# MOSES Review Panel:

# Strengths and Limitations of the MOSES Study

James Merchant

Chair

# Members of the MOSES Review Panel

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- **Jesus Araujo**, Associate Professor of Medicine, Director of Environmental Cardiology, David Geffen School of Medicine, UCLA
- **Nadia Hansel**, Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University
- **David Jacobs**, Professor, Epidemiology & Community Health, University of Minnesota
- **Susanne May**, Associate Professor, Department of Biostatistics, University of Washington
- **Jana Milford**, Professor, Department of Mechanical Engineering, University of Colorado–Boulder
- **Greg Wellenius**, Associate Professor, Department of Epidemiology, Brown University
- External consultant: **Charles Weschler,** Adjunct Professor, EOHSI – Exposure Science, Rutgers University

# Study Design: Strengths

- Well designed and executed-- high quality study
- Excellent collaboration with extensive oversight by HEI
  - Fidelity to protocol
  - Centralized analyses for certain endpoints
- Cross-over design with clean air and two ozone concentrations
- 90 participants—large for most human chamber exposure studies
  - Good power for primary outcomes
- Modeled after a clinical trial, focusing on primary and secondary outcomes

# Study Design: Limitations

- Healthy older, not elderly adults
  - Average age 60
  - BMI = 25, FEV1 = 104% predicted, exclusions for CVD conditions and medications: Very healthy panel
  - Mostly Caucasian: represents a small segment of general population
- Acute exposures only, limited range of exposure concentrations (by design)
- Designed as a clinical trial with primary outcomes
  - Difficult to maintain this design given many relevant secondary outcomes
  - Could also be analyzed as an observational epidemiologic study analyzing both primary and secondary outcomes

# Exposures

**Strengths**

- Ozone generation and measurements were excellent
- Well justified 70 ppb and 120 ppb concentrations

**Limitations**

- Primary ozone (by design)
  - Almost no reaction products or interactions with particles or other pollutants, as would happen in the real world

# Exposures

**Limitations (Continued)**

- One night hotel stay may not eliminate effects of daily exposure to background concentrations of ozone and other pollutants
- Should assess participants' prior exposures to ozone and other pollutants 1-3 days before
  - Could affect the outcomes
  - Chamber exposures may sometimes be lower than daily ambient exposures
- Very low particle counts differed among sites
  - Likely due to different instrument size cut-offs

# Statistical Analyses

**Strengths**

- Assigned data coordination and independent analysis team
- Analyses generally well designed and executed

**Recommendations**

- Look into conducting analyses by site
  - Rochester appeared to have higher values for CVD outcomes
- Further analyses needed regarding:
  - Prior exposures
  - Diary information
  - Health outcomes during exposures

# Cardiovascular Effects: Strengths

- Comprehensive array of endpoints
  - Primary endpoints were well powered
  - Covered variety of mechanistic pathways
  - Common laboratory analyses and ECG interpretation

- Confidence in mostly negative results across the board
  - Only endothelin-1 was increased
  - No changes in markers of systemic inflammation

# Cardiovascular Effects: Limitations

- Large variability in outcome measures could obscure effects

- Should assess certain endpoints in more detail
  - Possible ST segment changes were perhaps too easily dismissed
  - Would like more details on arrhythmias
  - Only one measure of lipid peroxidation
  - CVD outcomes during exposure were not (yet) reported
  - Unexplained decrease in nitrotyrosine

# Pulmonary Effects: Strengths

- Standardized protocols following well-accepted procedures
- Increase in lung function with clean air
  - Previously observed in panel studies
  - Likely related to exercise and/or diurnal variation
- Confirms pulmonary effects beginning at 70 ppb ozone
  - Attenuation of increase with clean air
- Concentration-related increase of PMN in sputum

# Pulmonary Effects: Limitations

- Respiratory symptoms *during* exposure were not (yet) reported
- Should analyze for a subgroup of "high responders"
  - Based on changes in lung function and PMN in sputum
  - If such a group exists, redo analyses and look for possible CVD effects
  - If not, confirms lack of CVD effect

# Conclusions

- Study confirms respiratory effects at 70 ppb ozone
- No evidence of cardiovascular effects at low levels in this highly selected population

***Caveats:***

- These are very healthy older, not elderly, adults
- Represent small segment of the general population
- Limited to acute, relatively low exposures of primary ozone
- Not combined with particulate exposure (by design)

- Need to explore prior exposures (up to 3 days)
- Need to explore possibility of a "responder" subgroup