



STATEMENT

Synopsis of Research Report 129

HEALTH
EFFECTS
INSTITUTE

Lung Inflammation and Exposure Spikes of Fine and Ultrafine Particles in Aged and Young Adult Rats

Epidemiologic studies have established an association between short-term increases in ambient levels of particulate matter and increases in morbidity and mortality, especially in older individuals with preexisting cardiovascular or respiratory disease. Despite the consistency of the epidemiologic findings, the biological mechanisms underlying these associations are not well understood. One set of research questions has focused on the role of particle attributes (such as size, surface properties, and composition) in causing adverse health effects.

In 1998, HEI issued Request for Applications (RFA) 98-1, "Characterization of Exposure to and Health Effects of Particulate Matter." In response, Dr Kristen Nikula and colleagues of the Lovelace Respiratory Research Institute proposed to systematically examine lung inflammation in young adult and old rats after inhalation of fine particles (< 2.5 μm in aerodynamic diameter) and ultrafine particles (< 0.1 μm in aerodynamic diameter) of different composition: relatively inert carbon and vanadium pentoxide (V_2O_5), which contains the transition metal vanadium, known to cause toxic effects upon inhalation in humans in occupational settings. In addition, they proposed to examine the effect of a short-term increase (spike) in particle exposure concentration on inflammatory response. The investigators hypothesized that a spike in particle concentration would cause a greater inflammatory response than exposure to a steady concentration at equal particle lung burden would. During the second year of the study, Dr Fletcher Hahn assumed primary responsibility for the research.

APPROACH

The investigators used a previously developed deposition model to estimate the relative deposition of fine and ultrafine particles. They had identified

predetermined concentrations to which rats would be exposed and used the model to make adjustments according to relative deposition. The model was designed to address several issues: (1) differences in deposition rate between ultrafine and fine particles; (2) differences between carbon and vanadium particle characteristics that may affect particle deposition; (3) differences in lung deposition between young adult and old rats due to differences in lung morphology; and (4) the need to incorporate a spike in exposure concentration into the model. Revisions to the model were made during the study, to add a clearance component, for example.

Rats were exposed for 5 hours/day for 17 consecutive days via nose-only inhalation to ultrafine or fine V_2O_5 or ultrafine carbon particles. Control groups were exposed to filtered air. On day 15, all rats were intratracheally instilled with endotoxin to produce mild inflammation. On days 16 and 17, some rat groups were exposed to higher concentrations of particles to mimic a short-term increase in air pollution. The other groups remained exposed to the same concentration as on days 1 through 15. Ultrafine V_2O_5 (35 nm count median diameter) concentrations were 50, 100, 150, or 200 $\mu\text{g}/\text{m}^3$; fine V_2O_5 (0.7 μm mass median aerodynamic diameter) concentrations were 150, 200, 500, or 1000 $\mu\text{g}/\text{m}^3$; ultrafine carbon (35 nm) concentrations were 150 or 200 $\mu\text{g}/\text{m}^3$. All rats were killed 18 hours after the end of exposure on day 17. They were examined for lung morphology, lung particle burden, and markers of inflammation and oxidative stress in lung tissue and bronchoalveolar lavage fluid.

RESULTS AND INTERPRETATION

In this complex study, the investigators found that exposure for 17 days to fine and ultrafine particles caused an inflammatory response in aged rats with mild inflammation induced by endotoxin

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treatment. A greater mass of ultrafine V_2O_5 particles than fine V_2O_5 particles was deposited in the lung at the same inhaled mass concentration. On the basis of equal predicted lung burden, more neutrophils were found in bronchoalveolar lavage fluid from rats exposed to ultrafine V_2O_5 than from rats exposed to fine V_2O_5 , indicating that ultrafine particles were more toxic. In general, exposure to ultrafine V_2O_5 caused greater lung responses (eg, LDH levels, neutrophil numbers, and production of mucus in small airways) than exposure to ultrafine carbon did. No major differences were found between aged and young adult rats exposed to fine V_2O_5 . The results of this study suggest that, under the experimental conditions used, both particle size and composition are important for particle toxicity. However, more research using different kinds of particles and animal models is needed before generalizing these results to the effects of fine and ultrafine particles in the ambient air pollution mixture.

Some uncertainty remains about Hahn and colleagues' comparison of the effects of fine and ultrafine vanadium because of uncertainties in the model. The model accounted well for several aspects of the experimental design, but it may not have accounted for some differences in particle characteristics between V_2O_5 and carbon, such as in solubility, porosity, and tendency to aggregate into larger groups or chains, which would be difficult to incorporate into any model. The investigators used an innovative approach of analyzing

data by predicted particle lung burden rather than exposure concentration to evaluate the effects of fine versus ultrafine V_2O_5 . Direct validation of the model remained incomplete, however, because lung burden was determined in only a subset of the rats exposed to V_2O_5 and because the method to measure carbon lung burden did not yield valid results (although the predicted lung burdens for carbon exposures were not used for data analysis).

An interesting and novel finding was that an increase in exposure concentration for 2 days after 15 days of exposure caused greater inflammatory effects than exposure at a constant level (either at the original lower or the final higher concentration). The increase in exposure concentration was modeled after epidemiologic observations that a short-term increase in ambient particulate matter concentration is associated with an increase in deaths and hospital admissions. There are some indications that such an association may exist regardless of the initial concentration, because similar short-term associations have been found in cities with different levels of pollution. In the current study, the increased effect of a spiked exposure concentration was found in rats exposed to fine or ultrafine particles of different composition, but not for all concentrations tested. More research is needed to further investigate and confirm the increased effect of a short-term spike in exposure concentration.