounts separately for each individual for salary and fringe benefits. Fringe benefits may be requested to the extent that they are treated consistently by the

applying organization as a direct cost to all sponsoring agencies.

The amount to be reimbursed to each individual, when added to his or her compensation for all other full-time duties, should not exceed the individual's base salary. In computing estimated salary changes, an individual's base salary represents the total authorized annual compensation that an applicant organization would be prepared to pay for a specific work period whether an individual's time is spent on sponsored research, teaching, or other activities. The base salary for the purposes of computing charges to an HEI Research Agreement excludes income that an individual may be permitted to earn outside of full-time duties to the applicant organization.

Where appropriate, indicate whether the amounts requested for the principal investigator and other professional personnel are for summer salaries or academic-year salaries and indicate the formulas for calculating summer salaries.

Indicate whether current rates or escalated rates are used. If escalation is included, state the degree (percent) and methodology, e.g., annual flat rate applied to base rate as of a specific date or a mid-pointed rate for the period of performance.

### CONSULTANT COSTS

Consultant service should be explained by indicating the specific area in which such service is to be used. Identify the contemplated consultants. State the number of days of such services estimated to be required and the consultant's quoted rate per day, and indicate the number of hours per day in which work will be performed. HEI's participation in consultant costs is subject to limits set by EPA regulations. (See also Additional Submissions on pages 35-36).

### EQUIPMENT

Provide an itemization and justification of all equipment to be purchased or fabricated for use in this study. Please note that HEI reimburses institutions only for those equipment items explicitly listed in the Approved Budget or subsequently authorized in writing by HEI's Director of Research or Director of Finance & Administration.

**ALTERATIONS AND RENOVATIONS**

The costs of construction per se are not permissible charges. If the costs of essential alterations of facilities, including repairs, painting, removal or installation of partitions, shielding, or air conditioning, are requested, itemize them by category and justify them fully. When applicable, indicate the square footage involved, giving the basis for the costs, such as an architect's or applicant's detailed estimate. When possible, submit a line drawing of the alterations being proposed.

**SUPPLIES AND OTHER EXPENSES**

All supplies and other expenses should be itemized in sufficient detail to allow reviewers to understand the major categories of expenditures (i.e., glassware, media, chemicals, animal purchase and housing, as well as publication costs, page charges, and books, listed by category and unit cost). Itemize and justify such items as patient compensation, travel, and per diem costs, rentals, leases, and computer costs. Unusually expensive items for special processes should be separately identified by quantity and price and the use or application thoroughly explained in the project plan. Each individual expense item must be categorized as supplies or other expenses according to the practices of the accounting office of your institution.

**TRAVEL EXPENSES**

Limit travel to one scientific meeting per year. Do not include the travel to the annual conference within the budget, since HEI will cover these costs directly. If travel is required for other purposes, indicate the estimated number of trips, destination, reason for travel, and cost. Identify and support any other special transportation costs attributable to the performance of this project. HEI pays for foreign travel only if it is approved in advance of the trip.

**SUBCONTRACTS**

Itemize and enter a total for these costs. Describe and justify all appropriate costs for services purchased for, or associated with, third parties, including applicable indirect costs. These costs may include, but are not necessarily limited to, consortium agreements or formalized collaborative agreements. Indirect costs for subcontracts are subject to HEI's 30% cap (see below). Develop separate budgets for the initial and future budget periods for each organization involved in consortium

arrangements or formalized collaborative agreements, and submit them using the appropriate budget form (F-5a and F-5b).

**INDIRECT COSTS**

Indirect costs are limited to a maximum of 30% of direct costs excluding equipment charges and subcontracts. Indirect costs cannot be greater than the government-negotiated rate for your institution. Expenses normally included in the calculation of the indirect cost rate may not be itemized as direct expenses. Please attach a copy of your institution's most recent approved indirect cost rate. Budget review will be delayed if the indirect cost rate certification is not attached.

The HEI Board of Directors has approved a very limited exception to this cap on indirect costs for organizations that can meet both of the following conditions: (1) the research institution provides a unique capability for a project essential to HEI's mission, and (2) the institution is prohibited by the U.S. Government from accepting less than full cost recovery.

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**PROJECT PLAN**

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(No application forms are provided but the investigator should adhere to the guidelines described below).

The Project Plan should include the sections listed below. Include sufficient information in the Project Plan and in any appendix to facilitate an effective review. Be specific and informative and avoid redundancies. Sections A, B, and C should total no more than four single-spaced pages using a font size no smaller than 10 point. The Institute reserves the right not to consider proposals that exceed this limit. Appendices may be provided as supplementary information, but review will be based mainly on the information provided in the Project Plan. Section D should be concise but adequately detailed to permit critical evaluation. There is no limit on page number for Section D.

**A. Objectives**

State concisely and realistically what the research described in this application is intended to accomplish and/or what hypothesis is to be tested.

**B. Anticipated Results and Significance**

Briefly sketch the background to the present proposal, critically evaluate existing knowledge, and specifically identify the gaps that the project is intended to fill. State concisely the importance of the research described in this

application by relating the specific aims to the stated objectives of HEI and explain the regulatory significance.

**C. Related Previous Studies**

Provide an account of, and references to, the principal investigator's previous studies pertinent to the application and/or any other information, including preliminary findings, that will help to establish the experience and competency of the investigator to pursue the proposed project. The appendix can be used for published references or details of available pilot studies.

**D. Experimental Plan and Methods**

Discuss in detail the experimental design and the procedures to be used to accomplish the specific aims of the project.

Define your study sample (such as cell type, animal strain, or subject population) and explain the rationale for choosing it. If the study involves human subjects, describe how they will be selected, and the informed-consent procedure. (See *Additional Submissions* below).

HEI is committed to research that can lead to a better understanding of health responses of all members of the general population, particularly the most sensitive. Accordingly, consider the composition of the study population, including gender, racial/ethnic composition, and other aspects that might affect response, and provide a rationale for the choice of composition.

Provide sufficient details of the experimental design and study protocol so that it can be understood clearly by the reviewers. Applicants are encouraged to provide details of exposure systems for specific pollutants (and the rationale for their selection), randomization procedures, methods used for any blinding of observations, and the proposed number of observations (including number of animals or subjects and exposure groups). Describe any new methodology and its advantage over existing methodologies.

Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims.

Include a description of the statistical methods to be used for analysis and interpretation of the data. Describe the proposed statistical procedures with sufficient detail to allow evaluation by a biostatistical reviewer.

Where appropriate, describe the procedures to be used to ensure that the quality of the data is adequate in view of the objectives of the study (see Quality Assurance on page 30). However, detailed QA information should not be submitted with the original application but will be re-

quested for successfully funded studies that meet the above criteria.

**E. Literature Cited**

References in the text should consist of author and year. Provide complete citations in alphabetical order at the end of the Project Plan.

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**ADDITIONAL SUBMISSIONS (APPLICATION FORM F-9)**

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**Human Subjects**

If Item 6 on the FACE PAGE of the application has been marked "YES," submit form HHS-310 (Page F-9 of HEI application form).

Safeguarding the rights and welfare of human subjects in projects supported by EPA grants is the responsibility of the institution, which receives or is accountable to EPA for the funds awarded for the support of the project. The EPA regulations require applicant institutions to comply with the Department of Health and Human Services (DHHS) guidelines for human subjects. The Health Effects Institute is responsible for ensuring that these guidelines are followed by all investigators funded by HEI.

The Institution must submit to HEI, for review, approval, and official acceptance, a written assurance of its compliance with guidelines established by the Department of Health and Human Services concerning protection of human subjects. However, institutions that have submitted and have had accepted general assurance to DHHS under these guidelines will be considered as being in compliance with this requirement. The DHHS's regulation, 45 CFR 46, is available from the Office for Protection from Research Risks, National Institutes of Health, Bethesda, MD 20892, or from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20420, USA.

If the application involves human subjects, Part D of the Project Plan should include the following information:

Identify the sources of the potential subjects, derived materials, or data. Describe the characteristics of the subject population, such as their anticipated number, age, gender, ethnic background, and state of health. Identify the criteria for inclusion or exclusion. Explain the rationale for research involving fetuses, in vitro fertilization, pregnant women, children, institutionalized mentally disabled subjects, prisoners, or other subjects, especially those whose ability to give voluntary informed consent may be in question.

Describe the recruitment and consent procedures to be followed, including the circumstances under which consent will be solicited and obtained, who will seek it, the nature of information to be provided to prospective subjects, and the methods of documenting consent. Include the consent form to be used.

Describe potential risks to the subjects—physical, psychological, social, legal, or other—and assess their likelihood and seriousness. Describe alternative methods, if any, that were considered and why they will not be used.

Describe the procedures for protecting against or minimizing potential risks and include an assessment of their likely effectiveness. Include a discussion of confidentiality safeguards, where relevant, and arrangements for providing medical treatment if needed.

Describe and assess the potential benefits to be gained by the subjects, as well as the benefits that may accrue to society in general as a result of the planned work.

Discuss the risks in relation to the anticipated benefits to the subject and to society.

If HEI decides to fund a study involving human subjects, the investigator will be asked to submit a detailed protocol before starting the study and to comply with HEI's special QA/QC procedures (see *HEI Project Negotiation, Project Management, and Investigator Commitment*). Approval of the study by the Institutional Review Board at the investigator's institution is required before starting a study with human subjects.

#### **Sponsor Participation**

If "YES" has been marked under sponsor participation on page F-7 of the application form, please explain on a separate sheet the nature of sponsor participation. Identify and explain the role of any individual employed by EPA or motor vehicle sponsors of HEI who is involved with any aspect of the proposed study. Also, list any resources provided by sponsors, including animals, equipment, and facilities. Please note that employees of organizations funding HEI cannot receive funds from HEI for salary or any other costs.

#### **Laboratory Animals**

The applicant shall provide with the application written assurance that any use of laboratory animals will comply with the provisions of the Animal Welfare Act (7 U.S.C. S 2131 et. seq.) and the guidelines set forth in the Guide for the Care and Use of Laboratory Animals. These documents are available from the Office for the Protection from Research Risks, National Institutes of Health,

Bethesda, MD 20892. If laboratory animals are to be used in the proposed studies, state the species, strains, ages, and numbers of the animals involved and the methods to be used to comply with the above-mentioned guidelines.

#### **Recombinant DNA**

Applicants proposing work with recombinant DNA should adhere to the current *NIH Guidelines for Research Involving Recombinant DNA Molecules*. A copy of the Guidelines is available from the Office of Recombinant DNA Activities, National Institutes of Health, Bethesda, MD 20892.

#### **Consultants**

Consultant arrangements must be confirmed in writing. Attach appropriate letters from each individual, confirming his or her role in the project.

#### **Quality Assurance**

It is HEI's policy to apply its special QA/QC procedures to all approved research projects that are anticipated to produce data of regulatory significance. This includes all human studies, as well as certain designated animal studies.

#### **Personal Data**

HEI has a continuing commitment to monitoring the operation of its review and award process to detect, and deal appropriately with, real or imagined inequities with respect to age, ethnicity, race, or gender of the proposed principal investigator. To provide HEI with the information needed to fulfill this commitment, we request that each applicant complete the optional personal data form and attach it as the last page of the signed original application. **Do not attach copies of the personal data form to the duplicated copies of this application.** Upon receipt at the HEI office, this form will be separated from the application and used only for internal HEI monitoring procedures.

**If you do not wish to provide this information, or do not complete the form, it will in no way affect consideration of your application.**





Application for  
**Health Effects Institute**  
**RESEARCH AGREEMENT**

All Agreements Use the Cost Reimbursement Format

\_\_\_\_\_  
*Number (Leave Blank)*

**1. TITLE OF APPLICATION** *(limit title to this space)*

**2. RESPONSE TO RFA OR RFPA NUMBER AND TITLE**

**3. TYPE OF ORGANIZATION** *(see instructions)*

- |   |   |   |
|---|---|---|
| <input type="checkbox"/> Private Non-Profit   | <input type="checkbox"/> Private Profit | <input type="checkbox"/> Minority Owned |
| <input type="checkbox"/> Educational  |   | <input type="checkbox"/> Small Business |
| <input type="checkbox"/> Public ( <input type="checkbox"/> Federal, <input type="checkbox"/> State, <input type="checkbox"/> Local) |   | <input type="checkbox"/> Woman Owned    |

**4. PRINCIPAL INVESTIGATOR**

**4A. NAME (LAST, FIRST, MIDDLE)**

**4B. MAILING ADDRESS** *(Street, City, State, Zip Code)*

*Signature and Date*

**4C. TELEPHONE NUMBER** *(Area Code, Extension)*

**4D. FAX NUMBER** *(Area Code)*

**4E. EMAIL**

**4F. POSITION TITLE**

**5. TOTAL COST REQUESTED FIRST 12-MONTH PERIOD**  
*(From Page F-4)*

\$ \_\_\_\_\_

**6. HUMAN SUBJECTS OR DERIVED MATERIALS INVOLVED?**

Yes                      No

**7. TOTAL COST REQUESTED ENTIRE PROJECT PERIOD**  
*(From Page F-5) / Number of Years*

\$ \_\_\_\_\_

**8. APPLICANT ORGANIZATION** *(Name, Address, and Congressional District)*

**9. NAME, TITLE, ADDRESS, EMAIL & TELEPHONE NUMBER OF INDIVIDUAL(S) AUTHORIZED TO NEGOTIATE AGREEMENT**

*Signature and Date*

**10. NAME, TITLE, ADDRESS, EMAIL & TELEPHONE NUMBER OF INDIVIDUAL(S) AUTHORIZED TO EXECUTE AGREEMENT**

*Signature and Date*



# TABLE OF CONTENTS OF APPLICATION

*Number pages consecutively at the bottom throughout the application. Type the name of the Principal Investigator at the top of each printed page and each continuation page.*

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E. Literature Cited

## ADDITIONAL SUBMISSIONS

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\* Indicates application elements for which HEI forms should be used.



## ABSTRACT OF PROJECT PLAN

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**PRINCIPAL INVESTIGATOR:** (Name, Title, and Institution)

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**PROJECT TITLE:**

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**ABSTRACT OF PROJECT PLAN:** Concisely describe the application's specific aims, methodology, and long-term objectives, making reference to the scientific disciplines involved and the relationship of the project to the objectives of HEI and the Request for Applications. The abstract should be self-contained so that it can serve as a succinct and accurate description of the application when separated from it. **DO NOT EXCEED ONE PAGE.**



**BUDGET FOR FIRST 12 MONTH PERIOD**

From			Through				
Personnel			Time Effort		Dollar Amount Requested (omit cents)		
NAME	Title or Position	Role in Project	%	Hours /Week	Salary	Fringe Benefit	Totals
		Principal Investigator					
<b>Subtotals</b>							
Consultant Costs							
Equipment (itemized)							
Supplies (itemized)							
Other Expenses (itemized)							
Travel (Domestic Only)							
Subcontracts							
Subtotal Direct Costs							
Indirect Costs - Limited to 30% of direct costs excluding equipment and subcontracts. See budget instructions. Please attach a copy of most recent approved indirect cost rate.							
<b>Total Costs (Also enter on page F-1, Item 5)</b>							


**BUDGET FOR FIRST 12 MONTH PERIOD (SUBCONTRACT)**

From			Through				
Personnel			Time Effort		Dollar Amount Requested (omit cents)		
NAME	Title or Position	Role in Project	%	Hours /Week	Salary	Fringe Benefits	Totals
		Principal Investigator					
<b>Subtotals</b>							
Consultant Costs							
Equipment (itemized)							
Supplies (itemized)							
Other Expenses (itemized)							
Travel (Domestic Only)							
Subtotal Direct Costs							
Indirect Costs - Limited to 30% of direct costs excluding equipment and subcontracts. See budget instructions. Please attach a copy of most recent approved indirect cost rate.							
<b>Total Costs (Also enter on page F-1, Item 5)</b>							

**BUDGET FOR TOTAL PROJECT**

BUDGET CATEGORY	1ST BUDGET PERIOD (FROM PAGE F-4)	ADDITIONAL YEARS SUPPORT REQUESTED		
		2ND	3RD	TOTAL
PERSONNEL (Salary and Fringe Benefits) (Applicant Organization Only)				
CONSULTANT COSTS				
EQUIPMENT				
SUPPLIES				
OTHER EXPENSES				
TRAVEL				
SUBCONTRACTS				
ALTERATIONS AND RENOVATIONS				
SUBTOTAL DIRECT COSTS				
INDIRECT COSTS (NOTE 30% CAP)				
TOTAL COSTS				
<b>TOTAL FOR ENTIRE PROPOSED PROJECT. (ALSO ENTER ON PAGE F-1, ITEM 7)</b>				

*JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any cost for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category. If a recurring annual increase in personnel costs is anticipated, give percentage.*


**BUDGET FOR TOTAL PROJECT (Subcontract)**

BUDGET CATEGORY	1ST BUDGET PERIOD (FROM PAGE F-4)	ADDITIONAL YEARS SUPPORT REQUESTED		
		2ND	3RD	TOTAL
PERSONNEL (Salary and Fringe Benefits) (Applicant Organization Only)				
CONSULTANT COSTS				
EQUIPMENT				
SUPPLIES				
OTHER EXPENSES				
TRAVEL				
ALTERATIONS AND RENOVATIONS				
SUBTOTAL DIRECT COSTS				
INDIRECT COSTS (NOTE 30% CAP)				
TOTAL COSTS				
<b>TOTAL FOR ENTIRE PROPOSED PROJECT. (ALSO ENTER ON PAGE F-1, ITEM 7)</b>				

*JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any cost for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category. If a recurring annual increase in personnel costs is anticipated, give percentage.*



## **OTHER SUPPORT**

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Describe current and pending grants or contracts from which the investigators proposed for this project are now drawing or anticipate drawing support. Identify program by title, agency, or organization supporting such work, and level of financial support given. Briefly describe the contents of each. If any of these overlap, duplicate, or are being replaced or supplemented by the present application, justify and delineate the nature and extent of the scientific and budgetary overlaps or boundaries.

### **PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR**

#### **(1) Active Support**

#### **(2) Pending Support**



**RESOURCES AND ENVIRONMENT**

**FACILITIES:** *Describe all the facilities to be used and, in the space provided, indicate their capacities, pertinent capabilities, relative proximity and extent of availability to the project. Using continuation pages if necessary, include a description of the nature of any collaboration with other organizations and provide further information in the RESEARCH PLAN.*

**Laboratory**

**Animal**

**Clinical**

**Computer**

**Other**

**MAJOR EQUIPMENT:** *List the most important equipment items available for this project, noting the location, and pertinent capabilities of each.*

**CONSULTANTS:** *Identify consultants by name and give area of expertise and daily fee to be paid.*

**SPONSOR PARTICIPATION**  YES  NO

*If yes, on a separate sheet identify and explain role of any individuals employed by the EPA or motor vehicle sponsors of HEI who are involved with any aspect of the project. Also, list any resources provided by sponsors (such as facilities or animals)*



## BIOGRAPHICAL SKETCH

Give the following information for professional personnel and consultants beginning with the Principal Investigator. Photocopy this page for each person.

NAME	TITLE	BIRTH DATE (Month, Day, Year)

**Education** (Begin with baccalaureate training and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE:** Concluding with present position, list in chronological order previous employment, experience, and honors. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application.

## Protection of Human Subjects Assurance Identification/Certificate/Declaration (Common Federal Rule)

*POLICY:* Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting the Common Rule (58FR28003, June 18, 1991) unless the activities are exempt from or approved in accordance with the common rule. See Section 101(b) the common rule for exemptions. Institutions submitting applications or proposals for support must submit certification of appropriate Institutional Review Board (IRB) review and approval to the Department or Agency in accordance with the common rule.

Institutions with an assurance of compliance that cover the research to be conducted on file with the Department, Agency, or the Department of Health and Human Services (HHS) should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency. Institutions which do not have such an assurance must submit an assurance and certification of IRB review and approval within 30 days of a written request from the Department or Agency.

1. Request Type <input type="checkbox"/> ORIGINAL <input type="checkbox"/> FOLLOWUP <input type="checkbox"/> EXEMPTION	2. Type of Mechanism <input type="checkbox"/> GRANT <input type="checkbox"/> CONTRACT <input type="checkbox"/> FELLOWSHIP <input type="checkbox"/> COOPERATIVE AGREEMENT <input type="checkbox"/> OTHER: _____	3. Name of Federal Department or Agency and, if known, Application or Proposal Identification No.
4. Title of Application or Activity		5. Name of Principal Investigator, Program Director, Fellow, or Other

6. Assurance Status of this Project (*Respond to one of the following*)

- This Assurance, on file with the Department of Health and Human Services, covers this activity:  
 Assurance identification no. M-\_\_\_\_\_ IRB identification no. \_\_\_\_\_
- This Assurance, on file with (*agency/dept.*) \_\_\_\_\_, cover this activity:  
 Assurance identification no. \_\_\_\_\_ IRB identification no. \_\_\_\_\_ (*If applicable*)
- No assurance has been filed for this project. This Institution declares that it will provide an Assurance and Certification of IRB review and approval upon request.
- Exemption Status:* Human subjects are involved, but this activity qualifies for exemption under Section 101(b), paragraph \_\_\_\_\_.

7. Certification of IRB Review (*Respond to one of the following IF you have an Assurance on file*)

- This activity has been reviewed and approved by the IRB in accordance with the common rule and any other governing regulations or subparts on (*date*) \_\_\_\_\_ by:  Full IRB Review or  Expedited Review.
- This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the common rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed and certification will be provided.		10. Name and Address of Institution	
11. Phone No. ( <i>with area code</i> )	12. Fax No. ( <i>with area code</i> )	13. Name of Official	
14. Title		15. Signature	
16. Date		16. Date	

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Public reporting burden for this collection of information is estimated to average 5 minutes per response. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: PHS Reports Clearance Officer (9999-0020 and 0925-0418), Room 737-F, Humphrey Building, 200 Independence Ave., S.W., Washington, D.C. 20201, Attn: PRA. Do not return the completed form to this address.

OPTIONAL FORM 310 (Rev. 1-95)  
 Sponsored by HHS/PHS/NIH



Attach this form to the signed original of the application. Do not duplicate.  
**PERSONAL DATA ON PRINCIPAL INVESTIGATOR**

Health Effects Institute has a continuing commitment to monitoring the operation of its review and award processes to detect and deal appropriately with any instances of real or apparent inequities with respect to age, sex, race, or ethnicity of the proposed principal investigator/program director.

To provide HEI with the information it needs for this important task, please complete the form below and attach it to the signed original of the application. Do not attach copies of this form to the duplicated copies of the application.

Upon receipt and assignment of this application by HEI, this form will be separated from the application. This form will not be duplicated, and it will not be a part of the review process. Data will be confidential. All analyses conducted on the data will report aggregate statistical findings only and will not identify individuals.

If you decline to provide this information, it will in no way affect consideration of your application.

Your cooperation will be appreciated.

---

DATE OF BIRTH (*month/day/year*)

SEX    \_\_\_ Female \_\_\_ Male

---

RACE AND/OR ETHNIC ORIGIN (*check one*)

- \_\_\_ American Indian or Alaskan Native
- \_\_\_ Asian or Pacific Islander
- \_\_\_ Black, not of Hispanic origin
- \_\_\_ Hispanic
- \_\_\_ White, not of Hispanic origin

NOTE: The category that most closely reflects the individual's recognition in the community should be used for purposes of reporting mixed racial and/or ethnic origins. Definitions are as follows:

American Indian or Alaskan Native: A person having origins in any of the original peoples of North America and who maintains cultural identification through tribal affiliation or community recognition.

Asian or Pacific Islander: A person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands. This area includes, for example, China, India, Japan, Korea, the Philippine Islands and Samoa.

Black, not of Hispanic origin: A person having origins in any of the black racial groups of Africa.

Hispanic: A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin, regardless of race.

White, not of Hispanic origin: A person having origins in any of the original peoples of Europe, North Africa, or the Middle East.

## APPENDIX A: HEI Strategic Plan for the Health Effects of Air Pollution (2000-2005)

HEI's strategic plan describes the projected research program and scientific review activities for the period 2000–2005. This plan was developed with ideas and input from HEI's sponsors, the scientific community, and other constituents. To provide information to applicants about HEI's mission, views about important research needs, and research priorities, several sections of the current strategic plan are included in this Appendix. The entire plan can be found on HEI's website at [www.healtheffects.org](http://www.healtheffects.org).

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### HEI STRATEGIC PLAN 2000–2005 (*Selected Portions*)

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#### INTERNATIONAL PERSPECTIVE

Current trends in environmental regulation and industrial development are converging in a manner that encourages a thoughtful and consistent approach to providing a scientific base that can inform decisions made in the US, Europe, and Asia. Industry, including management, manufacturing, and distribution, is increasingly global in nature. Environmental regulators are increasingly asking similar questions about the public health impacts of common pollutants, often at or nearly the same time. The EPA in 1997 and the European Commission in 1998 adopted stringent new standards for PM and relied in large measure on many of the same studies in the process. Both will be reevaluating the effects of fine particles within one year of each other (2002 and 2003, respectively).

Questions regarding the effects of air toxics such as butadiene, benzene, and diesel exhaust are relevant to regulators in Europe, Asia, and the US. As EPA seeks to define a new level for sulfur in gasoline, it has learned from the European and California experience with low-sulfur gasoline. Europe is moving ahead with a new regulatory approach, Clean Air for Europe, that will for the first time require an integrated, rather than a one-at-a-time, review of the effects of major air pollutants on a five-year cycle. This approach will, among other things, drive science to more fully understand the health effects of mixtures of pollutants and is directly relevant to questions being raised by regulators in the US.

The increasingly global nature of environmental questions has been recognized by industry, regulators, and environmental nongovernmental organizations alike, with regular transatlantic dialogues being carried out by all groups. While the breadth of these questions far exceeds

the ability of any one agency or institute to address, subsets of key questions may be effectively addressed by an HEI with a more international presence. Indeed, regular assessments of the effects of key pollutants are conducted by the World Health Organization and the International Agency for Research on Cancer, and HEI's research schedule can be adapted to help inform these efforts more directly. In pursuit of the best science to inform its industry and government sponsors in the US, HEI's research program has evolved to the point that it currently funds studies in several European and Asian nations. There are clear benefits to drawing on a base of international studies, and chief among these is the ability to provide a consistent scientific base to regulators in the transatlantic arena. Scientific studies can be designed to recognize both differences and consistencies in different areas and can be tailored to be relevant to broader regulatory needs. Economies of scale can be realized in study design, publication and communication, and emerging trends in research, and results can be identified, integrated, and disseminated clearly and quickly. These accomplishments can provide an early warning to design engineers in industry and to regulators concerned about protecting health and the environment.

Thus, initially HEI will continue the international perspective it brings to every aspect of its science priorities, enabling HEI to provide added value, at a relatively modest cost, to its work both in the US and internationally. Over time, as this plan is implemented and greater international funding develops, HEI will seek to establish a local presence in Europe and perhaps in Asia in order to ensure maximum impact.

#### PRIORITY TOPICS

##### Air Pollution Mixture

Polluted air is a complex mixture made up of vaporous, liquid, and solid components. The mixture varies greatly in composition and concentration in different regions of the US and around the world due to differences in contributions of various pollution sources and differences in weather and topography. The air pollution mixture also varies from day to day and in different seasons within a region. Most NAAQSs focus on specific compounds (termed criteria pollutants, such as ozone, carbon monoxide, and nitrogen dioxide) although interactions with other pollutants are considered in setting standards for individual pollutants. The NAAQSs for PM focus on complex mixtures within the air pollution mixture (PM<sub>2.5</sub> and PM<sub>10</sub>).

Because of the regulatory focus on specific compounds or groups of compounds, research has also tended to focus on single pollutants. However, different pollutants can cause similar responses, often through different mechanisms, and with two or more pollutants together, the response may be additive, more than additive, or less than additive. Knowledge about such interactions is taken into account in setting NAAQSs, but a more comprehensive effort is needed to understand the nature of these interactions and to account for them appropriately in air quality regulations. Besides the criteria pollutants regulated in the US by NAAQSs, a vast number of other pollutants are part of the air pollution mixture, including the 33 hazardous air pollutants identified in EPA's Urban Air Toxics Strategy. Figure 3 illustrates categories of air pollution of particular interest at this time.

In addition to understanding the interactive effects of pollutants, it is also important to understand how different components of a regulated mixture (PM<sub>10</sub> and PM<sub>2.5</sub>) contribute to its toxicity. In this way implementation of air quality standards for the mixture can be focused on the sources of greatest concern. This will become increasingly important as states begin to make decisions about controlling PM in 2005 and beyond.

Questions about mixtures of pollutants can be addressed at many levels, all of which will contribute to our

of pollutants in controlled exposure studies in animals and humans, evaluating the association of different pollutants with the same health effects in epidemiologic studies, and comparing the health effects of different mixtures from different sources. In continuing to contribute to understanding mixtures, HEI has selected three submixtures within the air pollution mixture for focus. These are

- particulate matter and gaseous pollutants,
- air toxics, and
- diesel emissions.

### Particulate Matter and Gaseous Pollutants

Ambient PM varies in size, chemical composition, and other physical and biological properties, depending on the sources of the particles and the changes they undergo in the atmosphere. The content of this complex mixture varies from place to place and from time to time in a given place. Anthropogenic sources of ambient particles include mobile sources (engines powered by diesel, gasoline, and other fuels), stationary sources (oil-fired and gas-fired boilers and electric power plants), and other sources (woodburning fireplaces, paved and unpaved roads, cigarette smoking, and food cooking).

Exposure to ambient particles has been associated with both acute and chronic health effects. In order to protect public health, EPA has set progressively more stringent mass emission standards for both mobile and stationary sources and has set ambient air quality standards for PM<sub>10</sub> and, more recently, PM<sub>2.5</sub>. HEI's toxicologic and epidemiologic research addresses two questions about the ambient PM mixture that HEI intends to continue and extend under this strategic plan.

- What components or attributes of the ambient PM mixture may be important in causing toxicity?
- How do other pollutants affect or contribute to the adverse effects of PM?

### Attributes of PM Mixture

Identifying the toxic components of PM is complex because of the large number of variables involved—including not just the many particle types and sizes but also the uncertainty about which health endpoints may be affected (asthma, cardiac function, susceptibility to respiratory infections), whether the human subjects or animal models used are sensitive, and the importance of factors such as copollutants.

Figure 3  
The Air Pollution Mixture

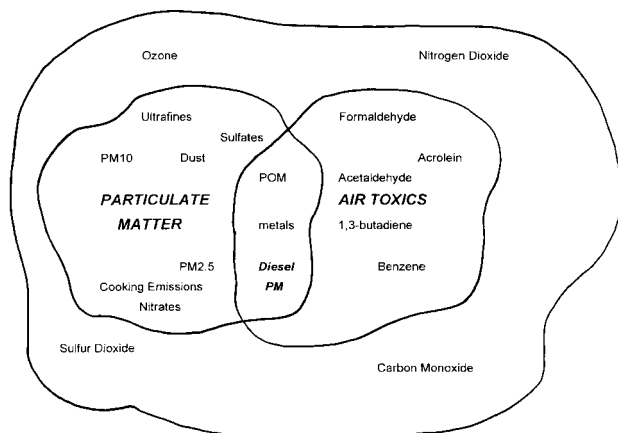


Figure 3. The Air Pollution Mixture

understanding of how the effects of pollutants combine. Examples of the range of approaches include studies investigating mechanisms of interaction of two pollutants at the molecular level, measuring the combined health effects

HEI is currently funding many studies designed to identify what aspects of the PM mixture are associated with toxicity. These studies, which involve a variety of potentially sensitive human subjects or animal models of disease, include: epidemiologic studies evaluating the association between various health endpoints and different fractions of PM (PM<sub>2.5</sub>, ultrafine particles, acid particles); and experimental studies exposing animals or human subjects to concentrated ambient particles in different cities with different particle characteristics, model particles of different sizes or chemical compositions (metals and peroxides) to test hypotheses about mechanisms of toxicity, and particles from different sources (such as diesel-exhaust particles, gasoline-exhaust particles, and coal fly ash).

All of these approaches have strengths and limitations, but we anticipate that together they will provide clues to follow in more targeted studies. Future research to understand the importance of different particle characteristics should also be guided by information about particle composition. Exposure assessment studies and emission characterization studies will identify the most relevant particles to test. In addition to particle characteristics that HEI has been investigating, future research should also consider the roles of organic compounds and of biological components, about which limited information is currently available.

### **Interactions of PM and Gaseous Pollutants**

Many epidemiologic studies of the association between particulate air pollution and changes in morbidity and mortality rates have suggested that pollutants other than particles are also involved in this association. The important issue is to ascertain what adverse effects PM alone may cause in sensitive groups and how gaseous pollutants (such as ozone and carbon monoxide) may alter or add to those effects. NMMAPS, an epidemiologic study funded by HEI, is an outstanding example of evaluating PM and other pollutants. This study is using the same analytic methods to look at many US sites with different patterns of air pollution.

Much of the epidemiologic research on PM in the last decade has focused on time-series studies investigating short-term elevations in PM levels. Effects of long-term exposure may be even more important. Epidemiologic research conducted to date has suggested that long-term exposure to air pollution causes increased mortality and chronic disease (US Environmental Protection Agency 1996b; American Thoracic Society 1996a,b). These

interpretations are complicated, however, by lack of information on historical levels of exposure and adequacy of control of the effects of other risk factors (Moolgavkar and Luebeck 1996; Gamble 1998). Although HEI has funded the reanalysis of two key studies of particulate air pollution and mortality to assess their validity, additional studies will be required to address remaining uncertainties.

Epidemiologic research on the effects of long-term exposure to air pollution is difficult and expensive. Two general approaches should be considered. A possibly cost-efficient approach would be to build on existing cohorts. This might be done by extending the follow-up of cohorts whose exposure to air pollution has already been characterized and in whom effects on the occurrence of chronic disease have been measured (eg, the Harvard Six Cities and ACS studies). Alternatively, investigators could add retrospective air pollution exposure assessments to existing studies of populations in which high quality health and covariate data have been, or are being, collected. Such cohorts have been assembled by the US National Heart Lung and Blood Institute, the Kaiser-Permanente Health Plan in California, and several ongoing multicenter case-control studies being coordinated by the International Agency for Research on Cancer in Eastern Europe and South Asia.

The ideal solution to potential limitations in current studies would be to conduct new, large prospective epidemiologic studies designed specifically to measure the effects of long-term exposure to air pollution. Much of what we currently know about the chronic effects of air pollution exposure we have learned from such efforts (eg, the Harvard Six Cities Study), but at present only the California Children's Health Study and the Swiss SAPALDIA have cohorts under active follow-up.

Such new efforts should establish cohorts in locations characterized by different sources and mixtures of air pollutants in order to allow estimates of the independent and joint effects of individual pollutants. The efforts might well be international in scope. In the US, the enhanced nationwide air pollution monitoring network that the EPA will soon put in place could provide a critical component to the design of such a study. HEI could, in partnership with other organizations, play an important role in planning and coordinating a long-term study.

A better understanding of both the short-term and long-term effects of air pollution, and the roles of various pollutants, is important in setting regulations to protect public health. Possible health endpoints include hospital

admissions for asthma, acute respiratory diseases or cardiovascular problems, development of chronic obstructive pulmonary disease, lung growth and development in children, and premature mortality. In addition to epidemiologic studies, experimental studies using animal models of human diseases or conditions could be used to explore combinations of pollutants, including concentrated ambient particles (CAP) in different locations. They could evaluate a range of endpoints to provide information on both acute and chronic effects and thus inform the design and interpretation of epidemiology studies. Human controlled-exposure studies could be used to gather information about how acute responses may relate to long-term damage or disease.

#### **Air Toxics**

Air toxics comprise a large and chemically varied group of air pollutants not currently regulated under NAAQSs but subject to regulation under the Clean Air Act Amendments. They are emitted from a large number of mobile, stationary, and area sources. In EPA's Integrated Urban Air Toxics Strategy, 33 high priority hazardous air pollutants have been named. This list includes several pollutants on which HEI is conducting research already (acetaldehyde, acrolein, benzene, 1,3-butadiene, formaldehyde). Many other pollutants on this list do not have sufficient information regarding exposure, reactivity, and health effects. HEI will examine this list of priority pollutants to identify critical issues and target those most relevant to our sponsors. HEI will work closely with EPA as the Urban Air Toxics Strategy research priorities are developed and continue to coordinate its research priorities with those of NUATRC so that the research of the two organizations will complement each other.

The overall goal of HEI's air toxics program has been to provide information that will reduce uncertainties in evaluating the human health risks associated with exposure to mobile-source air toxics. This goal has become increasingly important as the mobile-source air toxics we have studied have become central to larger urban air toxics efforts by EPA. In the coming years, HEI expects to continue these efforts, perhaps including additional air toxics such as polycyclic organic matter (POM). Most importantly, HEI will strive to place these effects into the broader pollution framework so that both the individual and combined effects can be better understood.

POM comprises a potentially important set of compounds (eg, PAHs). Listed in the Clean Air Act as a

mobile-source toxic air pollutant, POM is also among the priority hazardous air pollutants in the Integrated Urban Air Toxics Strategy. In Europe, an Air Quality Limit Value on POM is being established. POM compounds with five or more benzene rings are generally associated with PM; those with four or fewer rings are semivolatile and are partitioned between the particulate and gaseous phases. Consideration of POM must also include products of chemical or photochemical reactions in the environment. Health risks from exposure to POM compounds are poorly understood, especially when this exposure involves multiple POM compounds, as it does in the environment. Since particles may carry POM deep into the airways, the bioavailability of particle-associated POM is another area where research may help our understanding of the linkage between exposure and health effects. The role of organic compounds, including POM, is an important issue in understanding toxicity of diesel exhaust particles and other ambient PM.

#### **Diesel Exhaust**

Diesel exhaust is a complex mixture of vapor-phase and particulate species. The particles, which have a carbon core to which hydrocarbons are adsorbed, are mainly under 1  $\mu\text{m}$  in diameter. The gas phase compounds include irritants, mutagens, and carcinogens, such as nitrogen oxides, aldehydes, monocyclic aromatic compounds (eg, benzene), PAHs (with four or fewer rings), and nitro-PAHs.

Diesel exhaust, especially diesel particles, has been of interest to HEI throughout its history. With mounting concern about emissions of greenhouse gases and about availability of fossil fuels, diesel engines have become more desirable for the light-duty fleet in the US and are already being used more widely on a global basis. They emit less carbon dioxide ( $\text{CO}_2$ ) per unit of work done and have much better fuel economy than gasoline-powered engines. However, concerns remain about their high emissions of both particles and nitrogen oxides. Reducing these emissions has been difficult because changing combustion conditions to decrease particles tends to increase emissions of nitrogen oxides, and vice versa. Advanced technology engines, emission-control devices, and improvements in diesel fuel are being developed to address emissions concerns. The Partnership for a New Generation of Vehicles between the US Department of Energy and industry is considering using a new diesel engine in the so-called family car it is developing with a goal of much improved fuel economy (80 miles per gallon). New diesel engines in small European "city" cars provide a similar fuel economy.

HEI's Diesel Epidemiology Project, initiated in 1998, has focused mainly on epidemiologic studies of lung cancer and diesel particulate exposure. This project was designed to evaluate previous diesel epidemiology studies with respect to the adequacy of data for quantitative risk assessment of lung cancer, and to have input on the feasibility of HEI funding a large lung cancer epidemiology study that would better inform future risk assessments by regulatory agencies. However, from public health point of view, noncancer effects are likely to be at least as important, and perhaps more important because of potential effects on many more people. Thus, HEI's Research Committee will address a broad range of issues as it considers directions for diesel research over the next year.

#### **Diesel exhaust and lung cancer**

With respect to considering whether to undertake a major new epidemiology study of lung cancer and diesel exposure, the Diesel Epidemiology Project's Expert Panel recommended evaluating both ongoing studies, including HEI's feasibility studies, and attempts to improve exposure assessments for existing studies first. The panel also felt that including noncancer effects in future studies was important. Panel members thought that the comprehensive series of epidemiologic studies of miners being conducted by researchers at the National Cancer Institute and National Institute of Occupational Safety and Health could contribute to quantitative risk assessment. However, the final results of these studies are not expected until 2003, and the exposures are considerably higher than ambient levels. Results of the HEI feasibility studies will be available in the spring of 2000. As part of the review process for those studies, HEI will evaluate the indications for future research versus improving past studies by conducting retrospective exposure assessments based on those studies and other developments in diesel research. This evaluation will contribute to the Research Committee's thinking and decisions about future epidemiologic studies of long-term diesel exhaust exposure.

#### **Noncancer effects**

As the prevalence of asthma and other respiratory conditions has increased, air pollution, including diesel particulate matter, has been suggested as a possible cause. In Europe, where there is a higher proportion of diesel-powered vehicles, noncancer health effects pose considerable concern. Effects of potential interest include

exacerbation of asthma, respiratory airway inflammation, and allergic responses. The number of individuals experiencing these health effects is growing, especially among children in urban areas. This is an important area in which the research on diesel particulate matter could be combined with HEI's overall PM program.

#### **Mechanisms of effects**

Mechanisms involved in producing both cancer and noncancer health effects of particulate matter are poorly understood. Diesel particles are part of the ambient PM mixture, and it is important to understand mechanisms of toxicity for diesel particles along with other particles in the PM mixture. Understanding mechanisms of toxicity also is important in developing methods for comparative assessment of diesel particle emissions, especially at this time when diesel technology and emission-control devices are undergoing rapid development, with the goal of decreasing diesel particulate emissions significantly, but also the possibility of changing some aspects of the emissions in a deleterious way.

#### **Emerging Technologies and Fuels**

Research and development activity on engine and emission-control technologies and fuels as well as fuel additives has increased dramatically in recent years. This effort is driven by concerns about climate change and fuel availability as well as by air pollution. As the world's population has increased, the use of technology (including motor vehicles) in the developing world has grown and air pollution has become a critical problem in large, densely populated cities. With global "vehicle miles traveled" increasing rapidly, there is great concern about emissions of greenhouse gases such as CO<sub>2</sub> that contribute to global warming. Decreasing the emissions of toxic pollutants and greenhouse gases by individual motor vehicles is one important aspect of addressing these problems (along with finding ways to decrease the miles traveled by individual motor vehicles). In order to accomplish that goal, without inadvertently causing unexpected changes in emissions that increase toxicity, more comprehensive and timely evaluation of the potential health and environmental effects of technology and fuel developments is needed, along with evaluation of cost, feasibility, and other considerations. HEI has the capability of and interest in expanding its role in two areas: (1) providing research and testing related to changes in emissions with use of new fuels and technologies and (2) doing comprehensive comparative assessments of alternative approaches to addressing concerns about

pollutant emissions, fuel economy, CO<sub>2</sub> production, fuel availability, and engine performance.

HEI has been involved in many activities related to evaluating the health effects of fuels, fuel additives, and new technologies. These efforts have included characterization of emissions from diesel engines with different fuels and emission-control devices as well as research on the health effects of methanol, a potential alternative fuel (additives such as MTBE and other ethers), and in the future, metals. In addition HEI has conducted critical reviews of the literature for manganese (as part of the additive methylcyclopentadrenyl manganese tricarbonyl [MMT]), methanol, diesel exhaust, and oxygenates.

These efforts undertaken by HEI demonstrate its capability to address a wide range of issues related to fuels and technologies. However, these occasional efforts, undertaken when opportunities arise, are not an adequate way to approach such increasingly critical issues. Instead, HEI would like to collaborate with organizations involved in characterizing emissions, such as the Coordinating Research Council, Center for Environmental Research and Technology (University of California, Riverside), Desert Research Institute, or Southwest Research Institute, to provide appropriate and timely health effects research and testing. HEI would also like to collaborate with government agencies and other organizations to conduct broad comparative assessments of fuels and technologies.

Numerous compounds are being considered as additives to baseline gasoline (such as MMT) or diesel fuels to increase engine performance or to decrease emissions of certain pollutants, sometimes in conjunction with use of a particle trap (ferrocene, cerium). These additives and their combustion byproducts end up, to varying degrees, in the emissions and may be toxic. In addition, any new substance added to the fuel may affect the composition and toxicity of emissions in other ways. Section 211 of the Clean Air Act is designed specifically to deal with testing new fuel formulations and comparing the toxicity results to those with baseline gasoline. However, only certain additives are being tested under this rule, and even for those, additional research outside the 211 process would be valuable. A strategy is needed for assessing the effects of fuels and fuel additives in a timely way. Likewise, new technologies and engine modifications that are being developed, either to improve engine performance or to reduce exhaust emissions, may also produce unwanted changes in emissions that are harmful. Section 202 (a4) of the Clean Air Act is designed to ensure that “no emission device, system, or design” be

introduced if it “will cause or contribute to an unreasonable risk to public health.”

HEI would like to have a more substantial role in assessing new fuels and technologies in three ways.

**Evaluating health effects.** Depending on the fuel, additive, or technology under consideration, different health endpoints may be of concern (such as pulmonary and cardiovascular toxicity, asthma, neurotoxicity, or cancer). For new fuels or additives, pharmacokinetic information would be obtained for interspecies extrapolation. HEI has the ability to attract a range of scientists to its activities, giving it the flexibility to address a broad range of end points. Work in this area could include both mobilizing panels of experts to quickly screen available data and conducting new, targeted research. Reviews of emerging diesel technologies and new research on health effects emissions from these technologies are important areas where HEI could make a major contribution.

**Developing testing methods.** Sensitive, relevant tests for screening complex mixtures of pollutants need to be developed. A combination of in vitro and in vivo approaches would be useful. Appropriate animal models, selected to represent potentially sensitive subgroups, need to be utilized and, if necessary, developed. Some of HEI's ongoing PM research, which is comparing toxicity of different types of particles, can be considered methods development. This type of research requires iterative efforts over many years but is very important.

**Characterizing emissions.** Primary responsibility for emissions characterization rests with industry, with oversight from EPA. Where necessary and appropriate, HEI could supplement emissions characterization work undertaken by industry, which is not always readily available, by supporting research targeted at comparing emissions from different fuel formulations, fuels with and without an additive, and alternative technologies. As mentioned earlier, HEI also will want to partner with one or more organizations that characterize emissions to obtain data for health assessments.

#### **Results of Air Pollution Regulation: Accountability**

The US Clean Air Act is intended to protect the public health by regulating the levels of air pollutants in the ambient environment. The regulation of ambient levels of air pollution as a public health measure assumes (1) that the pollutants (or related compounds) are causally related to adverse health effects at observed ambient concentrations; and (2) that reducing their ambient concentrations will concomitantly reduce adverse health

effects in the US population. As the public discussion of the health effects of air pollution has sharpened in recent years, the need for additional research to empirically test the second assumption (that is, to measure the public health benefits of air quality regulation) is being raised with increasing frequency.

In several important cases, policy makers have been able to rely on a large body of research studies designed to evaluate the causal role of air pollution. For example, in the course of the recent review of the PM and ozone NAAQSs, several hundred research reports were reviewed and summarized in Criteria Documents. Staff Papers then drew upon those summaries to estimate the impact of current levels of air pollution on the health of the US population and to recommend action, anticipating a benefit to the public health.

In contrast, relatively few evaluations of the public health effects of air regulatory policies have been conducted. The most comprehensive such study, *The Benefits and Costs of the Clean Air Act 1970–1990*, was recently conducted by the EPA in response to Section 812 of the Clean Air Act Amendments of 1990 (US Congress, 1991). A prospective benefits study, also required by the Act, is now under way.

The planners of future research to measure the effect of air quality regulation on public health will need to consider several questions.

- What are the public health objectives, and anticipated benefits, of air quality regulation? What should be measured?
- What evidence of protective effects in the US population will be required to justify air quality regulation in terms of public health protection, and how can the accuracy of this evidence be assessed?
- What approaches can be used to estimate the public health benefits of air quality regulation?

To answer the first two questions will require input from a broad range of expertises and viewpoints such as public health workers and regulators as well as epidemiologists and physicians. Answers are required, however, in order to be able to address the third question and to design future studies.

Two general approaches underlie assessments of the impact of air quality regulation on public health. The *retrospective approach* combines the results of epidemiologic studies of air pollution and health effects (such as daily mortality rates due to cardiovascular

disease) with observed declines in ambient concentrations associated with regulatory activity in order to estimate benefits that may have resulted. This is the approach taken by the EPA in *The Benefits and Costs of the Clean Air Act 1970-1990*.

The *prospective, or surveillance, approach* involves sequential monitoring of health event rates and levels of ambient air pollution as they evolve in response to regulatory initiatives or other factors. This approach requires identification of certain sentinel health effects for ongoing surveillance and continuous, or at least periodic, measurement of air pollutants for a specified target population. Moreover, it requires a comprehensive approach to summary and analysis of these data over time. For the US population, such resources already exist to a large extent, at least as regards the criteria air pollutants. Mortality and morbidity data are available from the National Center for Health Statistics and Health Care Finance Administration, respectively, and air pollution data from the EPA's air quality database. The HEI-funded NMMAPS was designed by the investigators as a model for the use of these (or similar) data for ongoing surveillance of the acute health effects of air pollution and as a model for developing and funding research into priority new methods for measuring health benefits.

HEI will seek to contribute to measuring the health benefits of air pollution regulation in three ways: by organizing the multidisciplinary discussion that will be required to plan research on a conceptual level; by continuing to develop the NMMAPS model for a national surveillance approach to the acute effects of air pollution; and by identifying and funding research into development of new methods for measuring health benefits.

## CROSSCUTTING ISSUES

The crosscutting issues presented in this section describe important aspects of developing health effects information that will be emphasized broadly across pollutants and across issues in HEI's research program.

### Exposure assessment.

Knowledge of exposure to pollutants is necessary for assessing health risk from them. In recent years, HEI has begun to pay attention to this critical area and has funded studies of personal exposure to aldehydes and PM. In the future, exposure assessment should be an important crosscutting issue to be considered for all pollutants of interest.

### **Sensitive groups**

Identification of the population groups most sensitive to pollutants and the degree of sensitivity is necessary before standards can be set that protect the most sensitive groups. Factors that are important to consider are age, preexisting health conditions, gender, racial or ethnic background, genetic predisposition, and simultaneous or prior exposure to other substances. Understanding mechanisms of toxicity, another crosscutting issue, should provide clues as to who might be sensitive. With the rapidly developing identification of large numbers of genes, progress in understanding gene–environment interactions in the etiology of diseases should also move ahead. Many current studies in molecular epidemiology address the issue of gene–environment interactions in some way (for example, by comparing the responses to some exposure by stratification on a detoxification enzyme phenotype, such as glutathione S–transferase). While valuable, this approach represents only the surface of investigation into gene–environment interactions. Fundamental research is needed on some basic issues (such as the effects of dose level, multiple genetic factors, protective effects, and interactive mechanisms). Exploration of these issues should lead to a much deeper understanding regarding individual risk assessment of pollutants and contribute to regulatory decisionmaking and better understanding of issues related to protection of susceptible populations.

### **Mechanisms**

Understanding the mechanisms by which pollutants cause disease is an essential part of developing valid health effects information and appropriate markers of dose and effects.

### **Extrapolation**

Except when health effects are determined to occur in humans at ambient levels of exposure, effects must be extrapolated from higher exposure levels to lower exposure levels, or from an animal species to humans, or both. Extrapolation issues from high-dose to low-dose include the shape of the dose-response curve and the relation between mechanisms at different dose levels. Extrapolation issues from species to species include difference in the amount and distribution of the toxic agent in the lungs, differences in dose-response relationships, qualitative and quantitative differences in metabolism affecting the dose of active metabolites at target sites, and gender differences.

### **Biomarkers**

Assessing human health risks associated with exposure to low levels of potentially toxic or carcinogenic compounds is difficult, particularly when the risks are likely to be relatively small. Reliable biomarkers related to particular pollutants of interest can improve our understanding of the exposure–dose–response relationship and thus of comparing potencies across species. Of particular interest are (1) markers of uptake, metabolic activation, and detoxification; (2) markers of internal dose of metabolically activated compounds; and (3) markers of effects, such as early indicators of disease. HEI has pursued the development and validation of biomarkers in its air toxics program and will continue to use this approach in its future research.

### **Diseases**

Other potential crosscutting issues include diseases that have particular public health importance and may be affected by a number of pollutants of interest. Asthma is a good example. The incidence of asthma has been increasing around the world for several decades, and the cause or causes are not known. In this plan, we have raised concerns about asthma in conjunction with ozone, diesel particles, and more generally ambient particles. In inner city areas, asthma incidence in children is higher than in other areas; understanding the reason for this is important.

### **Methods development**

In addition to producing health effects information, HEI has contributed to the development of critical methods relevant to health effects research. Under this strategic plan, HEI will support development of methods as appropriate and needed to support its research goals. HEI may focus on some methods related to its priority research topics:

- understanding the relevance of various animal models to human diseases, and developing new animal models, as necessary;
- developing sensitive, relevant in vitro assays for assessing the relative toxicity of different types of particles or other pollutants;

- developing statistical methods for studying mixtures; and
- developing methods to estimate exposure measurement error in epidemiologic studies.

## REVIEW TOPICS

In addition to supporting research, HEI also contributes to regulatory decision making and research planning by providing in-depth reviews of selected and often controversial topics. These reviews have been conducted by ad hoc working groups that included members of the Research and Review Committees and leading experts who were appointed by the HEI Board of Directors. Examples include reviews or research planning efforts on gasoline vapors, methanol, electromagnetic fields, air pollution epidemiology, diesel exhaust, and oxygenates added to fuel. The Institute has published these reviews as HEI Special Reports and, in one case, as a supplement to Environmental Health Perspectives.

The HEI Special Reports are generally regarded as thorough, balanced, and credible. Several have had an impact in discussions of regulatory policy. For these reasons, some people regard them as among the most important contributions that HEI has made. Because of the extensive time commitments required to produce quality documents, we have been very selective in undertaking such reviews and have produced one about every other year.

Looking ahead to the next five years, a number of research programs are nearing completion and controversial issues are coming to light that would benefit from systematic review and analysis. These are outlined and discussed below. There are several challenges in making selections for the next five years. First, more topics are ripe for review than can reasonably be done. Second, if some reviews are to have an impact, their timing needs to be coordinated with the regulatory process. For PM, the time line is very short as it is unlikely that documents published after the spring of the year 2000 will affect preparation of the current EPA Criteria Document and Staff Paper. Third, new issues will emerge, and HEI will need to be poised to respond to some requests for reviews.

At least three HEI research program areas are expected to provide new insights and should be considered for special reviews: particulate matter, air toxics, and fuels.

## Particulate Matter

The PM program is probably HEI's most visible research program because of the regulatory controversies and the tight time line for the next review of the standard. Reports for the following programs or studies have been submitted and started review by the beginning of the year 2000:

- National Morbidity, Mortality, and Air Pollution Study,
- Particle Epidemiology Reanalysis Project, and
- epidemiology and toxicology reports dealing with mechanisms of particle-induced morbidity and mortality.

Other reports on particle characterization, personal exposure, and mechanisms of toxicity will be submitted in 2000 to 2001. Two reviews are being considered for 2000 to 2005.

A *targeted review* of what has been learned from the first phase of HEI's program on mechanisms of PM-induced toxicity could have an impact on the next review of the PM standard. Such a review could include an evaluation of the characteristics of PM that affect toxicity in animals and humans as well as health endpoints and/or populations that are affected. The review would use HEI-funded work as a starting point but would also include related research. Alternatively, these topics could be addressed in separate reviews. Also, a review could be conducted beginning in 2000 or 2001 of the data on relative toxicity associated with characteristics of the PM mixture, with the aim of informing ongoing control strategy choices being made to implement the PM NAAQS.

Another topic of interest would be characterizing the relationship between personal exposure to PM and exposure measured at stationary monitoring sites.

## Air Toxics

The first phases of HEI's benzene and butadiene programs are nearing completion. Aldehydes research is just getting under way. Possible reviews for this area in the near term are:

- status of development of butadiene biomarkers and understanding of mechanisms of action of butadiene, and
- status of development of benzene biomarkers and understanding of metabolism and effects at different exposure levels for benzene.

HEI has contributed significantly to both these areas and a review could draw on the results of the Institute's biomarker development and transitional epidemiology studies as well as other research. In the future, the aldehydes program may provide opportunities for a special review, which could be done in conjunction with NUATRC.

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## IMPLEMENTING THE STRATEGIC PLAN

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This section describes the activities that HEI is planning to undertake in the priority areas. Table 3 lays out the approximate timing proposed for these activities.

### INTERNATIONAL PERSPECTIVE

HEI will continue to conduct research in the most appropriate locales with the aims of informing up-coming US and other decisions and addressing common US, European, and Asian needs for scientific information for decision making. Over time, and as appropriate given enhanced funding from international sponsors, HEI will move to establish local presences in key international areas to more effectively respond to international decision-making needs.

### PRIORITY TOPICS

#### Air Pollution Mixture

##### Particulate Matter and Gaseous Pollutants

Over the next five years, HEI will complete and review PM studies currently under way and will conduct additional PM research following new planning efforts built on the PM assessment in the Criteria Document and discussions by CASAC. Activities will include:

- Continuing and expanding implementation for EPA of the World Wide Web inventory of PM research;
- completing and extending major projects evaluating the health effects of PM and gaseous pollutants (NMMAPS and the Particle Epidemiology Reanalysis Project), including continuing analyses using the existing databases, extension of the NMMAPS databases to more current air and health data, and collaborative joint analyses between NMMAPS and its European counterpart, APHEA;

- completing current personal exposure and controlled human exposure studies;
- completing initial toxicity studies of concentrated ambient PM mixture and its components, considering results of HEI and other research following CASAC's review, and planning focused, systematic investigations of PM components timed to inform upcoming implementation decisions by federal and state regulators; and
- initiating, if feasible and with appropriate partners, epidemiologic investigations of long-term exposure to PM and gaseous pollutants.

#### Air Toxics

HEI's plans for air toxics consist of building on its current research as well as organizing a major workshop to determine priorities for air toxics research over the next five years. Specific activities include:

- in the near term, conducting a workshop on mobile-source air toxics exposure and risk to inform EPA's development of its Mobile Source Air Toxics Rules;
- completing and following up on current benzene and butadiene biomarker and epidemiology studies (including further analyses of the Delzell butadiene cohort) and aldehydes exposure studies (including collaboration with NUATRC on the RIOPA project);
- conducting, in cooperation with EPA, a comprehensive research planning workshop to update HEI's 1993 report, Research Priorities for Mobile Source Air Toxics, and to set the stage for the next generation of research on air toxics; and
- initiating targeted investigations of air toxics of greatest concern that have not been fully studied (eg, POM, such as PAHs) and into methods for assessing effects of the air toxics mixture.

#### Diesel Exhaust

After current diesel feasibility studies are completed in early 2000, HEI will initiate a research planning effort to focus plans for new diesel health effects research. Activities will include:

	FY 2000	FY 2001	FY 2002	FY 2003	FY 2004	FY 2005
<b>Major Upcoming Regulatory Events</b>						
	<ul style="list-style-type: none"> <li>US PM NAAQS Criteria Document</li> <li>Tier 2 Standards</li> <li>EU Heavy-Duty Diesel Standards</li> </ul>	<ul style="list-style-type: none"> <li>Mobile-Source Air Toxics Rules</li> <li>EU Clean Air for Europe</li> <li>US decisions on diesel fuel</li> </ul>	<ul style="list-style-type: none"> <li>US PM NAAQS review</li> </ul>	<ul style="list-style-type: none"> <li>EU PM Limit Values review</li> </ul>	<ul style="list-style-type: none"> <li>US and EU Heavy-Duty Diesel Rules take effect</li> </ul>	<ul style="list-style-type: none"> <li>Looking Ahead</li> <li>State plans for PM</li> <li>2007 Rules for Heavy-Duty Diesel</li> <li>EU/US Auto/Fuel Standards</li> </ul>
<b>HEI Strategic Plan 2000–2005</b>						
<b>Air Pollution Mixture</b>						
• PM and Gases	<p>Implement, maintain and expand worldwide inventory of PM studies → → → → →</p> <p>Complete key PM and epidemiologic studies    Extend NMMAPS and Reanalysis Projects    Conduct NMMAPS collaboration with European APHEA project</p> <p>Complete current studies of comparative toxicity of PM components and CAP → →    Targeted and systematic studies of comparative toxicity of the PM mixture and of key components to inform implementation of PM standards → → →</p>					
• Air Toxics	<p>Complete current personal and controlled human exposure studies    Long Term Epidemiology Planning Workshop →    Initiate, with appropriate partners, epidemiologic studies of effects of long-term exposure to PM and other pollutants (requires additional funding) → → →</p> <p>Mobile-sources workshop</p> <p>Complete current benzene, butadiene, and aldehydes studies    Extend benzene, butadiene and aldehydes studies</p> <p>Air toxics research needs workshop    Initiate air toxics mixtures research (POM [PAHs] and others) → → →</p>					
• Diesel Exhaust	<p>Complete current diesel feasibility studies → Select best research directions    Initiate studies of acute noncancer effects</p> <p>Launch, if feasible and with funding partners, new epidemiologic study of long-term effects of diesel exposure (requires additional funding)</p>					
<b>Effects of Regulation (Accountability)</b>	<p>Science and stakeholder workshops on methods to measure accountability    Conduct research to develop measurement techniques</p> <p>Conduct research to measure health effects changes from reduced air pollution</p>					
<b>Emerging Technologies</b>	<p>Establish HEI Special Committee on Emerging Technologies to assess and screen technologies developed in response to PM, climate change, other drivers → → →</p> <p>Review Literature on Imminent Technology (eg, cerium)    Review Literature on Imminent Technology (eg, diesel controls)</p> <p>Initiate targeted research assessing consequences of most likely fuels and technologies → → →</p>					

**Table 3. Implementing the Strategic Plan**

- completing current feasibility studies undertaken to help in planning future diesel epidemiology studies by developing exposure methods and information and by identifying cohorts, and reviewing these studies as part of a diesel research planning effort;
- initiating new studies on acute, noncancer effects of exposure to diesel exhaust, placing them in the context of acute effects of other elements of the air pollution mixture; and
- launching, if feasible and with appropriate funding partners, a major new epidemiologic investigation of cancer and other long-term effects of exposure to diesel exhaust at exposure levels close to ambient levels.
- conducting, through the Special Committee on Emerging Technologies, focused reviews of literature on likely emerging technologies (eg, use of rare earth metals such as cerium, application of selective catalytic reduction for control of nitrous oxides, emerging fuel additives) to identify key health and environmental questions and priorities for research;
- conducting, through the Special Committee on Emerging Technologies and in collaboration with the Heinz Center, workshops on the health and environmental advantages and disadvantages of technologies likely to emerge in response to climate change; and
- initiating, under the guidance of the Research Committee and in partnership with existing emissions characterization organizations, targeted research on health and environmental consequences of key emerging technologies.

### **Emerging Technologies and Fuels**

Over the next five years, HEI plans to take a larger role in evaluating emerging technologies and fuels. In order to make informed decisions about which reviews and research to undertake, HEI will convene a new committee of technology experts and collaborate with other organizations in evaluating new technologies and conducting research. Actions that we project include:

- establishing the HEI Special Committee on Emerging Technologies to identify fuels and technologies that are likely to emerge in response to environmental regulation, climate change, and other drivers, and to evaluate these technologies for potential positive and negative health and environmental consequences;

### **Results of Air Pollution Regulation: Accountability**

HEI will organize and facilitate discussions of how to approach the evaluation of health benefits of air quality regulation, and then undertake appropriate methods and assessment research.

In cooperation with all stakeholders, HEI will conduct a series of workshops

- to identify key measures of the ability of air pollution regulation to improve public health,
- to examine existing scientific methods for making these measurements, and
- to identify priority needs for the development and implementation of methods to assess health changes resulting from regulation.

Based on the understanding developed in these workshops, HEI will initiate research to develop analytical methods and later to begin implementing efforts to assess accountability.

## APPENDIX B: HEI STUDIES AND RESEARCH REPORTS (1982-2000)

### **RFA 82-1: STUDIES ON THE METABOLISM AND BIOLOGICAL EFFECTS OF NITROPYRENE AND RELATED NITROPOLYCYCLIC AROMATIC COMPOUNDS**

**Frederick A. Beland**, University of Arkansas

The metabolic activation and DNA adducts of dinitropyrenes. (Report No. 4)

**James A. Bond**, Inhalation Toxicology Research Institute

Disposition and metabolism of free and particle-associated nitropyrenes after inhalation. (Report No. 2)

**John D. Groopman**, Boston University School of Public Health

DNA adducts of nitropyrene detected by specific antibodies. (Report No. 7)

**Alan M. Jeffrey**, Columbia University

Metabolic activation of nitropyrenes and diesel particulate extracts. (Report No. 34)

**Charles M. King**, Michigan Cancer Foundation

Metabolism and biological effects of nitropyrene and related compounds. (Report No. 16)

**Veronica M. Maher**, Michigan State University

Studies on the metabolism and biological effects of nitropyrene and related nitropolycyclic aromatic compounds in diploid human fibroblasts. (Report No. 17)

**Richard C. Moon**, IIT Research Institute

Respiratory carcinogenesis of nitroaromatics. (Report No. 32)

**Ronald K. Wolff**, Inhalation Toxicology Research Institute

Factors affecting possible carcinogenicity of inhaled nitropyrene aerosols. (Report No. 19)

### **RFA 82-2: CELLULAR AND BIOCHEMICAL MARKERS RELATED TO NONNEOPLASTIC CHRONIC LUNG DISEASE**

**Philip A. Bromberg**, University of North Carolina at Chapel Hill

Effects of ozone on airway epithelial permeability and ion transport. (Report No. 48)

**Edward D. Crandall**, Cornell University

Effects of nitrogen dioxide on alveolar epithelial barrier properties. (Report No. 13)

**Cleamond D. Eskelson**, University of Arizona

Pulmonary lipotropic factor. (Unpublished report)

**John N. Evans**, University of Vermont

Early markers of lung injury. (Report No. 29)

### **RFA 82-3: MODELS OF SUSCEPTIBLE POPULATIONS**

**Marie Amoruso**, University of Medicine and Dentistry of New Jersey

Estimation of risk of glucose 6-phosphate dehydrogenase deficient red cells to ozone and nitrogen dioxide. (Report No. 1)

**Laurence D. Fechter**, Johns Hopkins University

Neurotoxicity of prenatal carbon monoxide exposure. (Report No. 12)

**Jane Q. Koenig**, University of Washington

The effects of ozone and nitrogen dioxide on lung function in healthy and asthmatic adolescents. (Report No. 14)

**Joe L. Mauderly**, Inhalation Toxicology Research Institute

Influence of experimental pulmonary emphysema on toxicological effects from inhaled nitrogen dioxide and diesel exhaust. (Report No. 30)

**Joe L. Mauderly**, Inhalation Toxicology Research Institute

Effects of inhaled nitrogen dioxide and diesel exhaust on developing lung. (Report No. 8)

**Paul E. Morrow**, University of Rochester Medical Center  
Responses of susceptible subpopulations to nitrogen dioxide. (Report No. 23)

**Marc B. Schenker**, University of California at Davis  
Markers of exposure to diesel exhaust in railroad workers. (Report No. 33)

**RFA 82-4: INHALATION CARCINOGENESIS STUDIES IN RODENTS: MULTIFACTOR INTERACTIONS**

**Uwe Heinrich (Ulrich Mohr)**, Fraunhofer Institut für Toxikologie und Aerosolforschung

Investigation of a potential cotumorogenic effect of the dioxides of nitrogen and sulfur, and of diesel engine exhaust, on the respiratory tract of Syrian golden hamsters. (Report No. 26)

**RFA 82-5: DOSE TO TARGET TISSUE**

**Timothy Crocker**, University of California, Irvine  
Transport of macromolecules and particles at target sites for deposition of air pollutants. (Report No. 3)

**RFA 82-7: HEALTH EFFECTS INSTITUTE INVESTIGATORSHIPS**

**Susan Bagley**, Michigan Technological University

An investigation into the effect of a ceramic particle trap on the chemical mutagens in diesel exhaust. (Report No. 5)

**Deborah M. Drechsler-Parks**, University of California, Santa Barbara

Effect of nitrogen dioxide, ozone, and peroxyacetyl nitrate on metabolic and pulmonary function. (Report No. 6)

**RFA 83-1: CARDIOVASCULAR AND OTHER HEALTH EFFECTS OF CARBON MONOXIDE**

**Steven M. Horvath**, University of California, Santa Barbara

Maximal aerobic capacity at several ambient concentrations of carbon monoxide at several altitudes. (Report No. 21)

**James J. McGrath**, Texas Tech University Health Sciences Center

Cardiovascular effects of chronic carbon monoxide and high-altitude exposure. (Report No. 27)

**Arthur Penn**, NYU Medical Center

Determination of the atherogenic potential of inhaled carbon monoxide. (Report No. 57)

**SPECIAL REQUEST 1993**

Multicenter Study of Subjects with Angina: Acute effects of carbon monoxide exposure on individuals with coronary artery disease. (Report No. 25)

**Eugene R. Blecker and Sidney O. Gottlieb**, Johns Hopkins University School of Medicine

**Thomas E. Dahms and Bernard R. Chaitman**, St. Louis University Medical Center

**Jack D. Hackney and Ronald H. Selvester**, Los Amigos Research and Education Institute, Inc.

**Marcello Pagano**, Harvard School of Public Health

**RFA 83-2: NITROGEN OXIDES AND SUSCEPTIBILITY TO RESPIRATORY INFECTIONS**

**George J. Jakab**, Johns Hopkins University

Modulation of pulmonary defense mechanisms against viral and bacterial infections by acute exposures of nitrogen dioxide. (Report No. 20)

**Thomas J. Kulle**, University of Maryland

Susceptibility to virus infection with exposure to nitrogen dioxide. (Report No. 15)

**Richard Rose**, New England Deaconess Hospital  
Altered susceptibility to viral respiratory infection during short-term exposure to nitrogen dioxide. (Report No. 24)

**RFA 83-3: DOSE OF AIRBORNE POLLUTANTS TO TARGET TISSUES**

**Michael T. Kleinman**, University of California, Irvine  
The effects of exercise on dose and dose distribution of inhaled automotive pollutants. (Report No. 45)

**Morris B. Snipes**, Inhalation Toxicology Research Institute  
Effect of particle loading of the lung on clearance kinetics and particle microdistribution. (Unpublished report)

**Chia P. Yu**, S.U.N.Y. at Buffalo  
Predictive models for deposition of inhaled diesel exhaust particles in humans and laboratory species. (Report No. 10)

**RFA 83-4: EPIDEMIOLOGIC INVESTIGATION OF EFFECTS OF AUTOMOTIVE EMISSIONS**

**Michael Jacobsen**, Institute of Occupational Medicine, Edinburgh  
Respiratory infections in coal miners exposed to nitrogen oxides. (Report No. 18)

**Jonathan M. Samet**, University of New Mexico  
Nitrogen dioxide and respiratory infection: Pilot investigations. (Report No. 28)

**RFA 84-2: ACUTE EFFECTS OF CARBON MONOXIDE ON CARDIAC RHYTHM**

**Bernard R. Chaitman**, St. Louis University Medical Center  
Carbon monoxide exposure to subjects with documented cardiac arrhythmias. (Report No. 52)

**Jay P. Farber**, University of Oklahoma  
Carbon monoxide and lethal arrhythmias. (Report No. 36)

**David S. Sheps** University of North Carolina at Chapel Hill  
Effects of 4 percent and 6 percent carboxyhemoglobin on arrhythmia production in patients with coronary artery disease. (Report No. 41)

**Richard L. Verrier**, Harvard School of Public Health  
Acute effects of carbon monoxide on cardiac electrical stability. (Report No. 35)

**RFA 84-3: MECHANISMS OF OXIDANT INJURY**

**Bruce A. Freeman**, University of Alabama at Birmingham  
Oxidant injury to the alveolar epithelium: biochemical and pharmacologic studies. (Report No. 54)

**David A. Johnson**, East Tennessee State University  
Oxidant effects on rat and human lung proteinase inhibitors. (Report No. 37)

**Jerold A. Last**, University of California at Davis  
Synergistic effects of air pollutants: ozone plus a respirable aerosol. (Report No. 38)

**Gerald L. Mechanic**, University of North Carolina at Chapel Hill  
Biochemistry of lung connective tissue and physiology of emphysema. (Unpublished report)

**A. Keith Tanswell**, University of Western Ontario Medical Center  
Detection of paracrine factors in oxidant lung injury. (Report No. 22)

**Mark J. Utell**, University of Rochester Medical Center  
Mechanisms of nitrogen dioxide toxicity in humans. (Report No. 43)

**RFPA 84-5: NEW METHODS FOR ASSESSING HEALTH RISKS FROM AUTOMOTIVE EMISSIONS**

**Theodore T. Puck**, Eleanor Roosevelt Institute for Cancer Research

Genetic and biochemical approaches at the cellular level to toxicological assessment of environmental agents. (Unpublished report)

**RFA 85-1: HEALTH EFFECTS OF ALDEHYDES**

**Roland Grafstrom**, Karolinska Institutet

Pathological effects of automotive emission related aldehydes in cultured human epithelial cells. (Report not submitted)

**George J. Jakab**, Johns Hopkins University

Use of physical chemistry and in vitro exposure to investigate the toxicity of formaldehyde bound to carbonaceous particles in the murine lung. (Report No. 53)

**Andres Klein-Szanto**, Fox Chase Cancer Center

Effects of formaldehyde on xeno-transplanted human respiratory epithelium. (Report No. 51)

**George Leikauf**, University of Cincinnati

Mechanisms of aldehyde-induced bronchial reactivity: Role of airway epithelium. (Report No. 49)

**RFPA 85-2: NEW METHODS FOR ASSESSING EXPOSURE AND HEALTH RISKS FROM AUTOMOTIVE EMISSIONS**

**Roger W. Giese**, Northeastern University

Methods development toward the measurement of polyaromatic hydrocarbon-DNA adducts by mass spectrometry. (Report No. 61)

**RFPA 85-3: HEALTH EFFECTS OF AUTOMOTIVE EMISSIONS**

**Frederick A. Beland**, University of Arkansas

DNA binding by 1-nitropyrene and dinitropyrenes in vitro and in vivo: effects of nitroreductase induction. (Report No. 31)

**RFA 86-1: GENOTOXIC, CARCINOGENIC, AND COCARCINOGENIC EFFECTS OF OZONE**

**Carmia Borek**, Columbia University

Ozone carcinogenesis and cocarcinogenesis in vitro. (Unpublished report)

**Kenneth Donaldson, (John M. G. Davis)**, Institute of Occupational Medicine, Edinburgh

Leukocyte-mediated epithelial injury in ozone-exposed rat lung. (Report No. 44)

**David G. Thomassen**, Inhalation Toxicology Research Institute

The role of ozone in tracheal cell transformation. (Report No. 50)

**RFA 86-2: HEALTH EFFECTS OF DIESEL EMISSIONS**

**Susan Bagley**, Michigan Technological University

Characterization of particulate- and vapor-phase organic fraction emissions from a heavy-duty diesel engine equipped with a particle trap and regeneration controls. (Report No. 56)

**Frederick Beland**, University of Arkansas

Role of ring oxidation in the metabolic activation of 1-nitropyrene. (Report No. 46)

**Karam El-Bayoumy**, American Health Foundation

Biomonitoring of nitropolynuclear aromatic hydrocarbons via protein and DNA adducts. (Report No. 64)

**Alan M. Jeffrey**, Columbia University

Influence of particle-associated organic compounds on the carcinogenicity of diesel exhaust: identification of genotoxic components in diesel engine emissions by analysis of DNA damage and evaluation of suitability of assays for analysis of human exposure to these emissions. (Unpublished report)

**Veronica Maher**, Michigan State University

Mutations induced by 1-nitrosopyrene and related compounds during DNA replication in human cells and induction of homologous recombination by these compounds. (Report No. 55)

**Joe L. Mauderly**, Inhalation Toxicology Research Institute

Pulmonary toxicity of inhaled diesel exhaust and carbon black in chronically exposed rats: neoplastic and nonneoplastic lung lesions. (Report No. 68, Part I)

**Kurt Randerath**, Baylor College of Medicine

Pulmonary toxicity of inhaled diesel exhaust and carbon black in chronically exposed rats: DNA Damage. (Report No. 68, Part II)

#### **RFA 86-4: HEALTH EFFECTS OF AUTOMOTIVE EMISSIONS**

**Jerry K. Davis**, University of Alabama at Birmingham

Murine respiratory mycoplasmosis: A model to study effects of oxidants. (Report No. 47)

#### **EXTENSIONS**

**Jane Q. Koenig**, University of Washington

The effects of combined ozone and nitrogen dioxide in adolescent subjects. (Unpublished report)

**Jonathan M. Samet**, University of New Mexico

Nitrogen dioxide and respiratory illness in children. (Report No. 58 Part I: Health outcomes; Part II: Assessment of exposure to nitrogen dioxide; Part III: Quality assurance in an epidemiologic study; Part IV: Effects of housing and meteorologic factors on indoor nitrogen dioxide concentrations)

**Chia P. Yu**, S.U.N.Y. at Buffalo

Retention modeling of diesel exhaust particles in rats and humans. (Report No. 40)

#### **RFA 87-1: ACUTE AND CHRONIC EFFECTS OF ATMOSPHERIC OXIDANTS**

**Jane Q. Koenig**, University of Washington

Effects of oxidants, combined with sulfuric or nitric acid, on the pulmonary function of adolescents with asthma. (Report No. 70, Part I)

**Donald J. Massaro**, University of Miami School of Medicine

Tolerance to ozone: cellular and molecular basis. (Unpublished Report)

**Mark J. Utell**, University of Rochester School of Medicine

Effects of sequential sulfuric acid and ozone exposures on the pulmonary function of healthy subjects and subjects with asthma. (Report No. 70, Part II)

#### **RFA 87-2: BEHAVIORAL AND NEUROTOXICOLOGICAL EFFECTS OF METHANOL AND OTHER COMPONENTS OF AUTOMOTIVE EMISSIONS**

**Mary R. Cook**, Midwest Research Institute

Effects of methanol vapor on human neurobehavioral measures. (Report No. 42)

#### **RFA 87-3: NEW METHODS FOR ASSESSING HEALTH RISKS FROM AUTOMOTIVE EMISSIONS**

**James S. Ultman**, Pennsylvania State University

Non-invasive determination of respiratory ozone absorption: development of a fast-responding ozone analyzer. (Report No. 39)

#### **RFA 87-4: HEALTH EFFECTS OF AUTOMOTIVE EMISSIONS**

**Hanspeter R. Witschi**, University of California, Davis

Failure of ozone and nitrogen dioxide to enhance lung tumor development in hamsters. (Report No. 60)

**Beatrice A. Wittenberg**, Albert Einstein College of Medicine

Effects of carbon monoxide on the isolated heart muscle cells. (Report No. 62)

**OTHER 1987 (NOT RFA-DERIVED)**

**Timothy R. Fennell**, Chemical Industry Institute of Toxicology

Development of methods for measuring biological markers of formaldehyde exposure. (Report No. 67)

**RFA 88-1: OZONE AND CARBON MONOXIDE: ASSESSMENT OF POPULATION EXPOSURE AND DOSE**

**Jack D. Hackney**, Los Amigos Research and Education Institute, Inc.

Development of samplers for measuring human exposure to ozone: active and passive samplers for measuring human exposures to ozone. (Report No. 63)

**F. Dennis McCool**, Memorial Hospital of Rhode Island

Measurements of ventilation in freely ranging subjects. (Report No. 59)

**Jonathan M. Samet**, University of New Mexico

Assessment of heart rate as a predictor of ventilation. (Report No. 59)

**Yukio Yanagisawa**, Harvard School of Public Health

Development of samplers for measuring human exposure to ozone: a passive ozone sampler based on a reaction with iodide. (Report No. 63)

**RFPA 88-2: HEALTH EFFECTS OF AUTOMOTIVE EMISSIONS**

**Susan T. Bagley**, Michigan Technological University

Characterization of fuel and after-treatment device effects on diesel emissions. (Report No. 76)

**Frederick Beland**, University of Arkansas

DNA adduct formation and T lymphocyte mutation induction in F344 rats implanted with tumorigenic doses of 1,6-dinitropyrene. (Report No. 72)

**RFA 89-1: HEALTH EFFECTS OF METHANOL EXPOSURE: METABOLISM AND PHARMACOKINETICS; FETAL AND PERINATAL NEUROTOXICITY; REPRODUCTIVE TOXICITY**

**Thomas Burbacher**, University of Washington

Primate developmental effects of methanol. (Report No. 89)

**Michele Medinsky**, Chemical Industry Institute of Toxicology

Pharmacokinetics of methanol and formate in female cynomolgus monkeys exposed to methanol vapors. (Report No. 77)

**Gary M. Pollack**, University of North Carolina

Maternal-Fetal pharmacokinetics of methanol. (Report No. 74)

**Bernard Weiss**, University of Rochester

Developmental neurotoxicity of methanol exposure by inhalation in rats. (Report No. 73)

**RFA 89-2: HEALTH EFFECTS OF CHRONIC OZONE INHALATION - COLLABORATIVE NATIONAL TOXICOLOGY PROGRAM - HEALTH EFFECTS INSTITUTE STUDIES: PILOT STUDIES**

**Ling-Yi Chang**, Duke University

Immunocytochemical study of the effects of ozone on connective tissue. (HEI Communications No. 1)

**Robert A. Floyd**, Oklahoma Medical Research Foundation

Ozone mediated oxidative damage to lung nucleic acids. (HEI Communications No. 1)

**William C. Parks**, Jewish Hospital at Washington University Medical Center

Localization of matrix transcripts by in situ hybridization. (HEI Communications No. 1)

**Kent E. Pinkerton**, University of California at Davis

Ozone, extracellular matrix and epithelial adaptation. (HEI Communications No. 1)

**Derek Uchida**, National Jewish Center for Immunology and Respiratory Medicine

Assessment of airways responsiveness to inhaled methacholine in aged Fischer 344 rats. (HEI Communications No. 1)

**Renaud Vincent**, Duke University

Quantitative ultra-structural analysis of connective tissue in the lungs. (HEI Communications No. 1)

**RFA 89-3: MOTOR VEHICLE EMISSIONS: HEALTH EFFECTS STUDIES; EXPOSURE ASSESSMENT; METHODS DEVELOPMENT**

**Stephen A. Belinsky**, Inhalation Toxicology Research Institute

Pulmonary toxicity of inhaled diesel exhaust and carbon black in chronically exposed rats: identification of target genes involved in carbon black and diesel-induced lung cancer. (Report No. 68, Part III)

**Paul Howard**, Case Western Reserve University

The effects of copollutants on the metabolism and DNA binding of carcinogens. (Report No. 66)

**Petros Koutrakis**, Harvard School of Public Health

Development of samplers for measuring human exposure to ozone: a passive ozone sampler based on a reaction with nitrite. (Report No. 63)

**George Leikauf**, University of Cincinnati Medical Center

Activation of eicosanoid metabolism in human airway epithelial cells by ozonolysis products of membrane fatty acids. (Report No. 71)

**Veronica Maher**, Michigan State University

Mutation spectra from t-cells as a biomarker of human exposure to diesel exhaust. (Unpublished report)

**James Ultman**, Pennsylvania State University

Non-invasive determination of respiratory ozone absorption: the bolus-response method. (Report No. 69)

**RFA 90-1 PART A: HEALTH EFFECTS OF CHRONIC OZONE INHALATION - COLLABORATIVE NTP-HEI STUDIES: RESPIRATORY FUNCTION STUDIES**

**Jack R. Harkema**, Inhalation Toxicology Research Institute

Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies: effects on pulmonary function. (Report No. 65, Part V)

**John Szarek**, Marshall University School of Medicine

Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies: mechanical properties, responses to bronchoactive stimuli, and eicosanoid release in isolated large and small airways. (Report No. 65, Part II)

**RFA 90-1 PART B: HEALTH EFFECTS OF CHRONIC OZONE INHALATION - COLLABORATIVE NTP-HEI STUDIES: STRUCTURAL, BIOCHEMICAL AND OTHER ALTERATIONS**

**Ling-Yi Chang**, Duke University Medical School

Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies: morphometric analysis of structural alterations in alveolar regions. (Report No. 65, Part VIII)

**Jack Harkema**, Inhalation Toxicology Research Institute

Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies: effects on the nasal mucociliary apparatus. (Report No. 65, Part VII)

**Jerold A. Last**, California Primate Research Center

Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies: content and cross-linking of lung collagen. (Report No. 65, Part I)

**William C. Parks**, Jewish Hospital at Washington University

Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies: extracellular matrix expression in ozone-exposed lungs. (Report No. 65, Part IV)

**Kent E. Pinkerton**, University of California, Davis

Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies: changes in the tracheobronchial epithelium, pulmonary acinus, and lung antioxidant enzyme activity. (Report No. 65, Part IX)

**Bhandaru Radhakrishnamurthy**, Tulane University

Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies: effects of chronic ozone inhalation on complex carbohydrates of lung connective tissue. (Report No. 65, Part III)

#### **SPECIAL REQUESTS FOR COLLABORATIVE NTP-HEI STUDIES**

**Paul Mellick**, Battelle Pacific Northwest Laboratories

HEI/NTP collaborative study on chronic ozone exposure in rats - technical assistance. (Completed)

**Paul J. Catalano (Louise Ryan)**, Harvard School of Public Health and Dana-Farber Cancer Institute

Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies: robust composite scores based on median polish analysis. (Report No. 65, Part X)

#### **ADDITIONAL REPORTS FOR COLLABORATIVE NTP-HEI STUDIES**

Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies: background and project design. (Report No. 65 Part VI)

Consequences of prolonged inhalation of ozone on F344/N rats: collaborative studies: integrative summary. (Report No. 65 Part XI)

#### **RFA 90-2: CLINICAL STUDIES OF SENSITIVITY TO OZONE**

**John R. Balmes**, University of California, San Francisco

Airway inflammation and responsiveness to ozone in normal and asthmatic subjects. (Report No. 78, Part I)

**Mark W. Frampton**, University of Rochester Medical Center

Airway inflammation and responsiveness to ozone in nonsmokers and smokers; mediators of inflammation in bronchoalveolar lavage fluid from non-smokers, smokers, and asthmatic subjects exposed to ozone. (Report No. 78, Part II, III)

**Jack D. Hackney**, Los Amigos Research and Education Institute, Inc.

Response to ozone in the population: individual and seasonal factors. (Unpublished Report)

#### **RFA 90-3: OZONE INTERACTION WITH BIOLOGICAL MACROMOLECULES AND MOLECULAR DOSIMETRY**

**William A. Pryor**, Louisiana State University

Aldehydes (nonanal and hexanal) in rat and human bronchoalveolar lavage fluid after ozone exposure. (Report No. 90)

#### **RFA 90-6: THEORETICAL APPROACHES TO THE ANALYSIS OF HEALTH EFFECTS OF COMPLEX MIXTURES**

**William E. Bechtold**, Inhalation Toxicology Research Institute

Immunoaffinity chromatography in the analysis of toxic effects of complex mixtures. (HEI Communications No. 4)

**John G. Dorsey**, University of Cincinnati

Stationary-phase programming for liquid chromatography: A new concept for separating complex mixtures. (HEI Communications No. 4)

**Chris Gennings**, Virginia Commonwealth University

Using the parallel coordinate axis system to analyze complex mixtures: determining biological activity and interactions among components. (HEI Communications No. 4)

**David L. Springer**, Battelle Pacific Northwest Laboratories

Supercritical separation and molecular bioassay technologies applied to complex mixtures. (HEI Communications No. 4)

**RFA 91-1: EPIDEMIOLOGIC STUDIES OF THE HEALTH EFFECTS OF LONG-TERM OZONE EXPOSURE**

**Patrick L. Kinney**, New York University

An approach to retrospective estimation of lifetime ozone exposure using a questionnaire and ambient monitoring data (US sites). (Report No. 81, Part III)

**Dana P. Loomis**, University of North Carolina

Ozone exposure and daily mortality in Mexico City: a time series analysis. (Report No.75)

**William C. Navidi**, University of Southern California

Statistical methods for epidemiologic studies of the health effects of air pollution. (Report No. 86)

**John M. Peters**, University of Southern California

Acute effects of ambient ozone on asthmatic, wheezy, and healthy children. (Report No. 82)

**John D. Spengler**, Harvard University

Respiratory effects of chronic ozone exposure in children. (Unpublished Report)

**Ira B. Tager**, University of California, Berkeley

Variability of pulmonary function measures; an approach to retrospective estimation of lifetime ozone exposure using a questionnaire and ambient monitoring data (California sites). (Report No. 81, Part I, II)

**RFA 93-1: NOVEL APPROACHES TO EXTRAPOLATION OF HEALTH EFFECTS FOR MOBILE SOURCE TOXIC AIR POLLUTANTS**

**William E. Bechtold**, Inhalation Toxicology Research Institute

S-phenylcysteine in albumin as a benzene biomarker. (Unpublished Report)

**Ian A. Blair**, Vanderbilt University

Molecular dosimetry of 1,3-butadiene. (Report No. 92, Part IV)

**David Eastmond**, University of California, Riverside

Characterization and mechanisms of chromosomal alterations induced by benzene in mice and humans. (Completed)

**Rogene Henderson**, Lovelace Respiratory Research Institute

Carcinogenicity of 1,2,3,4-diepoxybutane. (Report No. 92, Part I)

**Assieh A. Melikian**, American Health Foundation

Development of liquid chromatography–electrospray ionization–tandem mass spectrometry methods for determination of urinary metabolite of benzene in humans. (Report No. 87)

**Leslie Recio**, Chemical Industry Institute of Toxicology

Roles of two metabolites of 1,3-butadiene in mediating its in vivo genotoxicity. (Report No. 92, Part II)

**Kenneth W. Turteltaub**, Lawrence Livermore National Laboratory and University of California, San Francisco

Benzene metabolism at doses relevant for human air exposures. (Completed)

**Vernon E. Walker**, New York State Department of Health

In vivo mutation of the endogenous hprt genes of mice and rats by 1,3-butadiene and its metabolites. (Report No. 92, Part III)

**RFPA 93-2: HEALTH EFFECTS OF EXPOSURE TO MOTOR VEHICLE EMISSIONS**

**Janet Arey**, University of California at Riverside

Evaluation of the potential health effects of the atmospheric reaction products of polycyclic aromatic hydrocarbons. (Report No. 84)

**Jack R. Harkema**, Michigan State University

Effects of chronic ozone exposure on the bony tissue of nasal turbinates in the rat: ozone induced atrophic rhinitis. (Report No.65, Part XII)

**Steven Kleeberger**, The Johns Hopkins University

Mechanisms of response to ozone exposure: the role of mast cells in mice. (Report No. 85)

**Robert R. Mercer**, Duke University

Morphometric analysis of alveolar responses to F344 rats to subchronic inhalation of nitric oxide. (Report No. 88)

**Kent E. Pinkerton**, University of California, Davis

Health effects of chronic ozone inhalation. (Report No. 65, Part XIII)

**Richard Schlesinger**, New York University

Ozone-induced airway hyper-responsiveness. (Completed)

**Steven Thom**, University of Pennsylvania

Vascular oxidative stress due to low concentrations of carbon monoxide. (Report No. 80)

**James S. Ultman**, The Pennsylvania State University

Improvement of a respiratory ozone analyzer. (Report No. 79)

**RFA 94-2: PARTICULATE AIR POLLUTION AND DAILY MORTALITY: IDENTIFICATION OF POPULATIONS AT RISK AND UNDERLYING MECHANISMS**

**Mark Goldberg (John Bailar)**, McGill University

Identifying subgroups of the general population that may be susceptible to short-term increases in particulate air pollution: a time series study in Montreal and Quebec. (Report No. 97)

**Douglas W. Dockery**, Harvard School of Public Health

Daily changes in oxygen saturation and pulse rate associated with particulate air pollution and barometric pressure. (Report No. 83)

**John J. Godleski**, Harvard School of Public Health

Mechanisms of morbidity and mortality from exposure to ambient air particles. (Report No. 91)

**Terry Gordon**, New York University Medical Center

Effects of concentrated ambient particles in rats and hamsters: an exploratory study. (Report No. 93)

**Günter Oberdörster**, University of Rochester Medical Center

Acute pulmonary effects of ultrafine particles in rats and mice. (Report No. 96)

**H. Erich Wichmann**, GSF-Forschungszentrum für, welt und Gesundheit, Neuherberg

Particulate air pollution and daily mortality: identification of populations at risk and underlying mechanisms of effect. (Report No. 98, Part I)

**RFPA 94-3: HEALTH EFFECTS OF EXPOSURE TO MOTOR VEHICLE EMISSIONS**

**Roger Giese**, Northeastern University

Characterization of environmental, polar PAHs. (Unpublished Report)

**Morton Lippmann**, New York University Medical Center

Association of PM components with daily mortality and morbidity in urban populations. (Report No. 95)

**Judith Zelikoff**, New York University Medical Center

Immunomodulation as a mechanism for PM<sub>10</sub>-induced effects upon host mortality. (Unpublished Report)

**RFQ-94: EPIDEMIOLOGISTS AND STATISTICIANS TO PARTICIPATE IN AN EVALUATION OF STUDIES OF THE ACUTE EFFECTS OF PARTICULATE AIR POLLUTION**

**Jonathan M. Samet**, Johns Hopkins University

Particulate air pollution and daily mortality: replication and validation of selected studies. (Phase I Special Report of the Particle Epidemiology Evaluation Project). Air pollution, weather, and mortality in Philadelphia 1973-1988 (Phase IB Special Report of the Particle Epidemiology Evaluation Project)

**Jonathan M. Samet**, Johns Hopkins University

The national morbidity, mortality, and air pollution study: (Report No. 94, Part I: Methods and Methodologic Issues (May 2000), Part II, National Morbidity, Mortality, and Air Pollution in the United States (June 2000))

**RFA 95-1: COMPARATIVE METABOLISM AND HEALTH EFFECTS OF ETHERS ADDED TO GASOLINE TO INCREASE OXYGEN CONTENT**

**Janet Benson**, Lovelace Respiratory Research Institute

The uptake, distribution, metabolism, and excretion of methyl-tertiary butyl ether inhaled alone and in combination with gasoline vapor. (Completed)

**Wolfgang Dekant**, University of Würzburg Germany

Biotransformation of MTBE, ETBE, and TAME after inhalation or oral ingestion in rats and humans. (Completed)

**Jun-Yan Hong**, Rutgers University

Role of human cytochromes P450 in the metabolism and health effects of gasoline ethers. (Completed)

**RFPA 95-2: REQUEST FOR PRELIMINARY APPLICATIONS ON THE HEALTH EFFECTS OF EXPOSURE TO MOTOR VEHICLE EMISSIONS**

**James Swenberg**, University of North Carolina at Chapel Hill

Hemoglobin adducts as biomarkers of 1,3-butadiene exposure and metabolism. (Report No. 92, Part V)

**RFQ 95-3: TRANSITIONAL EPIDEMIOLOGY STUDIES FOR BENZENE OR 1,3-BUTADIENE BIOMARKERS**

**Richard Albertini**, University of Vermont

Biomarker responses in butadiene exposed Czech workers: a transitional epidemiological study. (Completed)

**Qingshan Qu**, NYU Medical Center

The validation of biomarkers in humans exposed to benzene. (Completed)

**RFA 96-1: MECHANISMS OF PARTICLE TOXICITY: FATE AND BIOREACTIVITY OF PARTICLE-ASSOCIATED COMPOUNDS**

**Ann Aust**, Utah State University

Particle characteristics responsible for effects on human lung epithelial cells. (Completed)

**Per Gerde (Alan Dahl)**, Lovelace Respiratory Research Institute

Epithelial penetration and clearance of particle-borne benzo(a)pyrene. (Completed)

**Stephen Holgate**, Southampton General Hospital

The health effects of acute exposure to diesel exhaust and concentrated ambient particles. Part I: exposure of normal and asthmatic subjects to fresh diesel exhaust. (Completed)

**Debra Laskin**, Rutgers University

Role of peroxides and macrophages in fine particulate matter toxicity. (2001)

**Kent Pinkerton**, University of California, Davis

Mechanisms of particle toxicity in the respiratory system. (2002)

**RFPA 96-2: REQUEST FOR PRELIMINARY APPLICATIONS ON THE HEALTH EFFECTS OF EXPOSURE TO AIR POLLUTANTS FROM MOTOR VEHICLE EMISSIONS**

**Harvey Checkoway**, University of Washington

A case-crossover analysis of fine particulate matter air pollution and out-of-hospital sudden cardiac arrest. (Report No. 99)

**Jack Harkema**, Michigan State University

Effects of Mexico City air on rat nasal epithelium: morphometric analysis. (Completed)

**RFQ 97-1: EPIDEMIOLOGISTS AND STATISTICIANS TO PARTICIPATE IN A REANALYSIS OF COHORT STUDIES OF LONG-TERM MORTALITY AND PARTICULATE AIR POLLUTION**

**Daniel Krewski**, University of Ottawa

Reanalysis of the Harvard six cities study and the American cancer society study of particulate air pollution and mortality. (Special Report)

**RFA 97-2: ASSESSING PERSONAL EXPOSURE TO SELECTED ALDEHYDES USING CHEMICAL AND BIOLOGICAL TECHNIQUES**

**Fung-Lung Chung**, American Health Foundation

Effect of exposure to automobile exhaust on acrolein- and crotonaldehyde-derived DNA adducts in human lymphocyte DNA. (2001)

**Junfeng Zhang**, Rutgers University

Personal and microenvironmental measurements of human exposure to multiple aldehydes in three distinct urban areas. (2001)

**Sally L. Liu**, University of Washington.

Characterization of aldehyde exposure in general population. (Terminated after pilot study)

**RFPA 97-3: REQUEST FOR PRELIMINARY APPLICATIONS ON THE HEALTH EFFECTS OF EXPOSURE TO AIR POLLUTANTS FROM MOTOR VEHICLE EMISSIONS**

**Genevieve Matanoski**, Johns Hopkins University

Case cohort study on styrene exposure and ischemic heart disease. (Completed)

**James S. Ultman**, The Pennsylvania State University

Distribution of ozone in the intact human lung: intersubject variation in pulmonary response. (2002)

**RFA 98-1: CHARACTERIZATION OF EXPOSURE TO AND HEALTH EFFECTS OF PARTICULATE MATTER**

**Bert Brunekreef**, University of Wageningen

Personal exposure to fine and ultrafine particulate matter and its relationship to short-term changes in cardiovascular and respiratory health indicators. (2001)

**Beverly Cohen**, NYU Medical Center

Assessment of H<sup>+</sup> and ultrafine particles in indoor and outdoor air. (2001)

**Carole Conn**, Lovelace Respiratory Research Institute

Effects of transient exposure to fine particles on host response to influenza. (Terminated after pilot study)

**Douglas Dockery**, Harvard University

Association of particulate air pollution with arrhythmias recorded by implanted cardioverter defibrillators. (2001)

**Mark Frampton**, University of Rochester

Health effects of exposure to ultrafine carbon particles in healthy subjects and subjects with asthma. (2001)

**Henry Gong**, Rancho Los Amigos Medical Center

Controlled laboratory evaluation of acute cardiopulmonary responses to concentrated particulates. (2001)

**Fletcher Hahn (Kristen Nikula)**, Lovelace Respiratory Research Institute

Mechanisms of particle size- and composition-related adverse health effects in an aged sensitive population of rats. (2001)

**Jack Harkema**, Michigan State University

Effects of inhaled urban air particulates on normal and hypersecretory airways in rats. (2001)

**Petros Koutrakis**, Harvard University

Characterization of the particulate and gas exposures of sensitive sub-populations living in eastern U.S. metropolitan areas. (2001)

**George Leikauf**, University of Cincinnati

Pathogenomic mechanisms of particulate matter induced acute lung injury and inflammation. (Completed)

**Morton Lippmann**, NYU Medical Center

Personal exposure to particulate matter of outdoor origin. (Terminated after pilot study)

**Christine Nadziejko**, NYU Medical Center

Effect of concentrated ambient particulate matter on blood coagulation parameters in rats. (Completed)

**Annette Peters**, GSF-Forschungszentrum für Umwelt und Gesundheit

Particulate air pollution and the onset of nonfatal myocardial infarction – a case-crossover study. (2001)

**Barbara Turpin**, Rutgers University

Contributions of outdoor PM sources to indoor concentrations and personal exposures: a three-city study. (2001)

**Renaud Vincent**, Health Canada

Inhalation toxicology of ambient particulate matter: acute cardiovascular effects of resuspended EHC-93 urban particles in Wistar rats. (Completed)

**RFPA 98-2: REQUEST FOR PRELIMINARY APPLICATIONS ON THE HEALTH EFFECTS OF EXPOSURE TO AIR POLLUTANTS FROM MOTOR VEHICLE EMISSIONS**

**Daniel Grosjean**, DGA, Inc.

Airborne carbonyls from motor vehicle emissions. (Completed)

**Qingshan Qu**, NYU Medical Center

Genetic susceptibility to benzene hematotoxicity. (2000)

**Vernon Walker**, NYS Department of Health

Genotoxicity of 1,3 butadiene and its epoxy intermediates in mice and rats. (2002)

**RFA 98-3: EPIDEMIOLOGIC INVESTIGATIONS OF HUMAN POPULATIONS EXPOSED TO DIESEL ENGINE EMISSIONS: FEASIBILITY STUDIES**

**Paolo Boffetta**, International Agency for Research on Cancer

Feasibility of an epidemiology study of diesel engine emissions in central Europe and the Commonwealth of independent states. (Completed)

**Murray Finkelstein**, McMaster University

Cancer and diesel exhaust exposure in railroad workers: a feasibility study. (Completed)

**Eric Garshick**, Brigham and Women's Hospital

Lung cancer risk and the quantitative assessment of diesel exhaust exposure in the US trucking industry: a feasibility study. (Completed)

**David Kittelson**, University of Minnesota

Diesel aerosol exposure measurements: a feasibility study. (Completed)

**Alan Gertler (William Pierson)**, Desert Research Institute

Ambient sampling of diesel particulate matter. (Completed)

**Barbara Zielinska**, Desert Research Institute

Diesel emissions exposure measurements in underground mines. (Completed)

**RFPA 98-4: REQUEST FOR PRELIMINARY APPLICATIONS FOR RESEARCH ON METALS EMITTED BY MOTOR VEHICLES**

**Thomas Gunter**, University of Rochester

A mitochondrial role in manganese toxicity. (Completed)

**James Schauer**, University of Wisconsin

Characterization of emissions and human exposure to metals emitted from motor vehicles. (2003)

**Robert Yokel**, University of Kentucky

Manganese toxicokinetics at the blood-brain barrier. (2002)

**RFA 98-5: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD**

**Francesca Dominici**, Johns Hopkins University

Air pollution and daily mortality in a national sampling frame: statistical challenges. (2003)

**RFPA 98-6: REQUEST FOR PRELIMINARY APPLICATIONS ON THE HEALTH EFFECTS OF AIR POLLUTION**

**Elizabeth Delzell**, University of Alabama at Birmingham

An updated study of mortality among North American synthetic rubber industry workers. (2001)

**Susanne Hering**, Aerosol Dynamics

A personal particle speciation sampler. (2000)



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