MOSES Review Panel: Strengths and Limitations of the MOSES Study

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Members of the MOSES Review Panel

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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
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