

Mechanisms of Particulate Toxicity: Findings of the Three Campus Study

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California Air Resources Board

California Environmental Protection Agency

Good morning Chairman Lloyd and members of the Board.

This morning we are going to report on the findings of a recently completed, ARB-funded three-campus study investigating the biological mechanisms of particulate matter toxicity in human asthmatics and animals that are models for responses in humans.

Background

- ◆ Ambient particulate matter (PM) has been associated with adverse health effects
 - New California standards for PM
- ◆ Biological mechanisms are largely unknown
- ◆ Three interrelated studies investigated possible mechanisms for PM adverse health effects
 - UC Davis, UC Irvine, and UCSF

Hundreds of studies have shown statistically significant associations between exposure to ambient particulate matter and adverse health effects, such as increased respiratory symptoms, reduced lung function growth in children, increased hospitalization and emergency room visits for cardiopulmonary causes, and even an increase in death due to cardiopulmonary causes. In California alone, PM exposure contributes to thousands of cases of illness and death each year.

Based on this information, the Air Resources Board adopted more health protective air quality standards for PM in 2002. Also, the US EPA is currently reviewing the national standards in order to provide adequate protection of public health.

However, one piece of the puzzle remains, which is the biological mechanisms explaining the reported associations. To fill this data gap, the ARB funded in 1999 three University of California campuses (Davis, Irvine, and San Francisco) to conduct interrelated experiments designed to investigate how particles might induce adverse health consequences in susceptible humans as well as in animals. Each team of researchers investigated related questions, but from different perspectives.

Study Design

◆ Subjects/Models

- UC Davis: rat model of allergic airway disease
- UC Irvine: rat model of elderly humans
- UCSF: asthmatic adults

◆ Exposure Conditions

- 4-6 hour exposures on single or multiple days
- ~250 $\mu\text{g}/\text{m}^3$ PM (ammonium nitrate & elemental carbon)
- PM plus 0.2 ppm ozone (O_3)

◆ Endpoints

- Airway inflammation & lung function
- Heart rate, blood pressure & heart rate variability

To study the mechanism of PM toxicity, two of the groups used animal models that mimic human diseases or conditions. The use of animal models allows investigation of endpoints that cannot be studied in humans for ethical or logistical reasons.

The UC Davis investigators used a specific rat strain that is a model for allergic airway disease that has some similarities to human asthma. The Irvine group utilized a strain of older rats to investigate likely responses of elderly humans. To round out the project, UC San Francisco studied adult human asthmatics.

All three groups of investigators used similar 4 to 6 hour exposures on one or several consecutive days, and ammonium nitrate and elemental carbon particles from the same sources, and all three groups used a total particle concentration of about 250 micrograms/cubic meter. Ammonium nitrate and elemental carbon are two of the main components of California particulate matter. In some studies, 0.2 parts per million ozone was also included. The similar experimental designs and exposures at all three research sites made it possible to perform comparisons of the responses in the animals to those of the human subjects. Collectively, the three groups investigated several potential mechanisms whereby particle exposure could lead to tissue and organ damage. These mechanisms were examined by measuring endpoints such as airway inflammation and changes in lung function, heart rate, blood pressure, and heart rate variability. The last variable is particularly interesting since reduced heart rate variability is a risk factor for heart attacks.

The major findings of the studies are summarized in the next two slides.

Key Findings

UC Davis (allergic rats)

- ◆ PM exposure did not enhance allergic airway inflammation
- ◆ PM exposure increased epithelial cell proliferation (lung damage)

UC Irvine (elderly rats)

- ◆ Multi-day PM exposure decreased blood pressure and heart rate variability
- ◆ No cardiovascular responses from single day exposures

The group at UC Davis was successful in developing and characterizing an animal model of allergic airways disease. These animals exhibit some, but not all, of the characteristics of human asthma. The results of studies with these animals showed that particle exposures on three or six consecutive days did not enhance allergic airways inflammation, contrary to the study's hypothesis. However, particle exposures did lead to epithelial cell proliferation, and repeated episodes of this can lead to permanent lung damage.

The UC Irvine investigators showed that a 4-hour exposure on three consecutive days induced decreases in blood pressure and heart rate variability in elderly rats. However, single-day exposure to either particles or particles plus ozone induced no cardiovascular responses.

Key Findings (cont'd)

UCSF (asthmatic adults)

- ◆ Airway inflammatory changes confined to PM plus O₃ exposures
- ◆ 4-hour exposure to PM alone induced a small decrease in lung function
- ◆ Exposure to PM plus O₃, was associated with significant changes in heart rate variability

The studies at UC San Francisco with asthmatic humans found that PM plus ozone exposures did induce significant airways inflammation in these asthmatic subjects. However, no airway inflammatory changes were observed with particle exposure alone, in agreement with the findings on allergic rats at UC Davis.

A 4-hour exposure to particles alone did induce a small but significant decrease in one measure of lung function, a finding that was unexpected, and needs to be replicated.

The most significant and surprising result of the UC San Francisco component of the study was the finding that exposure to particles plus ozone, but not to particles alone, was associated with a significant reduction in heart rate variability. This result is in contrast to those from the elderly rat model at UC Irvine, which showed reduced heart rate variability with exposure to particles alone.

Conclusions

Particulate matter (ammonium nitrate plus elemental carbon) induces adverse effects in:

- ◆ Animal model of allergic airway disease
- ◆ Animal model of the elderly
- ◆ Asthmatic humans exposed to PM plus O₃

Results support link between PM and adverse health effects



Collectively, the results of these studies suggest that particles of ammonium nitrate and elemental carbon, at concentrations that may occur on the very worst days, can induce:

Adverse health effects in both of the animal models studied, as well as in asthmatic humans (that are also exposed to ozone).

Although these studies only begin to address the mechanisms of particulate matter toxicity, the results presented today do provide evidence linking particulate matter exposure to adverse health effects.

That concludes my presentation. Thank you, and we would be pleased to answer any of your questions.