



## HEALTH EFFECTS INSTITUTE

# REQUEST FOR QUALIFICATIONS FOR A DATA ANALYSIS CENTER

AUGUST 2010

### SUMMARY

**The Health Effects Institute (HEI) is seeking a qualified statistical data analysis center to develop an analysis plan, manage data, and analyze data collected in a multicenter controlled ozone exposure study in human volunteers.**

**The data will be collected in three centers in the United States. Each center will expose approximately 30-36 subjects.**

### BACKGROUND

HEI is an independent nonprofit organization jointly funded by the U.S. Environmental Protection Agency (EPA) and the auto industry to investigate the health effects of air pollution.

In February 2010, HEI issued RFA 10-1 “Cardiovascular effects of exposure to low levels of ozone in the presence and absence of other pollutants.” The RFA sought studies to evaluate cardiovascular and respiratory effects in healthy human volunteers, age 55 and above, exposed to clean air, a low ozone concentration, and a high ozone concentration in a controlled laboratory setting. Understanding the effects of ozone at low exposure concentrations would inform the EPA’s decisions regarding setting the future level of the National Ambient Air Quality Standards for ozone.

#### **Rationale for RFA 10-1**

Ozone is a photochemical oxidant formed in the lower atmosphere, in the presence of sunlight, through complex photochemical reactions among pollutants created from anthropogenic and natural sources. Human exposure to increased levels of ozone produces adverse respiratory and cardiovascular responses and may also have other effects. Ozone is one of the six criteria pollutants regulated by the EPA under the Clean Air Act. The literature on the health effects of ozone has been extensively and recently reviewed by both the National Research Council (NRC) (2008) and the EPA (US EPA 2006; 2007).

HEI issued RFA 10-1 in an attempt to fill an important gap in knowledge, namely the health effects of exposure to low levels of ozone – in the presence or absence of other air pollutants – on the cardiovascular system. The NRC (2008) committee noted that, while “Human chamber and toxicologic studies have yielded strong evidence indicating that short-term exposure to ozone can exacerbate lung conditions, causing illness and hospitalization, and can potentially lead to death, the available evidence on ozone exposure and exacerbation of heart conditions, which is less abundant, points to another concern. Epidemiologic studies have also found that exposure to ozone is associated with adverse lung and heart effects.”

The available studies suggest that healthy subjects in their 20s, exercising for relatively long periods of time (thus simulating a healthy worker laboring heavily outdoors in the summer), show a dose-related decrease in forced expiratory volume in 1 second ( $FEV_1$ ) when exposed to ozone at levels  $\geq 0.07$  ppm; the results of studies employing exposure at 0.06 ppm of ozone are inconsistent. However, they did not focus on effects of ozone on the cardiovascular system and the effects of ozone exposure on the cardiovascular system at such low levels are not known. A few investigators, however, have examined the cardiovascular effects of ozone at considerably higher concentrations. For example, in healthy and hypertensive volunteers exposed to 0.3 ppm ozone for 3 hours, Gong et al. (1998) did not find statistically significant differences between the healthy and hypertensive groups following ozone exposure; however,

they reported finding larger pre-exposure to post-exposure changes in heart rate and pressure-product rate for ozone compared to filtered air. They interpreted these findings as suggesting that ozone exposure can increase myocardial work and impair pulmonary gas exchange. This study was done on a relatively small number of subjects, the subjects were older, with average age at 53 for the hypertensive group and 44 for the healthy group and they exercised intermittently during exposure. Thus, our knowledge regarding the effects of low (near ambient) levels of ozone exposure on the human cardiovascular system is very limited.

Within this context, HEI decided to issue an RFA for studies on the effect of exposures to ozone on the human cardiovascular system and the influence of other air pollutants on such effects.

Studies were to be conducted in two phases:

Phase I would focus on investigation of the cardiovascular effects of ozone at near ambient levels in the laboratory: human volunteers, ages 55 to 70 with no clinically diagnosed cardiovascular disease, will undergo controlled chamber exposure to ozone, at concentrations of 0.06 and 0.10 ppm, while exercising intermittently. Cardiovascular (primary endpoints) and other physiological responses (secondary endpoints, such as pulmonary function and systemic makers of acute inflammation) would be measured.

Phase II studies would be conducted at sites proposed by investigator teams, where ozone concentrations are comparable to the levels used in the Phase I laboratory studies, but in the presence of other ambient pollutants among which PM is of special interest. The subject selection criteria and study protocol in Phase II would be as similar as possible to those employed in Phase I to maximize comparability between the two phases. The three teams of investigators who have been selected will meet to establish a common protocol for the studies.

#### **Brief Description of the Funded Human Controlled Exposure Studies**

Three studies for Phase 1 were selected among those submitted in response to the RFA. (No studies for Phase II are currently funded.) The studies will be conducted at three research centers - the University of California at San Francisco (CA), the University of Rochester (NY), and the University of North Carolina at Chapel Hill (NC).

A total of about 90-100 subjects will be exposed to clean air, a low ozone concentration, and a high ozone concentration in a randomized order for a total of 3 exposures per subjects. The subjects will be recruited and tested over a period of three years. Subjects will have to meet a number of inclusion criteria and sign the informed consent in order to enter the study. The subjects will be evaluated on the day of the exposure and on the following day with a total of 6 days of observation per subject. The types of health outcomes to be measured include: markers of inflammation and oxidative stress in sputum, respiratory function, cardiac function and vascular parameters of prothrombotic status and endothelial function. It is likely that the analyses of some of the biological samples and the electrocardiogram tracings will be conducted in a single laboratory. Some additional details about the studies can be in found in the attached RFA10-1.

#### **OBJECTIVE OF THIS REQUEST FOR QUALIFICATIONS**

The objective of this RFQ is to seek a well-qualified **statistical data-analysis center to develop the plan for analyses and manage and analyze the data collected in a multicenter ozone exposure study in human volunteers.**

#### **Rationale for the RFQ**

Human controlled exposure studies take a long time to carry out due to the time required to recruit the subjects and test them at different pollutant doses and allowing for a reasonable "wash-out" period between each exposure. The multicenter design offers the advantage of allowing larger numbers of subjects to be studied in a shorter period of time. From the onset of this program, HEI decided that the data collected at each of the three research centers using a common protocol would be transferred to a central data management and analysis center, designated by HEI where pooled analysis of the data will be performed. Separate statistical analyses including endpoints not part of the common protocol may be conducted by each center.

In addition to supporting a data analysis center, HEI will also contract with a QA/QC team to conduct audits at each of the centers, including the data analysis center. The QA/QC team will report to the HEI staff, who will correspond with the centers as needed to insure the proper correction of any errors.

### **Role of the data-analysis center**

The main roles of the data-analysis group are to:

- Work with the investigators at each center to develop a plan for data analysis of the combined data from the three centers based on the draft common protocol that the investigators are developing. During this process the analysts will have the opportunity to provide comments on the protocol. The plan for data analysis will be an integral part of the protocol and will be reviewed and approved by HEI's Research Committee, HEI's committee of outside experts that recommends studies for funding.
- Provide a data management plan to the three centers and manage the data in accordance with this plan.
- Participate in the design of data collection forms and in establishing procedures for QA/QC of the data.
- Perform the analyses of the combined multi-center data. It is expected that the analysts will largely work independently of the individual research groups, but will engage them at some steps of the analyses. One or more workshops will be organized to give the opportunity to the data analysis group to present to and discuss the results of the analyses with the original research groups.
- Participate in the writing of the final report to HEI (and other peer-reviewed publications). At the end of an HEI study the entire investigator team writes up a report that is independently reviewed by HEI's Review Committee, an outside panel of experts with no overlap with the Research Committee that originally funded the study.
- Be part of the Data Safety and Monitoring Committee (in conjunction with some members of the HEI Research Committee). This will entail:
  - Establishing procedures for the timely submission of data from the centers, monitoring the quality of the data, and reporting interim results of the analyses to HEI and the centers' investigators.
  - Approving additional analyses of the pooled data by the individual research centers after completion of the pooled analyses by the data analysis center.

### **APPLICATION PROCESS**

The application should consist of the following components:

1) Cover page (Form F-1)

2) Statement of Qualifications (6-page maximum) consisting of:

- a) Brief narrative of the general types of analyses that may be conducted when combining data from multiple centers and when repeated measurements are made in the same subjects. Issues that will need to be addressed include, but are not limited to, linear versus nonlinear dose-response curves, multiple testing, repeated measurements analysis, and the validity of combining data from different centers.
- b) List of the personnel involved.
- c) Description of qualifications of the principal investigators and his or her collaborators and of how the team qualifications and prior experience are relevant to managing and analyzing the data from these studies. Expertise in running a data analysis center and setting up automatic data submission procedures and in multicenter studies and/or clinical trials is highly desirable.

3) Description of the facilities, including data security procedures, available at the applicant institution. Also include information on a) quality control and assurance of data collection and management and b) other support (Form F-6).

4) A tentative budget for the study assuming that time would be spent in the first year to work with the investigator teams to develop and finalize the plan for data analyses and the data management plan. The assumed start date should be December 1, 2010. Budget forms (Forms F4a and F5a - and 4b and 5b if applicable) should be used. Time and travel expenses should be budgeted for the likelihood of 3 face-to-face meetings with the investigators in each year of the study. While some preliminary analyses of a partial set of data may be conducted during the course of the study, it should be assumed that the formal data analyses will not start until all the data have been collected and the codes broken. If subject recruitment is consistent throughout the three years of the study, all data should be collected by March 2014. HEI expects that the data analysis center will complete the analyses in no more than 6 months

5) Curriculum vitae of the key personnel involved (Form F-8).

## APPLICATION DUE DATE

The application should be submitted in electronic form by **October 7, 2010**, to Ms. Sarah Rakow at [srakow@healtheffects.org](mailto:srakow@healtheffects.org). The application forms required for this application can be found on the HEI web site <http://www.healtheffects.org/RFA/Forms/RFAforms.htm>. No specific form is required for the Statement of Qualifications. Additional information about RFA 10-1 can be found at <http://www.healtheffects.org/funding.htm>.

For questions about the RFQ please contact Dr. Maria Costantini ([mcostantini@healtheffects.org](mailto:mcostantini@healtheffects.org); +1-617-488-2302).

## REVIEW OF RFQ APPLICATIONS

The HEI Research Committee will review the applications based on the quality of the narrative, expertise of the team, and reasonableness of the proposed costs. A response to all applicants will be provided by **November 15, 2010**.

The HEI Research Committee will also be responsible for overseeing and reviewing the data analysis plan and monitoring the progress of the analyses throughout the duration of the study.

## REFERENCES

Gong Jr H, Wong R, Sarma RJ, Linn WS, Sullivan ED, Shamoo DA, Anderson KR, Prasad SB. 1998. Cardiovascular effects of ozone exposure in human volunteers. *Am J Respir Crit Care Med* 158:538-546.

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U.S. Environmental Protection Agency. 2006. Air Quality Criteria for Ozone and Related Photochemical Oxidants. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Research Triangle Park, NC. EPA 600/R-05/004aF.

U.S. Environmental Protection Agency. 2007. Review of the National Ambient Air Quality Standards for Ozone: Policy Assessment of Scientific and Technical Information. Research Triangle Park, NC. EPA-452/R-07-007.