STATEMENT

Synopsis of Research Report 117

HEALTH EFFECTS INSTITUTE

# Peroxides and Macrophages in Toxicity of Fine Particulate Matter

Epidemiologic studies have established an association between short-term increases in ambient levels of particulate matter and increases in morbidity and mortality. The biological mechanisms underlying these associations are not well understood, however. Dr Debra Laskin of Rutgers University and colleagues tested the hypothesis that oxidants in ambient air, such as hydrogen peroxide, may be transported by fine particulate matter into the lungs and thus contribute to lung tissue injury. HEI funded this study because the project could provide insight into transportation of volatile compounds into the lung and provide valuable information on the health effects of particles and peroxides.

## APPROACH

The investigators proposed to use ammonium sulfate particles because of their prevalence in the ambient air of the eastern United States and their reportedly low toxicity in animals and humans. Rats inhaled ammonium sulfate (450 µg/m$^3$; particle size 0.45 ± 0.1 µm), hydrogen peroxide (10, 20 or 100 ppb), or combinations thereof, for 2 hours on a single occasion. Concentrations of hydrogen peroxide and ammonium sulfate were approximately one to two and two orders of magnitude greater than concentrations in ambient air, respectively. The investigators assessed lung tissue injury and presence of inflammatory markers in the lung. They also assessed activation of alveolar macrophages, which are involved in the first line of defense against foreign materials that enter the lung. Exposures with $^{18}$O-labeled hydrogen peroxide were conducted to measure deposition in the lung. Additional experiments assessed lung injury and inflammation, after rats inhaled an organic peroxide (cumene hydroperoxide), and investigated hydrogen peroxide formation in an indoor environment.

## RESULTS AND INTERPRETATION

Laskin and colleagues found little evidence for lung inflammation in rats exposed to ammonium sulfate, confirming its low toxicity. They did find some evidence for lung inflammation and activation of alveolar macrophages in rats exposed to hydrogen peroxide gas alone. They consistently found increased neutrophil influx into the lung and increased neutrophil adherence as well as increased tumor necrosis factor α expression in lung tissue in rats exposed to hydrogen peroxide gas. Less consistent changes were observed in other inflammatory endpoints, such as superoxide anion and nitric oxide production and heat shock protein expression by alveolar macrophages. Many other inflammatory endpoints were not changed, however.

After exposure to hydrogen peroxide in combination with ammonium sulfate, the investigators also observed increased neutrophil influx and adherence as well as increased tumor necrosis factor α expression. They presented some evidence that the inflammatory effects of combined exposure might have been greater than exposure to hydrogen peroxide alone. Caution is needed in interpreting these data, however, due to a lack of quantification of certain endpoints, such as neutrophil influx into lung tissue and heat shock protein expression by alveolar macrophages, and a lack of dose-response relations for other endpoints, such as superoxide anion and nitric oxide production by alveolar macrophages.

These results were supported by the presence of $^{18}$O in cells and fluid from bronchoalveolar lavage after exposure to $^{18}$O-labeled hydrogen peroxide alone and, to a greater extent, in combination with ammonium sulfate. These results suggest that ammonium sulfate particles can transport hydrogen peroxide into the lower airways and induce inflammation.

*Continued*

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr Debra L Laskin at Environmental and Occupational Health Sciences Institute, Rutgers University, and the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, Piscataway, New Jersey. The complete report, *Peroxides and Macrophages in Toxicity of Fine Particulate Matter*, can be obtained from HEI or our website (see reverse side). LASKIN 117

Exposure to cumene hydroperoxide had fewer effects than hydrogen peroxide exposure on inflammatory endpoints, but it is not clear whether these results are generalizable to other organic peroxides, which may have different chemical reactivity and toxicity. Finally, the investigators demonstrated that low levels of hydrogen peroxide may form in indoor environments under highly polluted conditions.

**SUMMARY**

Laskin and colleagues have shown that hydrogen peroxide reaches the lower lung when inhaled alone and in combination with particles, leading to some inflammatory changes in lung tissue at concentrations that are one to two orders of magnitude greater than concentrations in ambient air. Caution is needed in interpreting these data, however, owing to a lack of quantification of certain endpoints and a lack of dose-response relations for other endpoints. Whether ammonium sulfate or other particles indeed promote transport of peroxides and other oxidants into the lung at ambient concentrations, thereby increasing the possibility for adverse health effects, is still uncertain and remains to be investigated further.

# Peroxides and Macrophages in the Toxicity of Fine Particulate Matter in Rats

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