Human Health Impacts of Ambient Air Particles
Morton Lippmann, NYU School of Medicine

Session on: Challenges in Characterizing Small Particles,
Washington, DC, October 25, 2010

Particle Volume Distributions by Particle Size for Various PM Sources
Cardiovascular Mortality and Lung Cancer
Affected by Long-Term Fine Particulate Matter Exposure


Relative Risks and 95%ile CI’s for 10 µg/m³ increase in annual PM$_{2.5}$ mass concentration. Size of the dot corresponds to the relative number of deaths.
Average NMMAPS Daily Mortality Coefficient for 60 U.S. Cities for PM$_{2.5}$ vs. its Measured Components

Differences in mortality rs per the 5th-to-95th percentile difference in FPM and FPM components across NMMAP MSAs (for the 60 MSAs for which FPM speciation data were available).

From: Lippmann et al. (2006)
Air Pollution Enters the Body Through the Nose and/or Mouth and Penetrates into the Deep Lung
Particle Deviation from Flow Streamlines During Inhalation for Different Deposition Mechanisms
Human Health Impacts of Ambient Air Particles

- **CURRENT KNOWLEDGE**

- PM$_{2.5}$ mass been has been a useful surrogate index of adverse health risks, and it correlates better with cardiovascular effects than other monitored air pollutants, but its risk coefficient varies, presumably due to differences in PM composition.

- PM$_{10}$ mass, which is often dominated by PM$_{2.5}$ mass, is a poor indicator of the respiratory system risks associated with the PM$_{10-2.5}$ that deposits within the tracheobronchial airways, and the role of PM$_{10-2.5}$ composition is unknown.

- Neither of the current mass-based PM indices is at all useful as an index of the risks associated with ultrafine PM (UFP).

- It is highly likely that more optimal indices based on other particle size ranges and/or PM chemical component compositions can be shown to exist.

- EPA is considering reducing the annual PM$_{2.5}$ NAAQS from 15 down to 11 to 13 ug/m$^3$. Meeting a limit at the lower end of this range may be impossible in most U.S. urban areas, especially within the next 5 years. A focus on reducing the most toxic chemical components is needed.
Study of PM$_{2.5}$ Source and Component Concentrations on Mortality in the American Cancer Society II (ACS) Cohort.

George Thurston, PI.
U.S. Spatial Maps of Mean Source-Specific PM$_{2.5}$ Impacts
Distribution of PM$_{2.5}$ and Components within New York City (NYC). Morton Lippmann, PI.
Nickel

Vanadium
<table>
<thead>
<tr>
<th>Exposed</th>
<th>Exposure</th>
<th>Associations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Adults</td>
<td>Ambient Air (Hong Kong)</td>
<td>Ni &amp; V intervention with &lt; annual mortality</td>
<td>Hedley et al. 2002,4</td>
</tr>
<tr>
<td>Human Adults</td>
<td>Ambient Air (60 US cities)</td>
<td>Ni &amp; V variation with average daily mortality</td>
<td>Lippmann et al. 2006</td>
</tr>
<tr>
<td>Human Adults</td>
<td>Ambient Air (72 US counties)</td>
<td>Ni &amp; V variation with average daily mortality</td>
<td>Dominici et al. 2007</td>
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<tr>
<td>Human Adults</td>
<td>Ambient Air (25 US cities)</td>
<td>Intercity variation in PM$_{2.5}$-mortality associated with Al, As, Ni, &amp; SO$_4^-$..</td>
<td>Franklin et al. 2008</td>
</tr>
<tr>
<td>Human Adults (Males only)</td>
<td>Ambient Air (US cities)</td>
<td>Traffic density, Ni, &amp; V with annual mortality</td>
<td>Lipfert et al. 2006</td>
</tr>
<tr>
<td>Human Adults</td>
<td>Ambient Air (9 CA counties)</td>
<td>OC &amp; EC with daily mortality</td>
<td>Ostro et al. 2006</td>
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</table>
### Table 2. Associations of PM$_{2.5}$ Sources and Components with Non-Fatal Health Effects in Humans

<table>
<thead>
<tr>
<th>Exposed</th>
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<th>Associations</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Human Adults</td>
<td>2h CAPs (Chapel Hill)</td>
<td>Fe/Se/SO$_4^-$(with $&gt;$ in PMNs in BALF) Cu/Zn/V with $&gt;$ fibrinogen in blood</td>
<td>Ghio et al. 2000</td>
</tr>
<tr>
<td>Human Adults</td>
<td>2h CAPs + O$_3$ (Toronto)</td>
<td>OC with BAD ($p=0.04$). EC, Cd, K, Zn, Ca, &amp; Ni ($p=0.06-0.17$) OC with $&gt;$ blood pressure</td>
<td>Urch et al. 2004</td>
</tr>
<tr>
<td>Human Adults</td>
<td>Ambient Air (Copenhagen)</td>
<td>V &amp; Cr with oxidant stress and DNA damage.</td>
<td>Sorensen et al. 2005</td>
</tr>
<tr>
<td>Human Adults</td>
<td>Ambient Air (Amsterdam, Helsinki, Erfurt)</td>
<td>traffic with ST-segment depression. EC with oxidative stress.</td>
<td>Lanki et al. 2006</td>
</tr>
<tr>
<td>Human Adults</td>
<td>Ambient Air (Taipei)</td>
<td>SO$_4^-$(but not OC or EC) with $&lt;$ HRV</td>
<td>Chuang et al. 2007</td>
</tr>
<tr>
<td>Asthmatic Children</td>
<td>Ambient Air (New Haven)</td>
<td>motor vehicle exhaust with wheeze. Road dust with shortness of breath</td>
<td>Gent et al. 2009</td>
</tr>
<tr>
<td>Asthmatic Infants</td>
<td>Ambient Air (Bronx)</td>
<td>Ni, V, &amp; Zn with wheeze and cough. EC with cough</td>
<td>Patel et al. 2009</td>
</tr>
<tr>
<td>Healthy Children</td>
<td>Ambient Air (Southern CA)</td>
<td>EC with lung growth (10 to 18 yrs)</td>
<td>Gauderman et al. 2004</td>
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<tr>
<td>Human Adults</td>
<td>Ambient Air (Hong Kong)</td>
<td>Ni &amp; V with bronchial hyper-reactivity</td>
<td>Hedley et al. 2002, 2004</td>
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<tr>
<td>Human Adults</td>
<td>Ambient Air (London)</td>
<td>BS with plasma fibrinogen</td>
<td>Pekkanen et al. 2000</td>
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<tr>
<td>Human Adults</td>
<td>Ambient Air (14 US cities)</td>
<td>motor vehicles, oil combustion, &amp; metals processing with CVD hospital admissions</td>
<td>Janssen et al. 2002</td>
</tr>
<tr>
<td>Human Adults</td>
<td>Ambient Air (106 US counties)</td>
<td>Ni, V, &amp; EC with CVD hospital admissions (single pollutant), only Ni in multipollutant.</td>
<td>Bell et al. 2009</td>
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<tr>
<td>Exposed</td>
<td>Exposure</td>
<td>Associations</td>
<td>Reference</td>
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<tr>
<td>Dogs</td>
<td>Boston CAPs</td>
<td>Al/Si with &gt; PMNs in BALF, peripheral WBC Count, and circulating lymphocytes</td>
<td>Clarke et al. 2000</td>
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<td></td>
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<td>Ni/V with PMNs and BALF macrophages</td>
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<td>Br/Pb with PMNs in BALF</td>
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<td>Rats</td>
<td>Boston CAPs</td>
<td>Si, V, Pb, SO$_4^{2-}$, &amp; Br with &gt; PMNs</td>
<td>Saldiva et al. 2002</td>
</tr>
<tr>
<td>Rats</td>
<td>Boston CAPs</td>
<td>Al, Si, &amp; Fe with &gt; TBARS</td>
<td>Rhodes et al. 2005</td>
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<td></td>
<td></td>
<td>Cr, Zn, &amp; Na with PMNs in BALF</td>
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<tr>
<td>Rats</td>
<td>Boston CAPs</td>
<td>Fe, Mn, Cu, &amp; Zn with lung oxidants</td>
<td>Gurgueira et al. 2002</td>
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<td>Fe, Al, Si, &amp; Ti with heart oxidants</td>
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<tr>
<td>Dogs</td>
<td>Boston CAPs</td>
<td>Crustal elements with with occlusion-induced</td>
<td>Wellenius et al. 2003</td>
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<td></td>
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<td>ST-segment depression</td>
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<td>Rats</td>
<td>RTP CAPs</td>
<td>Zn with plasma fibrinogen levels</td>
<td>Kodavanti et al. 2000</td>
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<tr>
<td>Mice</td>
<td>Tuxedo CAPs</td>
<td>Ni, Cr &amp; Fe with &gt; HR &amp; &lt; HRV</td>
<td>Lippmann et al. 2006</td>
</tr>
<tr>
<td>Mice</td>
<td>Tuxedo CAPs</td>
<td>SO$_4^{2-}$ with HR during exposure</td>
<td>Lippmann et al. 2005</td>
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<td></td>
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<td>Ni &amp; V with HR following exposure</td>
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<tr>
<td></td>
<td></td>
<td>Soil elements with HRV following exposure</td>
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<td></td>
<td></td>
<td>Br, Fe, &amp; EC with HRV later in the day</td>
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<tr>
<td>Mice</td>
<td>Los Angeles CAPs</td>
<td>EC &amp; OC with IL-5 and IgG1 @ 50 m from Freeway.</td>
<td>Kleinman et al. 2007</td>
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</tbody>
</table>
# TABLE 4. HEALTH IMPACTS OF SUBCHRONIC ANIMAL EXPOSURES TO AMBIENT AIR PM$_{2.5}$

A VARIETY OF HEALTH EFFECTS IN LAB ANIMALS IN VIVO AND CELLS IN VITRO HAVE BEEN REPORTED, BUT RESPONSIBLE COMPONENTS NEED TO BE IDENTIFIED.

**HEALTH EFFECT** (Reference)

- **Acute Increase in HR in ApoE$^{-/-}$ Mice:** (Hwang et al. 2005)
- **Acute Decrease in HRV in ApoE$^{-/-}$ Mice:** (Chen & Hwang. 2005)
- **Increase in Aortic Plaque in ApoE$^{-/-}$ Mice:** (Chen & Nadziejko. 2005)
- **Degeneration of Dopaminergic Neurons in ApoE$^{-/-}$ Mice:** (Veronesi et al. 2005)
- **NF-$k$B Expression in Lung Cells in vitro by PM$_{2.5}$ Ni:** (Maciejczyk & Chen. 2005)
- **Long-term Exposure on Atherosclerogenesis in ApoE$^{-/-}$ Mice:** (Sun et al. 2005)
- **Acute Increase in HR and Decrease in HRV in ApoE$^{-/-}$ Mice by PM$_{2.5}$ Ni:** (Lippmann et al. 2006)
- **Increase in Cytokine Production in Microglial Cells in vitro by PM$_{2.5}$ Ni:** (Sama et al. 2007)
Table 4 (continued) Human Health Impacts of Ambient Air Particles

- **Potentiation of Hypertension via ROS-mediated Activation in Rats** (Sun et al. 2008)
- **Tissue Factor Expression in Atherosclerosis in ApoE\(^{-/-}\) Mice** (Sun et al. 2008)
- **Induced Vascular Oxidant Stress & Atherosclerosis in ApoE\(^{-/-}\) Mice** (Ying et al. 2009)
- **Role for RhoA/Rho-kinase in C57BL/6 Mice** (Ying et al. 2009)
- **Adipose Inflammation & Insulin Resistance in Diet-Induced Obesity in C57BL/6 Mice** (Sun et al. 2009)
- **Induction of Non-Alcoholic Fatty Liver in C57BL/6 Mice** (Tan et al. Manuscript)
- **Perivascular Fat and Vascular Dysfunction in C57BL/6 Mice** (Sun et al. manuscript)
- **Childhood obesity in C57BL/6 and p47\(^{phox}\) Mice** (Xu et al. 2010)
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- Potentiation of Hypertension via ROS-mediated Activation in Rats (Sun et al. 2008)
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- Induction of Non-Alcoholic Fatty Liver in C57BL/6 Mice (Tan et al. Manuscript)
- Perivascular Fat and Vascular Dysfunction in C57BL/6 Mice (Sun et al. manuscript)
- Early PM$_{2.5}$ Exposure Enhances Obesity in Mice: Role of p47$^{phox}$ (Xu et al. in press)
Boxplot of PM Components in Detroit and Seattle

Red: Detroit  Blue: Seattle
Cardiovascular Disease Mortality of PM Components in Detroit and Seattle

In Detroit, PM$_{2.5}$, NO$_2$, CO, and EC were significantly associated with cardiovascular mortality in warm season. In Seattle, PM$_{2.5}$, NO$_2$, CO, EC, Al, Ni, and K were significantly associated with cardiovascular mortality in cold season, while in warm season, only Fe and K showed significant associations. Cardiovascular mortality in Detroit appear to be associated with traffic-related components and gaseous pollutants, whereas in Seattle, the components and gases associated with cardiovascular mortality also include other combustion sources such as residual oil burning and wood smoke.
Subjects Recruitment:
30 healthy nonsmoking female subjects (at age 60 to 65) were recruited from each site of Jinchang (smelter city) and Zhangye (control city), Gansu, China.

Exposure Measurement:
PM$_{2.5}$ samples were collected daily on Teflon filters for: 1) gravimetric analysis of PM$_{2.5}$; 2) XRF analyses of 34 elements.

Measurements of Biological Endpoints:
1) * IL-6, CRP, MCP-1, ICAM-1, and VCAM-1 were measured in plasma samples by ELISA kits;
2) * Intima-media thickness (IMT) of carotid artery was measured by B-mode ultrasound imaging;
3) * Circulating endothelial progenitor cells (CEPCs) were enumerated by flow cytometry according to combinations of various surface markers;
4) * Vascular endothelial growth factor (VEGF) and stromal-cell derived factor-1 (SDF-1), the two important proteins involved in the mobilization, homing, and differentiation of CEPCs, were measured by ELISA kits;

Statistical analyses:
A t-test was used to detect the differences in all measured biological endpoints between groups. Pearson correlation analysis was employed to evaluate the associations of IMT with other biomarkers.
Nickel Smelter Study - Summary and Conclusions

SUMMARY
• The ambient concentrations of PM$_{2.5}$ were comparable (Jinchang and Zhangye).
• Ni was ~76-X higher in Jinchang; Cu, As, and Se were 25, 17, and 7-X higher.
• IL-6 and CRP were significantly higher in Jinchang subjects.
• IMT was significantly thicker in Jinchang subjects.
• CEPCs, were significantly lower in Jinchang subjects.
• VEGF was higher in Jinchang subjects, but w/o statistical significance.
• IMT correlated negatively with the number of CEPCs while positively with MCP-1.

CONCLUSIONS
• Ni is likely the agent most responsible for PM$_{2.5}$-induced cardiovascular effects.
• Cu, As, and/or Se may also play a role.
• The reduced capacity of endothelial repair may partially explain the critical roles of Ni in PM$_{2.5}$-associated CVD.
Comparative Toxicity of CAPs, Sidestream Cigarette Smoke, and Diesel Engine Exhaust. Lung-Chi Chen, PI.

- We compared the plaque progression produced by subchronic exposures to concentrated ambient PM$_{2.5}$ (CAPs) at Sterling Forest (SF) in Tuxedo, NY and at Mount Sinai School of Medicine (MS) in Manhattan in ApoE$^{-/-}$ mice with that produced by: 1) comparable exposures to freshly generated sidestream cigarette smoke (SS); 2) whole diesel engine exhaust (WDE); and 3) the gaseous component of WDE.
## Comparative Exacerbation of Atherosclerosis in ApoE⁻/⁻ Mice by PM Mixtures in Tuxedo, NY

<table>
<thead>
<tr>
<th>Type of PM</th>
<th>PM Concentration ((\mu g/m^3))</th>
<th>Duration (months)</th>
<th>% increase in Plaque Area</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>480</td>
<td>6</td>
<td>25</td>
<td>Chen et al 2009b</td>
</tr>
<tr>
<td>CAPs</td>
<td>105</td>
<td>5</td>
<td>38</td>
<td>Quan et al 2009</td>
</tr>
<tr>
<td>WDE</td>
<td>436</td>
<td>5</td>
<td>13</td>
<td>Quan et al 2009</td>
</tr>
<tr>
<td>DEG</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>Quan et al 2009</td>
</tr>
<tr>
<td>CAPs+DEG</td>
<td>113</td>
<td>5</td>
<td>21</td>
<td>Quan et al 2009</td>
</tr>
</tbody>
</table>

**Notes:**
Results from ApoE⁻/⁻ mice fed normal chow, as measured by ultrasound biochemistry (UBM). CAPs: concentrated ambient particles; SS: side stream smoke \((CO=1\text{ppm})\); WDE: whole diesel exhaust \((CO=5\text{ppm})\); DEG: diesel gases associated with 436 \(\mu g/m^3\) PM in WDE.

\(\dagger\): These exposures were performed simultaneously.
HUMAN HEALTH IMPACTS OF AMBIENT AIR PM

SUMMARY OF CURRENT KNOWLEDGE

- Epidemiological studies using speciation data show stronger associations of cardiopulmonary effects with transition metals than with PM$_{2.5}$ mass.
- Toxicological studies provide support for the influence of transition metals.
- Chemical Speciation Network (CSN) data on PM$_{2.5}$ components have been essential to the progress to date in demonstrating stronger associations for metals than for PM$_{2.5}$ mass.
- CSN data on PM$_{2.5}$ components have been too limited in terms of frequency to adequately support definitive time-series studies.
- CSN data on PM$_{2.5}$ components have been too limited in spatial coverage to adequately identify the effects of PM components that are not uniformly distributed.
- An expanded CSN network can support epidemiological research that could provide a sound basis for the development of NAAQS for toxic PM components that contribute only small fractions of PM mass, permitting more targeted controls to benefit public health at lower overall cost and societal disruption.
HUMAN HEALTH IMPACTS OF AMBIENT AIR PM

ACKNOWLEDGEMENTS

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* a Center Grant (ES 00260) from the National Institute of Environmental Health Sciences (NIEHS).
References Cited in Tables 1 - 3:


Hedley AJ, Chau PYK, Wong CM (2004). The change in sub-species of particulate matter [PM_{10}] before and after an intervention to restrict sulphur content of fuel in Hong Kong. Poster presented at Better Air Quality/Asian Development Bank Meeting at Agra, India.


Human Health Impacts of Ambient Air Particles

- REFERENCES CITED in TABLE 4 for the VARIOUS HEALTH EFFECTS ASSOCIATED WITH SUBCHRONIC AMBIENT AIR PM$_{2.5}$ INHALATION EXPOSURES

REFERENCES CITED in TABLE 4 FOR THE VARIOUS HEALTH EFFECTS (Continued)

- Sun Q, Lumeng CN, Ying Z, Wang A, Yavar Z, Odin J, Lippmann M, Chen L-C, and Rajagopalan S. Particulate air pollution and vascular dysfunction: Role of perivascular fat. (manuscript)
- Tan HH, Guo J, Friel MI, Alvarez CE, Chen LC, Sun Q, Friedman SC, Odin J, and Alina J. Enhancement of fatty liver disease progression and TLR-4-dependent Kupfer cell activation by air particulate matter. (manuscript)