



STATEMENT

Synopsis of Research Report 112

HEALTH
EFFECTS
INSTITUTE

Effects of Particles on Lung Inflammation in Healthy and Asthmatic Volunteers

BACKGROUND

Epidemiologic studies have noted that short-term increases in ambient levels of particulate matter (PM) are associated with hospital admissions and deaths from cardiovascular and respiratory disorders. These studies have suggested that individuals with preexisting diseases, such as cardiovascular disease or asthma, are more susceptible to the effects of air pollution than healthy individuals. However, the biologic mechanisms that underlie this association and the role that the composition and size of PM may have in causing adverse health effects are not well understood.

One hypothesis about how PM may exert its effects is that when it deposits in the airways, it activates a cascade of inflammatory events, a part of the body's natural defense systems. Dr Holgate and an international team of collaborators had observed some of these inflammatory changes in lung fluids and blood from humans exposed to PM. They wanted to investigate whether such changes could also be observed in lung tissues. They proposed that such changes may be related to the chemical composition of PM (diesel exhaust vs concentrated ambient particles [CAPs]), and expected that changes would be more pronounced in people with asthma than in healthy people. The Swedish government and the US Environmental Protection Agency funded the human exposure studies (diesel exhaust in Sweden; CAPs in the US) that provided tissue samples. Recognizing an opportunity for one laboratory to analyze tissues obtained after different exposures, HEI funded Holgate's lung tissue studies in the United Kingdom. Part I of the Investigators' Report describes the effects of diesel exhaust on inflammatory markers in healthy and asthmatic participants. Part II describes the effects of CAPs from the eastern US on inflammatory markers in healthy participants only.

APPROACH

At the Swedish laboratory, 25 healthy and 15 asthmatic participants were exposed for 2 hours to diesel exhaust ($100 \mu\text{g}/\text{m}^3$ PM concentration) or to filtered air on separate days. At the US laboratory, 12 healthy participants were exposed for 2 hours to filtered air and 30 different healthy participants were exposed to a range of CAPs concentrations ($25\text{--}311 \mu\text{g}/\text{m}^3$; median $108 \mu\text{g}/\text{m}^3$). In both studies, lung function was assessed before and immediately after exposure. To obtain lung tissues and fluids, all participants in Sweden underwent bronchoscopy 6 hours after exposure; in the US, lung tissues were obtained 18 hours after exposure from 11 control and 10 CAPs-exposed participants (range $38\text{--}311 \mu\text{g}/\text{m}^3$; median $84 \mu\text{g}/\text{m}^3$). Tissue samples were sent to Dr Holgate in the United Kingdom for analysis of inflammatory markers, including numbers of specific white blood cells, expression of activation markers, and levels of cytokines. Whereas Holgate's laboratory focused on analyzing lung tissues, the other laboratories also analyzed lung function, lung fluids, and blood. To appropriately interpret Holgate's results, it is important to also consider the results from the other laboratories.

RESULTS AND INTERPRETATION

Part I: Exposure of Healthy and Asthmatic Subjects to Diesel Exhaust

For both healthy and asthmatic participants, the investigators observed a small increase in airway resistance (meaning the airways were slightly more constricted) immediately after exposure to diesel exhaust.

For healthy participants, of the many biochemical markers of inflammation that were assessed, some were significantly changed 6 hours after exposure to diesel exhaust. For example, in lung fluids, the percentages of neutrophils and lymphocytes increased and the percentage of macrophages

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decreased (a complementary response). This group also showed increased levels of cytokines measured in lung fluids (interleukins [IL] 6 and 8) and in lung tissues (IL-8), and increased levels of cellular adhesion molecules in lung tissues (vascular cell adhesion molecule 1 and P-selectin). Protein and messenger RNA levels of other inflammatory markers were unchanged. It is difficult to arrive at a simple unifying description of these complex inflammatory changes and their biological relevance.

For participants with asthma, the only inflammatory changes observed after exposure to diesel exhaust were a decrease in the percentage of eosinophils in lung tissues and fluids and an increase in levels of the cytokine IL-10 in lung tissues. (IL-10 has antiinflammatory effects and is currently being considered as a treatment for asthma.) These findings warrant further research.

The investigators expected that asthmatic participants would show more inflammatory changes than healthy participants because epidemiologic studies had found an association between increased asthma symptoms and high levels of air pollution on certain days. However, Holgate and colleagues did not find inflammatory changes in asthmatic participants after controlled exposure to diesel exhaust. It is possible that exposure at these relatively low levels would be less likely to cause inflammation. In addition, the small number of participants studied and the greater variability (compared with healthy participants) observed in their inflammatory parameters heighten uncertainty and lessen the likelihood of finding significant effects. In addition, it is unclear whether exposure affected ventilation differently in the two groups; a change in ventilation could affect the number and size of particles that reached the deeper lung.

Part II: Exposure of Healthy Subjects to Concentrated Ambient Particles

The investigators found no changes in lung function immediately after exposure. At 18 hours after exposure to CAPs but not to filtered air, they observed an increase in blood fibrinogen levels, and a higher percentage of neutrophils and a lower percentage of macrophages in lavage fluids (again, a complementary response). They found no differences in any of the inflammatory markers evaluated in bronchial tissues.

DISCUSSION OF BOTH STUDIES

Comparing the results of these two studies with results from other PM studies is difficult. In the current diesel

exhaust study, many markers of inflammation were studied but few changed; of those that changed, the magnitude of the change was modest. Other studies have shown greater inflammatory effects after diesel exhaust exposure. Several reasons for the differing results among studies are plausible. The times at which endpoints were assessed differed among studies: Given that the spectrum of inflammatory events spans hours to days after exposure, the current diesel exhaust study focused on early inflammatory events by measuring markers at 6 hours after exposure. Other studies, including the current CAPs study, investigated inflammatory responses at 18 to 24 hours after exposure. Furthermore, because so few markers of inflammation changed in the current studies, it is possible that these changes occurred by chance.

One unresolved issue is that the exposure atmospheres included gaseous pollutants. In the CAPs study, gases were present at ambient levels and are unlikely to have influenced the results. In the diesel study, however, levels of nitrogen dioxide, for example, were relatively high. Because gases such as ozone and nitrogen dioxide are known to affect lung function and inflammation at fairly low concentrations, it is possible that small amounts of these gases influenced the results.

CONCLUSIONS

The current study is an early effort to investigate and compare effects of diesel exhaust and CAPs exposure on lung tissues obtained via bronchial biopsies from humans. Amidst a number of negative results, the study found that, after exposure to diesel exhaust, (1) lung function (airway resistance) changed modestly in both healthy participants and participants with asthma; and (2) healthy participants exhibited small changes in some markers of inflammation but participants with mild asthma did not. After exposure to CAPs, the study found no changes in bronchial tissues; however, the small number of participants and the variability in CAPs concentrations complicate interpreting and comparing these findings with results from the diesel exhaust exposures.

A consistent pattern of inflammation after exposure to a variety of PM mixtures in many studies has not emerged to date. In part, this may be due to different experimental approaches and to measuring different inflammatory markers at different times after exposure.