HEI

STATEMENT

Synopsis of Research Report 126

HEALTH EFFECTS INSTITUTE

Effects of Controlled Exposure to Ultrafine Carbon Particles in Healthy and Asthmatic People

Ambient particles are a complex mixture whose size, chemical composition, and other physical and biological properties vary with location and time. Regardless of the characteristics at a single site, however, epidemiologic studies have reported that short-term increases in low levels of particles are associated with short-term increases in illness and death. Remaining questions about the health effects of particles include the specific characteristics of particles—especially size and chemical composition—and the biological mechanisms that may explain the reported associations.

To address some of these critical issues, Health Effects Institute issued Request for Applications (RFA) 98-1, "Characterization of Exposure to and Health Effects of Particulate Matter" in 1998. A component of the RFA was to promote evaluation of health effects of controlled exposure to particles in animals and healthy people as well as in those who might be more susceptible to particle exposure. People with asthma are one of the groups considered particularly susceptible to the effects of airborne particles.

HEI funded two studies to address this issue in human volunteers who were either healthy or had mild asthma. One was the current study, led by Dr Mark Frampton, University of Rochester School of Medicine and Dentistry, Rochester, New York, to evaluate the effects of inhalation exposure to ultrafine (<0.1 µm diameter) carbon particles, which some scientists believe are more effective than larger particles in causing health effects (the ultrafine hypothesis of particle toxicity). The second study, led by Dr Henry Gong of Los Amigos Research and Education Institute, Downey, California, investigated the effects of exposure to fine (0.1–2.5 µm in diameter) concentrated ambient particles (CAPs) derived from the Los Angeles area.

As one of the consequences of an HEI-sponsored workshop held before the studies began, Frampton and Gong developed exposure and study protocols that were similar to those being used in CAPs studies underway at the US Environmental Protection Agency research facility in Chapel Hill, North Carolina. In this way, results of the studies could more easily be compared with each other. HEI published the results of the Gong study in 2003.

APPROACH

Healthy and mildly asthmatic men and women were exposed via a mouthpiece over 2 hours to laboratory-generated ultrafine carbon particles (average diameter approximately 0.025 µm) and on a different occasion to filtered air as follows:

- 12 healthy participants were exposed at rest to 10 µg/m^3 particles or air;
- 12 healthy participants were exposed to particles (10 and 25 µg/m^3) or air during intermittent exercise on a stationary bicycle (15-minute cycles of rest and exercise over 2 hours); and
- 16 asthmatic volunteers were exposed to either 10 µg/m^3 particles or air using the same intermittent exercise protocol used for the healthy exercising volunteers.

Frampton and colleagues hypothesized that ultrafine particle exposure would activate leukocytes (white blood cells) and endothelial cells (cells lining blood vessels to form part of the interface between blood and tissue cells) and lead to an inflammatory response in the airways and in the blood. The investigators further hypothesized that effects would be greater in people with asthma than in healthy people. Their proposed study also anticipated that particle exposure might affect

Continued

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr Mark W Frampton at the University of Rochester, Rochester NY. The complete report, *Effects of Exposure to Ultrafine Carbon Particles in Healthy Subjects and Subjects with Asthma*, can be obtained from HEI or our website (see reverse side). FRAMPTON 126

respiration and cardiac electrophysiologic function. The investigators therefore measured multiple indices of pulmonary and cardiac function as well as blood parameters at different times before, during, and up to 21 hours (45 hours for asthmatics) after exposure to particles or filtered air. To measure inflammatory responses in the airways, Frampton and colleagues collected sputum at screening and 22 hours after exposure. In addition, they calculated the number and mass of inhaled particles that deposited in the lungs of asthmatic and healthy participants.

RESULTS AND INTERPRETATION

Healthy resting people had no detectable changes in airway, systemic, or cardiac electrophysiologic endpoints at any time measured during or after inhalation exposure to 10 $\mu g/m^3$ particles. In exercising healthy and asthmatic participants, Frampton and colleagues did not detect changes in any airway inflammatory endpoint during or after exposure to 10 or 25 $\mu g/m^3$ particles. These findings are noteworthy in the light of the investigators' novel finding that, at the same inhaled concentration of particles, about 50% more particles deposited in lungs of asthmatic people than in healthy people. In addition, these researchers calculated that over 4 times as many particles were deposited in the lungs of exercising participants as in the lungs of resting participants. Thus, even though the dose of particles delivered to the lungs of exercising asthmatic people may have been approximately 6 times the dose delivered to the lungs of resting healthy people, ultrafine particles had no effects on the airways. Further, the concentration of particles of the size used in this study was 10 to 100 times higher than average concentrations of ultrafine particles reported in urban air.

Some systemic and cardiovascular changes were associated with particle exposure in healthy and asthmatic exercising volunteers. The pattern and magnitude of these changes were similar in the two groups, differing from the investigators' prediction of greater responses in the asthmatic participants.

Exposure to ultrafine particles was associated with changes in numbers of certain leukocytes in the blood of healthy and asthmatic exercising volunteers. The numbers of some types of leukocytes decreased but the total number of leukocytes did not change. Expression of some adhesion molecules on the surface of leukocytes, a characteristic of cell activation, was also changed. The significance of these observations is not clear. The investigators speculate that exposure to particles mildly constricts pulmonary blood vessels, activating vascular endothelial cells and preventing outflow of activated leukocytes from the lungs into the circulation. An alternative possibility to explain the findings is that the particles are selectively toxic to activated cells. In addition, as the investigators appropriately note, the changes detected may also have been chance findings that can occur at random and are more likely to be seen when evaluating multiple endpoints.

The investigators also found small changes in cardiac repolarization, the time taken between the electrical stimuli governing contraction and relaxation of the heart. Again, the biological or clinical significance of these small changes in healthy and asthmatic individuals is unclear.

CONCLUSIONS

This innovative and technically complex study used state-of-the-art measurements to assess responses to inhaled ultrafine particles in healthy and asthmatic volunteers. The particles were generated in a laboratory and did not contain toxicologically important components such as metals and organic compounds, but they were relevant to real world exposures because carbon is a major component of airborne particles from urban settings. The concentration of ultrafine particles used, however, was 10 to 100 times higher than the average concentrations reported in urban air.

Frampton and colleagues found few airway, systemic, or cardiac electrophysiologic changes associated with ultrafine particle exposure. The clinical significance of any of the changes is not clear. Thus, in this limited set of healthy and mildly asthmatic participants, the effects of exposure to ultrafine carbon particles did not support the hypothesis that ultrafine particles are more toxic than larger components of the particle mix. This paucity of effects is consistent with the results of studies conducted in North America with human exposures to concentrated fine particles.

Future controlled exposures should include particles of different sizes and composition, different susceptible populations (such as those with cardiovascular disease), a larger number of participants, longer exposure durations and higher concentrations; and different endpoints to increase the statistical and scientific strength and thus provide a stronger test of the ultrafine hypothesis.

HEALTH EFFECTS INSTITUTE

Charlestown Navy Yard
120 Second Avenue
Boston MA 02129-4533 USA

+1-617-886-9330
+1-617-886-9335 fax

pubs@healtheffects.org
www.healtheffects.org