



# STATEMENT

Synopsis of Research Report 104

HEALTH  
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## Acute Cardiovascular Effects in Rats from Exposure to Urban Ambient Particles

### BACKGROUND

Particulate matter (PM) in ambient air is a complex mixture containing particles of different sizes and chemical composition. Short-term increases in ambient PM levels have been associated with short-term increases in morbidity and mortality from cardiovascular causes. However, the biologic mechanism by which PM may affect cardiovascular events and the roles of particle size and composition are not well understood. One hypothesis is that particle deposition in the lung induces the release of factors that affect blood cells and vessels throughout the body. The Health Effects Institute funded the study described in this report to address this hypothesis and to elucidate how the chemical composition of the particles could change the effects of PM on the cardiovascular system.

### APPROACH

Dr Renaud Vincent and his colleagues of Health Canada, Ottawa, hypothesized that ambient PM would cause changes in certain cardiovascular parameters; for example, heart rate and blood pressure or the concentration of compounds that regulate the constriction and dilation of blood vessels. The investigators implanted rats with radiotransmitters (to collect continuous data on heart rate, blood pressure, and body temperature) and indwelling catheters for repeated blood sampling. The animals were exposed for 4 hours to clean air or one of four types of resuspended particles: ambient particles (Ottawa dust), ambient particles that had been washed in water to remove soluble components, diesel soot, or carbon black. The investigators used stored resuspended particles rather than fresh particles to ensure that particle concentration and chemical composition were identical among experiments. The investigators measured several endpoints in the rats' blood and plasma (endothelins, nitric oxide products, and catecholamines), changes in heart rate, blood pressure, and general activity, and injury to lung tissue.

### RESULTS AND IMPLICATIONS

The investigators found that exposure to urban PM, washed urban PM, and diesel soot (but not carbon black) caused an increase in endothelin-3 and to a lesser extent endothelin-1. This is important because endothelins help to regulate normal cardiovascular homeostasis between vasoconstriction and vasodilation. Elevation of endothelin-1 is an indicator of the severity of congestive heart failure in some patients and may predict cardiac death, whereas its decrease may herald an improvement in symptoms; elevation of endothelin-3 may be associated with systemic vasoconstriction in cardiac patients.

Urban PM also caused an increase in blood pressure; the effect disappeared when washed particles were used. The increase in blood pressure was not observed with diesel soot or carbon black. This indicates that one or more of the soluble components in the unwashed urban particles may be responsible for the blood pressure effects of urban PM. The investigators suggested that soluble metals may have been responsible for this adverse effect; among other candidates, zinc may be important because zinc-dependent enzymes are involved in the regulation of endothelins, which may then impact blood pressure. Whether this is indeed the case remains to be determined.

The increase in blood pressure after exposure to urban PM was small, however, and its significance is unclear because the stress caused in the animals by handling and surgery was substantial; this was reflected in the variability of the baseline physiologic parameters (ie, heart rate, blood pressure, and body temperature) and blood catecholamine measurements. The study could have benefitted from additional analyses of changes in electrocardiogram or in the daily rhythm variations in heart rate and blood pressure. Additional short-term and transient changes in these physiologic parameters at different time

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benefitted from additional analyses of changes in electrocardiogram or in the daily rhythm variations in heart rate and blood pressure. Additional short-term and transient changes in these physiologic parameters at different time points after exposure to the particles, if present, would strengthen the argument that PM may have adverse effects on the cardiovascular system.

The investigators found no evidence of damage to lung epithelial cells from exposure to any of the particles by using an assay that measured lung cell proliferation several days after exposure. These findings confirm previous studies with the same urban particles in the same laboratory. In those studies, however, urban PM did increase other indices of lung injury, ie, levels of inflammatory markers in lung lavage fluid. It is possible that exposure to washed urban particles, diesel soot, or carbon black might also have affected those markers of lung inflammation.

The use of resuspended particles rather than fresh particles was a valid choice to ensure the stability of the administered concentration and the chemical composition of the particles among experiments. The relevance of the effects of resuspended particles to those observed with fresh particles is in question, however, because they likely underwent chemical and physical changes during storage. Due to aggregation, these particles are presumably larger than fresh particles and it is unclear whether larger particles penetrate the deep

lung. Nevertheless, the finding that both resuspended ambient particles and diesel soot affected the same endothelins strengthens the confidence in these data.

Main strengths of this study were that the investigators compared several classes of particles and measured diverse endpoints. The finding that urban PM changed endothelin levels might be strengthened by future research using several PM concentrations and by reconstituting the urban PM from the washed PM, which would show whether or not adding the soluble components to the washed particles would restore the biologic effects.

In conclusion, the investigators found effects on endothelins after exposure to resuspended urban PM, washed particles, and diesel soot, and effects on blood pressure after exposure to urban PM. Although extrapolating results from animal studies to humans and from the high levels used in this study to ambient levels always involves uncertainties, these findings open interesting avenues to further explore the possible mechanisms by which inhaled PM may cause adverse cardiovascular events. More research is needed to assess whether changes in endothelin levels would occur in humans exposed to ambient levels of particulate matter, and whether these changes may contribute to the adverse cardiovascular events that have been associated with air pollution episodes in epidemiology studies.

# Inhalation Toxicology of Urban Ambient Particulate Matter: Acute Cardiovascular Effects in Rats

## Investigators' Report

### Methods and Study Design

- Animals
- Electrocardiogram and Blood Pressure Radiotransmitters
- Data Acquisition
- Source of Particles
- Nose-Only Inhalation Exposures
- Sampling Particles for Chemical Analysis
- Elemental Analysis of the EHC-93 Particles
- Plasma Endothelins, Catecholamines, and Tyrosines
- Nitric Oxide-Related Compounds in Whole Blood
- Lung Histology and Autoradiography
- Particle Dosimetric Modeling
- Statistical Methods and Data Analysis: Primary Endpoints of Effects, Cardiovascular Telemetry Data, and Biochemistry Data

### Results

- Monitoring Animal Data
- Development of the Exposure Atmospheres
- Lung Histology and Autoradiography
- Physiologic and Biochemical Endpoints
- Dosimetric Modeling

### Discussion, Conclusions, and Implications of Findings

## Health Review Committee's Commentary

### Introduction

### Background

### Technical Evaluation

- Aims and Objectives
- Study Design
- Methods
- Results: Comments on Key Findings

### Discussion

- Endothelins
- Particles
- Animals and Surgery
- Blood Measurements
- Telemetry Measurements
- Lung Injury Assessment
- Statistics

### Summary and Conclusions

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