



STATEMENT

Synopsis of Research Report 96

HEALTH
EFFECTS
INSTITUTE

Acute Pulmonary Effects of Ultrafine Particles in Rats and Mice

INTRODUCTION

Many epidemiologic studies, carried out in diverse locations with varying levels and composition of ambient particulate matter and other air pollutants, have reported associations between small increases in the level of particulate matter and increases in daily morbidity and mortality. The strongest associations appear to be in the elderly and in individuals with cardiopulmonary conditions such as chronic obstructive pulmonary disease (COPD). However, a biological mechanism linking low-level particle exposure and pathophysiologic effects has not been established. Assessing the effects of inhaled particulate matter in appropriate animal models is critical to learning how such pollutants may exert adverse health effects.

Ambient particulate matter varies in size and chemical composition. Some scientists have hypothesized that very small particles (less than 100 nm in diameter) are particularly toxic. Although they constitute only about 1% to 8% of the mass of particulate matter in ambient air, these ultrafine particles are present in very high numbers, have greater total surface area than larger particles, and may deposit in greater numbers in the lungs. The Health Effects Institute funded the animal study described in this report to address whether and how ultrafine particles might exert effects in the airways.

APPROACH

Dr Günter Oberdörster, from the University of Rochester School of Medicine and Dentistry, and his colleagues hypothesized that inhaled ultrafine particles induce an inflammatory response in the airways of mice and rats and that animals with

preexisting airway inflammatory conditions may be particularly vulnerable. The investigators focused on inhaled carbon and platinum particles because these elements are constituents of particles found in urban atmospheres. They also evaluated the effects of Teflon fumes containing ultrafine Teflon particles, which are not representative of ambient particles but have been shown to induce a potent inflammatory response leading to severe physiologic effects in rats. They exposed animals to 100 $\mu\text{g}/\text{m}^3$ carbon and platinum particles for 6 hours and to 40 $\mu\text{g}/\text{m}^3$ Teflon particles for 15 minutes. These concentrations are much higher than those of ultrafine particles in ambient air. The investigators also evaluated the effects of intratracheal instillation of ultrafine titanium dioxide particles and, in separate experiments, the effects of coexposure to ultrafine carbon particles and ozone, a gaseous environmental pollutant that can induce inflammation.

The investigators tested small numbers of young and old mice and rats that were healthy or had pulmonary conditions. They used mice injected with elastase to model humans with emphysema; old *Tsk* mice, a strain with a genetic defect in lung development, to model the effects of chronic emphysema and age; and mice and rats pretreated with the bacterial product endotoxin to model humans who have a bacterial airway infection. Pulmonary inflammation was evaluated by measurement of cellular and biochemical parameters in bronchoalveolar lavage fluid, focusing on increases in the percentage of neutrophils and production of reactive oxygen species, which appeared to be the most sensitive indicators of a response. Measurements of cytokine and chemokine messenger RNA levels in tissue extracts as well as histologic assessments were performed.

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RESULTS AND CONCLUSIONS

Inhalation of ultrafine carbon or platinum particles, or Teflon particles in the absence of Teflon-generated gaseous components, did not induce an inflammatory response in either young or old healthy mice and rats. Ultrafine particle exposures had limited effects in some of the animal models of pulmonary dysfunction tested and no effect in others. For example, ultrafine carbon and platinum particles induced small inflammatory responses in both young and old elastase-treated mice, but ultrafine carbon particles had no effect in the old *Tsk* mice used to model chronic emphysema, either with or without endotoxin pretreatment. In rats preexposed to endotoxin, ultrafine carbon particles induced a small inflammatory response over background airway inflammation in young but not old animals. By contrast, a complex statistical analysis of their results led the investigators to conclude that older age and a compromised or sensitized respiratory tract increased sensitivity to ultrafine particle effects in mice and rats. These conclusions are overstated, however, given that the responses to ultrafine particles were small and occurred only in some animal models and certain end points.

Instilling ultrafine titanium dioxide particles directly into the trachea of mice, a technique that bypasses the nasal filtering mechanisms and delivers a much higher concentration to the lungs than inhalation, induced a strong inflammatory response. Inhalation of ultrafine Teflon fumes in rats also induced a strong inflammatory response, but only if the fumes contained *both*

ultrafine Teflon particles and gaseous components. Coexposure to ultrafine carbon particles and ozone induced responses that appeared to be additive, less than additive, or more than additive compared with responses to the separate components, depending on the model and end point tested. These results suggest that ultrafine particles may induce inflammatory responses in the airways in some circumstances: for example, when high doses are deposited in the lower respiratory tract by intratracheal instillation or when the particles are combined with potentially toxic gases.

In conclusion, the investigators conducted an interesting study in healthy mice and rats and in mice and rats with preexisting airway conditions to address the important issue of whether ultrafine particles induce an inflammatory response in the airways. The findings provide little evidence that inhaled ultrafine particles cause inflammation, however. This may be due to limitations in the study's design, which include small numbers of animals and experiments, uncertainties about the susceptibility of the animal models used to the effects of ultrafine particles, and the relative toxicity of the particles studied compared to particles of different chemical composition. These uncertainties make it difficult to extrapolate the results of this study to possible effects of ultrafine particles on humans. Additional research in humans and in a variety of animal models evaluating multiple endpoints and particles is required to evaluate further whether ultrafine particles induce inflammatory or other adverse health effects.