Ambient Particles, Their Toxic Components, Sources and How They Impact Health

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Variation in source, season and atmospheric processes influence chemical and toxicological characteristics of particles

- PM sources and particle characteristics
- Freeway/mobile source associated health effects
- PM toxicity in relation to mechanistic hypotheses
  - Oxidative stress and catalytic ROS generation
  - Cellular uptake of ultrafines
- Key accomplishments and future research questions
Studies of PM Sources and Atmospheric Chemistry

Three Zones of PM Exposure:
- Zone of influence: adjacent to primary emissions sources
- Source sites: influenced by a variety of sources
- Receptor sites: influenced by transport and atmospheric chemistry

West  East

Prevailing winds in the Los Angeles Basin

Dispersion  Transformation Chemical reaction

Zone of Influence of Emissions/Sources

Freeways

Urban/Downtown Los Angeles, beyond immediate zones of influence

“Source” areas

Inland-Eastern Los Angeles Basin regions

“Receptor” areas
Spatial Distribution of Particle Phase Phenanthroquinone in the LA Basin

Particle-phase

ng/m³

LOM ATA SMA LCR LAH LBC ALP MRL LKE SDS RIV UPL

West East
Effect of Transport on PAH Size Distribution (Source/Receptor)

Figure - Fernandez A., Miguel A.H, Jaques, P. and Sioutas, C. *Aerosol Science and Technology*, 2003

**Downey Regular MOUDI - Aug.-Oct. 2000**

- Fraction by mass (Source)

**Riverside Regular MOUDI - Aug.-Oct. 2001**

- Fraction by mass (Receptor)
Use of Source Tracers in PM Exposure and Toxicology Research

Which sources pose the greatest risks to public health?

- Characterize physical/chemical characteristics including source tracers
- Conduct toxicological studies to differentiate toxicity
- Analyze associations between toxicity and source tracers to determine relative source toxicity

How do source contributions to ambient PM samples vary from:

- Site to site?
- Over the course of the day? Seasons?
- Between size fractions?

Approach: Evaluate concentrations/size distribution of individual organic compounds to trace primary and secondary sources of PM:

Markers have been developed for vehicles, cooking, wood smoke and photochemistry

Mobile Source Studies

- Particle mass remains relatively constant with distance from freeway; size distribution changes considerably.

- Concentrations of nanoparticles (<20 nm) are much higher in winter than summer, suggesting that these particles are volatile, formed by condensation of organic vapors after they leave the tailpipe.


- Kittleson et al., Inhal. Tox.-16, 2004:

**Figure 1.** Comparison of decay of particle number concentrations in summer and winter in the size range of (a) 6-12 nm, (b) 12-25 nm, (c) 25-50 nm, (d) 50-100 nm, and (e) 100-200 nm near the 405 freeway.
Recent Studies from PM Centers and EPA: Freeway Exposures and Mobile Source Effects

Studies in mice, rats and humans have reported effects of health endpoints in several target tissues/organ systems:

1. **Cardiovascular effects** in aged rats (2 studies) and in humans (3 studies)
2. **Allergic airways responses** in sensitized mice
3. Children’s Health Study **asthma prevalence**
4. Children’s Health Study **lung development**
5. Traffic density study of effects on **human fetal development**
6. **Brain inflammation responses** in mice
Exposure to Traffic and the Onset of Myocardial Infarction

**Results:** An association between exposure to traffic and myocardial infarction onset one hour later was observed (odds ratio: 2.9; 95% confidence interval: 2.2 to 3.8, p<0.001).

Time spent in cars, public transport and on bicycles was consistently connected with an increased risk for myocardial infarction.

**Conclusions:** Transient exposure to traffic might pose a risk in persons vulnerable to myocardial infarctions.

Peters et al., NEJM, 2004, In press
Recent Studies of Freeway Exposures and Mobile Source Effects: Cardiovascular effects

- Exposures to on-road particles produce effects on the pulmonary and cardiovascular system in compromised aged rats, including observed acute phase response and inflammatory cell activation (Elder et al. *Inh Tox* 2004) as well as changes in heart rate and blood pressure (Kleinman et al. *In Preparation*).

- Study of healthy men exposed during driving (the “Trooper Study”) noted a significant association between in-vehicle PM 2.5 exposure levels and changes in heart rate variability (HRV) and other cardiac endpoints. (Riediker et al., *AJRCCM* 2004)

- Gong et al. have completed the first ultrafine exposures on human subjects (healthy and asthmatic) and have seen a significant change in heart rate variability.

![Graph showing SDNN (5 min rest): Healthy (red line) & Asthmatic (blue line) Subjects](image)
Recent Studies of Freeway Exposures and Mobile Source Effects: Pulmonary and Allergic Airways Responses

- Markers of **allergic and inflammatory airways responses** increased in sensitized mice exposed to mobile source emissions short distances from a freeway. *Kleinman et al, 2004*
  - Greater responses at 50m compared to 150m from the freeway

- **Asthma prevalence** in the Children’s Health Study is associated with residential distance to freeway, both within and across communities. *Gauderman et al, 2004.*

- Current levels of air pollution associated with mobile sources have chronic, adverse effects on **lung development** from the age of 10-18 years leading to clinically significant deficits in attained FEV1 as children reach adulthood. *Gauderman et al, 2004.*
Recent Studies of Freeway Exposures and Mobile Source Effects: Children’s Health Study - Prevalence of Asthma by Distance to the Freeway

<table>
<thead>
<tr>
<th>Distance to the Nearest Freeway (Kilometers)</th>
<th>Total</th>
<th>All Subjects</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>(%)</td>
<td>OR\textsuperscript{a}</td>
</tr>
<tr>
<td>&gt;0.5</td>
<td>104</td>
<td>(13.5)</td>
<td>2.00</td>
</tr>
<tr>
<td>0.5 – 1.0</td>
<td>169</td>
<td>(18.9)</td>
<td>2.92</td>
</tr>
<tr>
<td>1.0 – 1.5</td>
<td>146</td>
<td>(16.4)</td>
<td>2.33</td>
</tr>
<tr>
<td>1.5 – 2.0</td>
<td>102</td>
<td>(10.8)</td>
<td>1.48</td>
</tr>
<tr>
<td>2.0 – 3.0</td>
<td>138</td>
<td>(15.9)</td>
<td>2.38</td>
</tr>
<tr>
<td>3.0 – 7.0</td>
<td>210</td>
<td>(7.6)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Trend test\textsuperscript{b} \quad p=0.01

\textsuperscript{a} Odds ratio relative to the 3.0 – 7.0 km group, based on the combined model with adjustment for sex, race, Hispanic ethnicity, and cohort

\textsuperscript{b} Test of trend in odds ratio across distance groups
Recent Studies of Freeway Exposures and Mobile Source Effects: Children’s Health Study - Lung Development and Exposure to Air Pollution

Proportion of 18-year olds with FEV1 below 80% of the predicted value

Recent Studies of Freeway Exposures and Mobile Source Effects: Residential Proximity to Freeway Truck Traffic and Pre-term and LBW Babies

<table>
<thead>
<tr>
<th>Number of freeway trucks passing within 750 feet of a home per day</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 13,290 trucks</td>
<td>(n=4,346; 26,606)</td>
</tr>
<tr>
<td>≥ 8,684 heavy-duty diesel vehicles</td>
<td>1.23 (1.06-1.43)</td>
</tr>
<tr>
<td></td>
<td>1.18 (1.02-1.37)</td>
</tr>
</tbody>
</table>

Model adjusted for all maternal risk factors as covariates, background air pollution concentrations and census block-group level socio-economic status
Distance Weighted Traffic Density and Preterm Birth in LA: 1994-1996
(Case N=17,706; Control N=26,005)

Recent Studies of Freeway Exposures and Mobile Source Effects: Central Nervous System
Kleinman et al., in preparation, 2004

Brain Inflammation Markers
Tissue from Mice Exposed 150m Downwind of a Heavily Trafficked Road

Significant Difference from Air-Exposed Control Values (* p < 0.05; ** p < 0.01)
Mechanistic Hypotheses as a Basis for Studying PM Toxicity and Health Effects

- PM contains pro-oxidative chemicals
- Organic chemicals and metals located on the PM matrix are responsible for toxicity
- PM generates reactive oxygen species $\rightarrow$ oxidative stress
- Oxidative stress $\rightarrow$ pro-inflammatory effects
- Inflammation $\rightarrow$ adjuvant effects in asthma, cardiovascular disease and other endpoints
- Susceptibility to oxidative stress-related health effects may be modulated by anti-oxidant defenses
Pathways of Oxidative Stress

High GSH/GSSG Ratio

Low GSH/GSSG Ratio

Level of oxidative stress

Cell response pathway: Normal
Anti-oxidant Defense
Inflammation
Toxicity

Dose

Xiao, et al.
Compounds Capable of Catalytic Redox Activity and Oxidative Stress Production

Metal ++ → Quinone → Electron → Metal ++ → Quinone → Oxygen → Metal ++ → Quinone → Superoxide → Superoxide → Superoxide → Superoxide → Hydrogen peroxide

Superoxide → Hydrogen peroxide +

Electron → Metal +++ → Quinone → Hydroxyl → Hydroxyl → Hydroxyl → Hydroxyl
Particle Size and Composition: Relation to Toxicity

Table 5
Contrasting features of coarse, fine, and ultrafine particles\(^a\)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Particle mode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coarse (PM(_{10}))</td>
</tr>
<tr>
<td>Size</td>
<td>2.5–10 (\mu)m</td>
</tr>
<tr>
<td>Organic carbon content</td>
<td>+</td>
</tr>
<tr>
<td>Elemental carbon content</td>
<td>+</td>
</tr>
<tr>
<td>Metals as % of total elements</td>
<td>+++</td>
</tr>
<tr>
<td>PAH content</td>
<td>+</td>
</tr>
<tr>
<td>Redox activity (DTT assay)</td>
<td>+</td>
</tr>
<tr>
<td>HO-1 induction</td>
<td>+</td>
</tr>
<tr>
<td>GSH depletion</td>
<td>+</td>
</tr>
<tr>
<td>Mitochondrial damage</td>
<td>None</td>
</tr>
</tbody>
</table>

\(^a\) [85].

Redox Activity of Ambient PM: Effect of Location and Size Fraction

Redox activity

![Bar chart showing redox activity in different locations and size fractions.]
Mitochondria: An Important Subcellular Target of PM and a Source of ROS Generation

Hypothesis:
Differential Cytotoxic Effects of Diesel Exhaust Particulate Fractions Are Caused by Selective Perturbation of Mitochondrial Functions

- Potential changes in the mitochondrial membrane
- Mitochondrial PTP opening
  - swelling
  - calcium retention capacity
  - oxygen uptake
Recent Findings from the PM Centers Augment the Literature that Associates PM and Reactive Oxygen Species/Oxidative Stress

**ROS activity in ambient PM samples:**
- Vary by location and time-of-year.
- Vary by size fraction: Smaller PM fractions (10-56 nm) had dramatically higher ROS concentrations. Venkatachari et al, Atm. Chem. 2004

**Biological markers of ROS production:**
- Increased oxidative stress markers and inflammatory effects in rat lung after exposure to concentrated ambient particles (CAPs). Rhoden et al, Tox Sci 2004
- Oxidative damage (TBARS) was correlated with the metal content of CAPs. Rhoden et al, Tox Sci 2004
- Increased ROS in heart and lung of rats with short term CAPs exposure. Gurgueira et al, 2002
Summary of PM Center Accomplishments

- **Atmospheric chemistry** has a significant effect on PM composition.

- A wider range of **target tissues and health endpoints are associated with PM exposure** than was known in 1997.

- Results from diverse types of studies has strengthened the evidence that **mobile sources are highly relevant** to the public health risks posed by ambient PM.

- **Improved mechanistic understanding** of PM toxicity has evolved:
  - Ultrafine particles
  - Mitochondrial uptake
  - Organic compounds and metals capable of catalytically generating oxidative stress has been shown.
Key Questions for Future Work

- **Which sources pose the greatest risks to public health?**
  → Need for studies of the relationships among specific sources, including mobile sources, atmospheric chemistry products, wood smoke, cooking and others, and toxicity-health effects

- **What are critical characteristics of PM in relation to toxicity?**
  → Further evaluation of size fractions needed; implications for PM regulation
  → Relationship between toxic mechanisms and specific toxic components

- **Which health effects are most sensitive to low levels of PM?**
  → More quantitative exposure-response data are needed
  → Role of susceptibility findings including gene-environment interactions in determining most sensitive endpoints