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

John R. Froines, Ph.D.

Southern California Particle Center and Supersite

EPA Particulate Matter Research Centers Program

Accomplishments Reviewed in this Presentation

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:

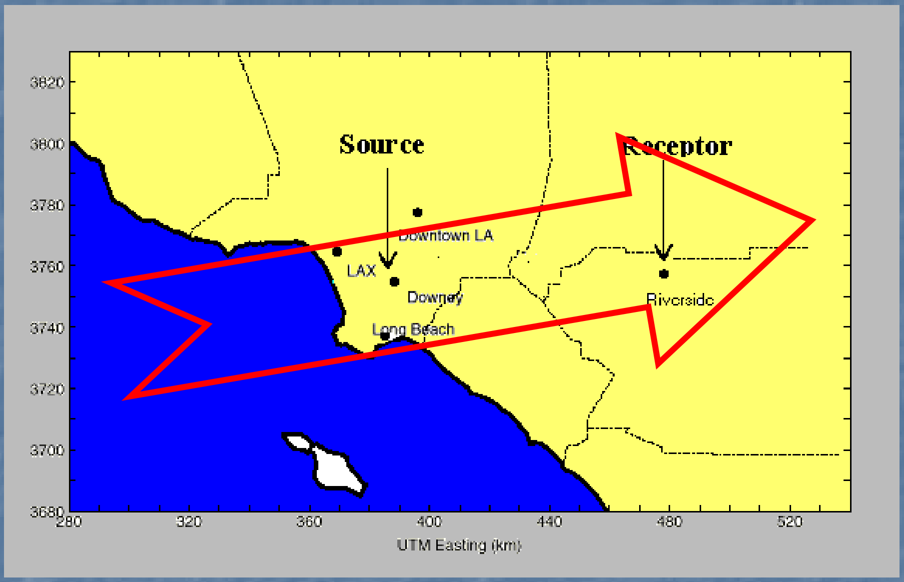
Zone of influence: adjacent to primary emissions sources

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

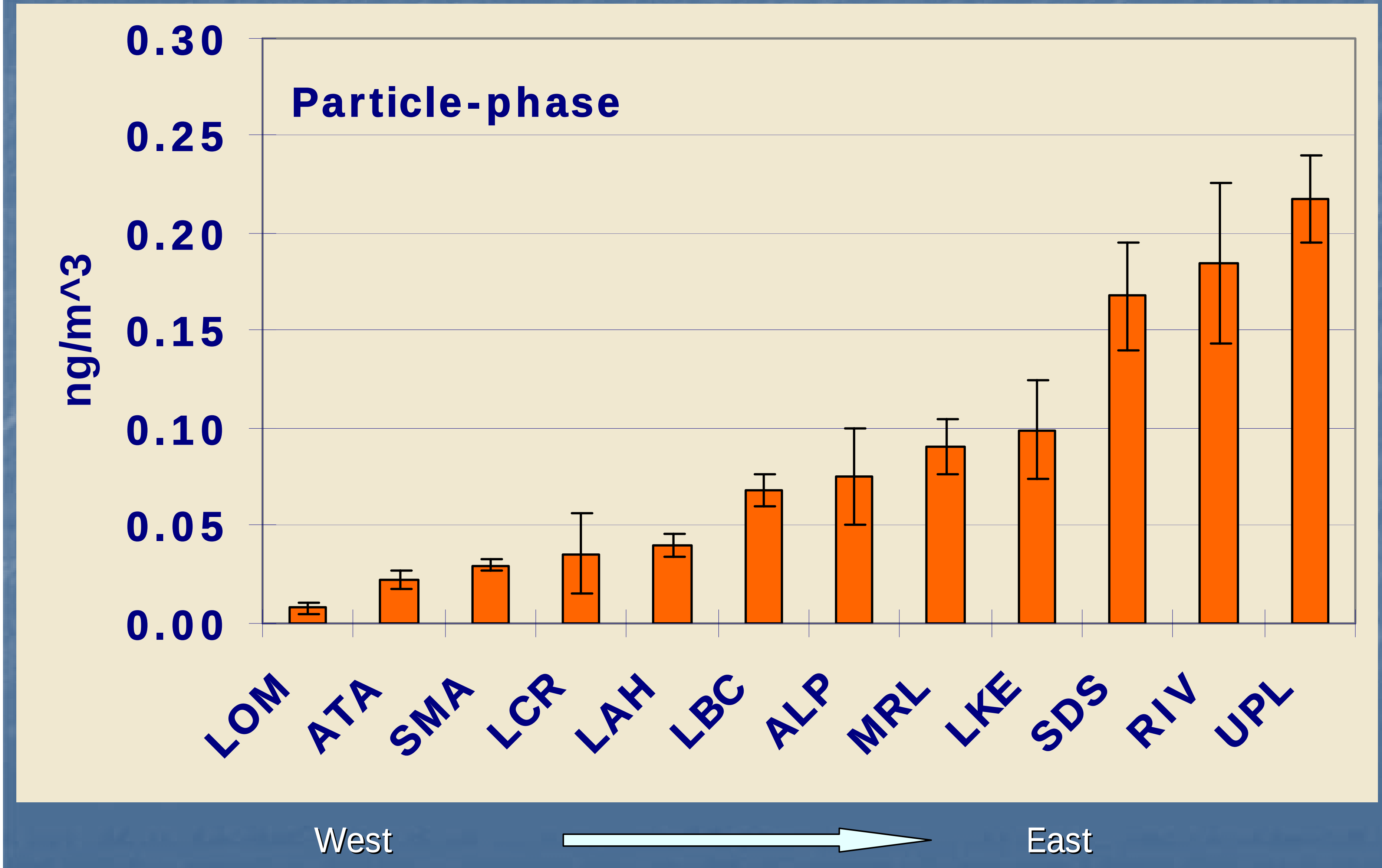
"Source" areas

→

Inland-Eastern Los Angeles Basin regions

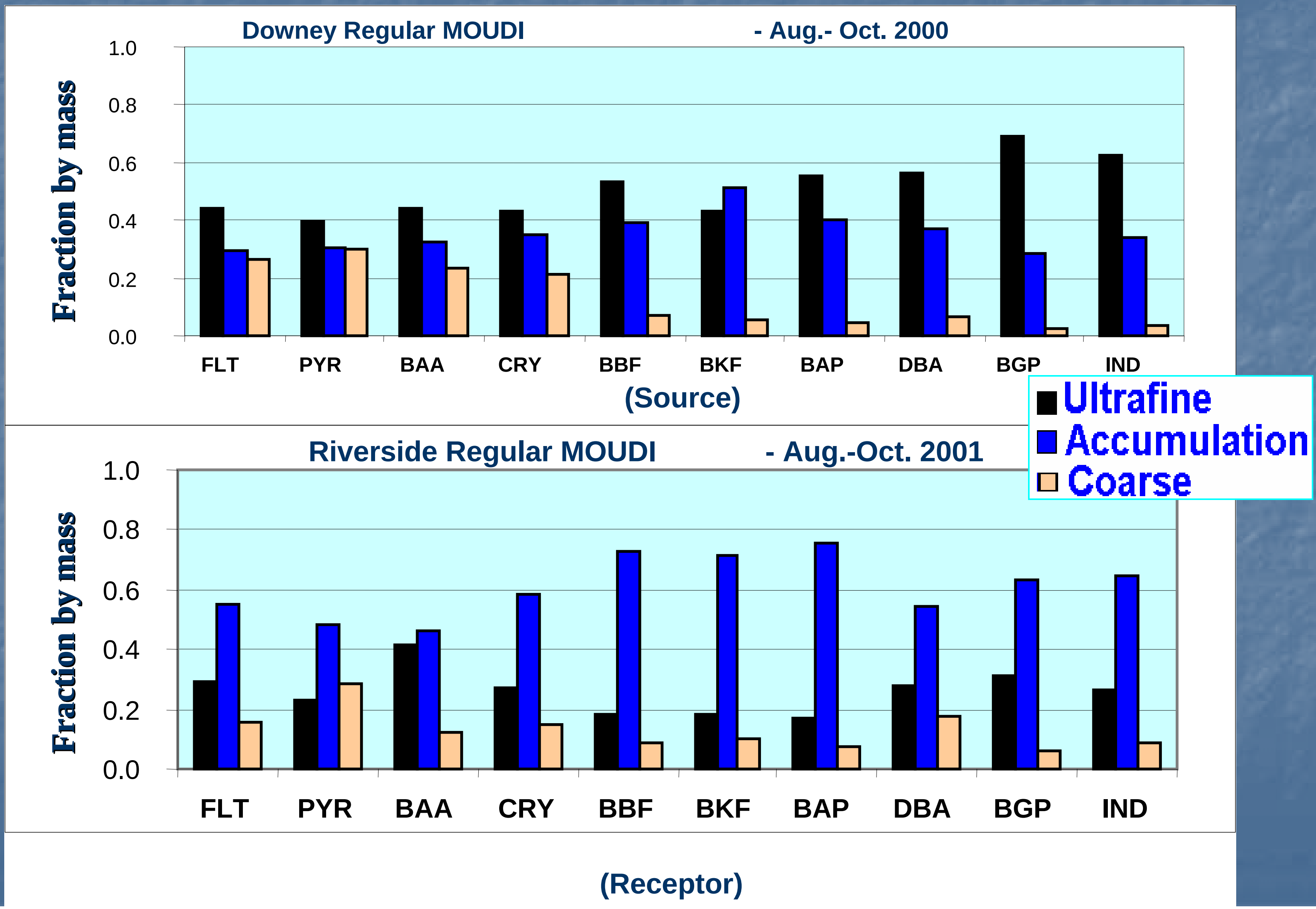
"Receptor" areas

Spatial Distribution of Particle Phase Phenanthroquinone in the LA Basin



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

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



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:

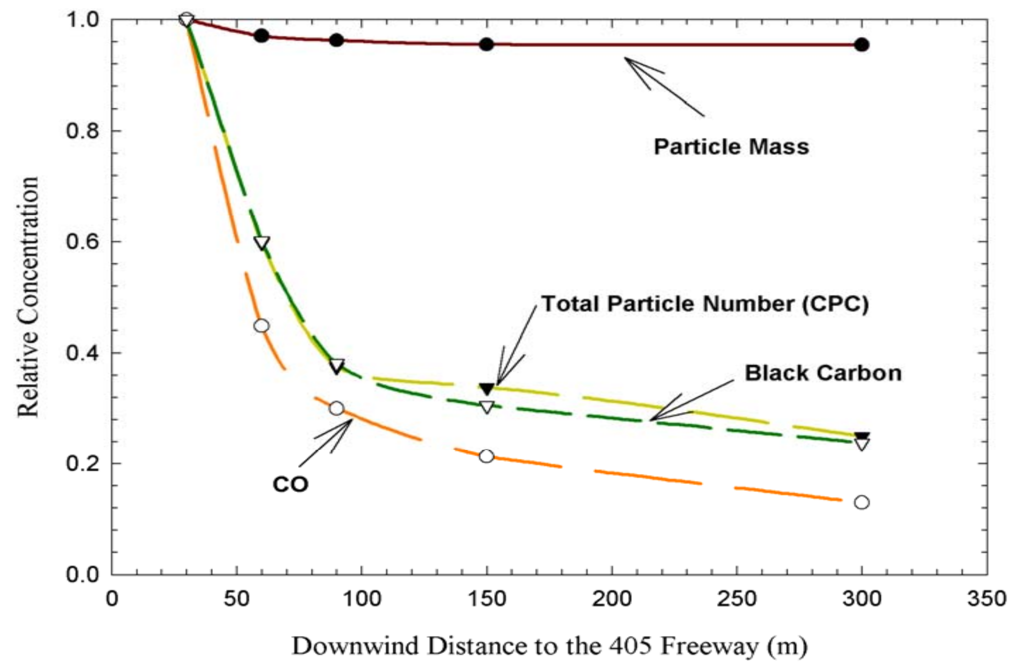
- Site to site?
- Over the course of the day? Seasons?
- Between size fractions?

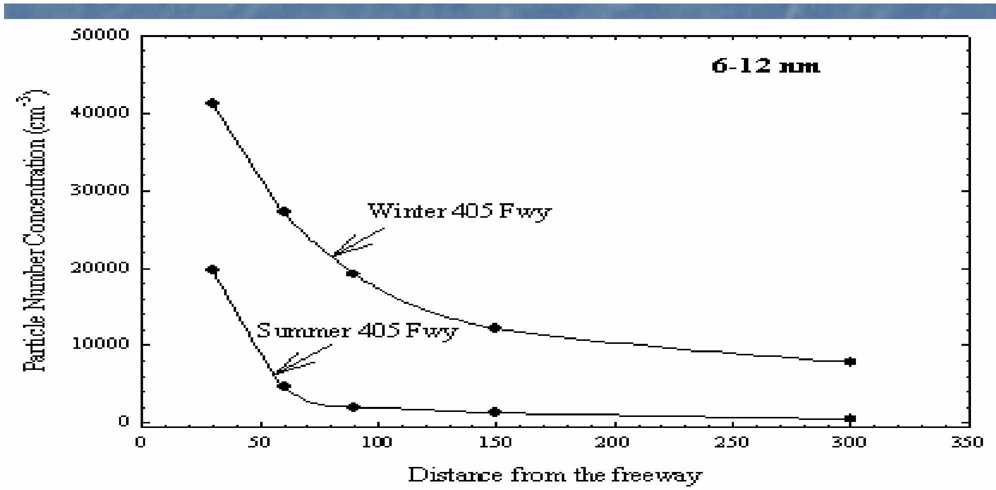
Approach: Evaluate concentrations/size distribution of individual organic compounds to trace primary and secondary sources of PM:

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

Fine, P.M., Chakrabarti, B, Krudysz M., Schauer J.J. and Sioutas*, C. *Environmental Science and Technology*, 2004.

Mobile Source Studies





(a)

Figure 4. 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.

- 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.

- **Zhu, Y., Hinds, W.C., Kim, S., Shen, S. and Sioutas*, C. "*Aerosol Science and Technology,* 38, 5-13, 2004.**

- Highway study found "Most of the particles consisted of volatile material."

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

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

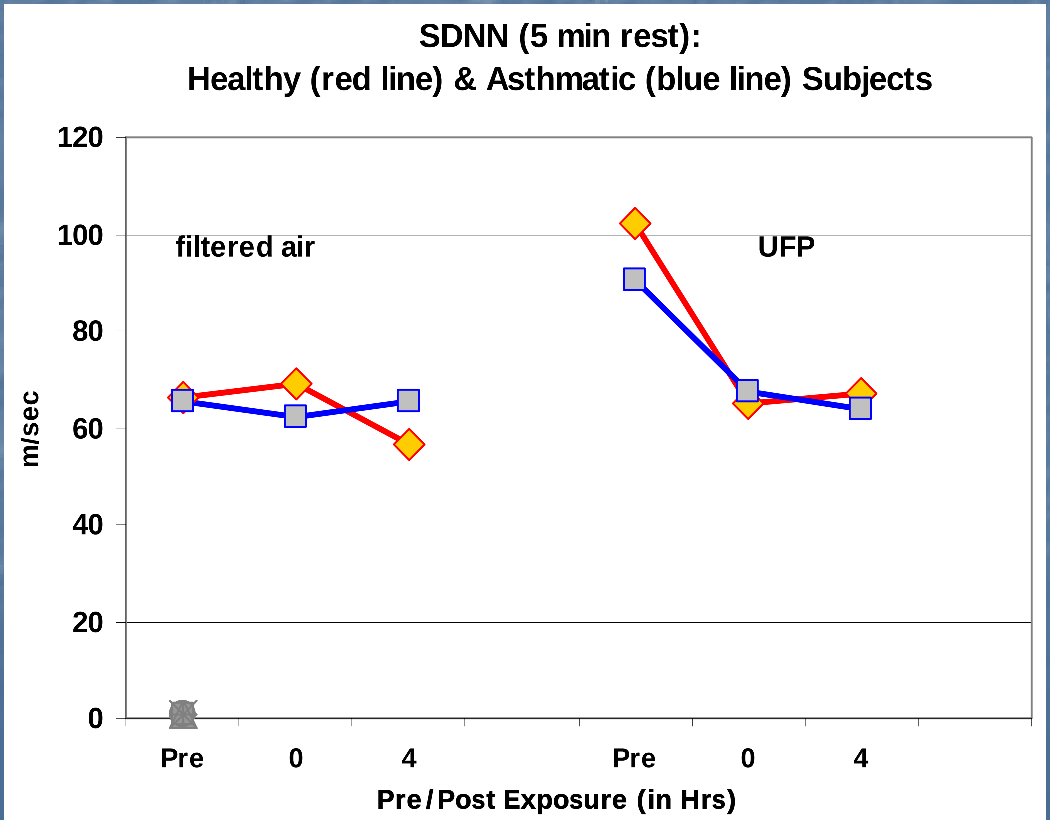
Recent Studies of Freeway Exposures and Mobile Source Effects:

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.



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 sensitized 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

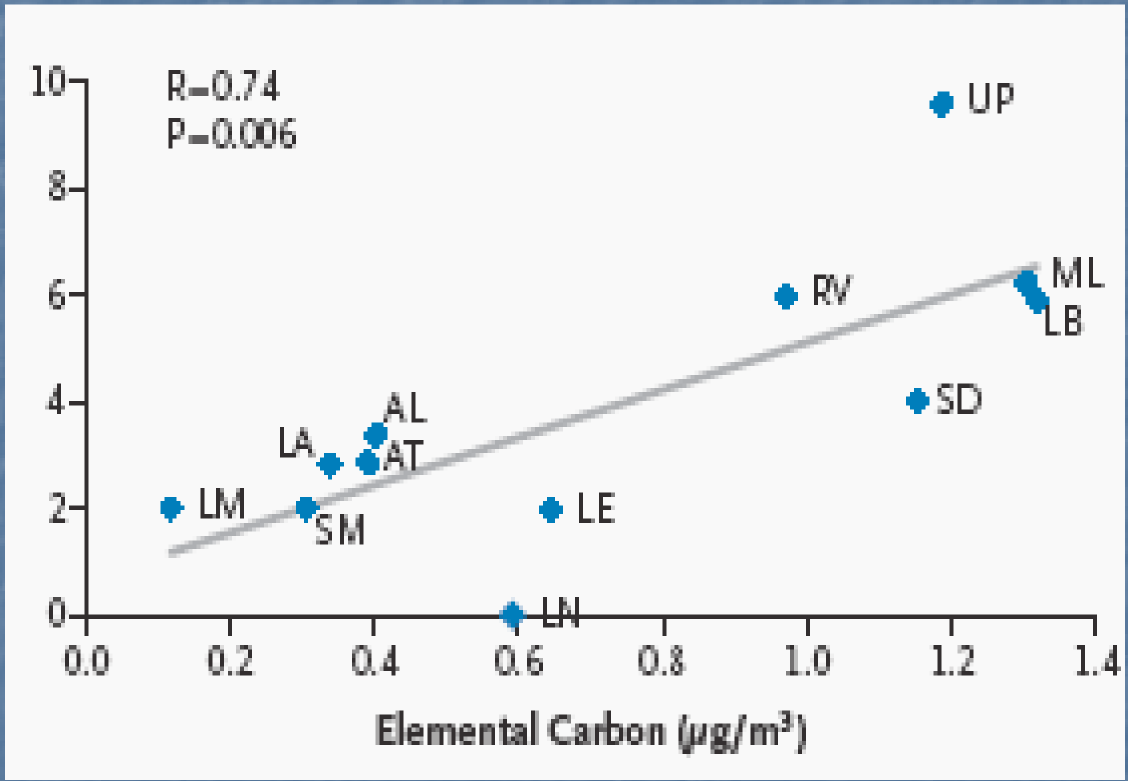
Distance to the Nearest Freeway (Kilometers)	All Subjects		
	Total	Asthma	
	N	(%)	OR[a]
>0.5	104	(13.5)	2.00
0.5 – 1.0	169	(18.9)	2.92
1.0 – 1.5	146	(16.4)	2.33
1.5 – 2.0	102	(10.8)	1.48
2.0 - 3.0	138	(15.9)	2.38
3.0 – 7.0	210	(7.6)	1.00
Trend test[b]			p=0.01

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

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

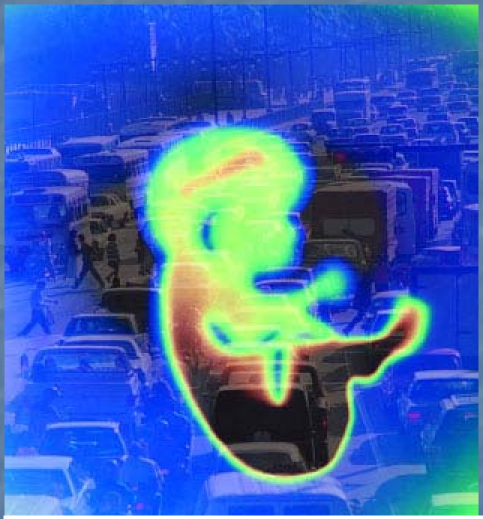
Proportion of 18-year olds with FEV1 below 80% of the predicted value



Gauderman, et al. 2004 New England Journal of Medicine

Recent Studies of Freeway Exposures and Mobile Source Effects:

Residential Proximity to Freeway Truck Traffic and Pre-term and LBW Babies



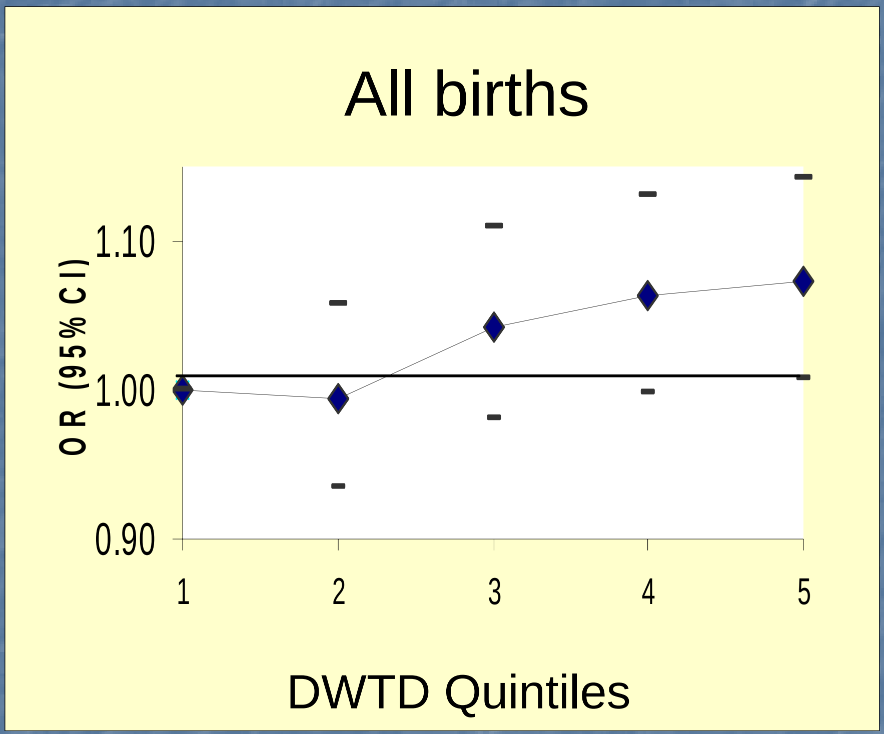
Infants born between 1997-2000 in Los Angeles County

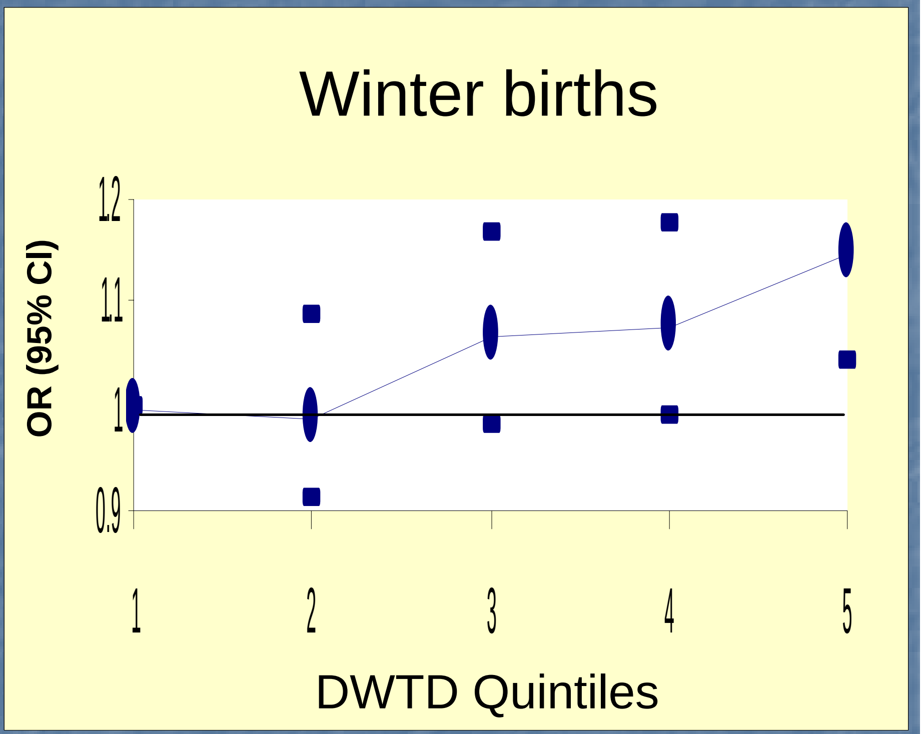
Number of freeway trucks passing within 750 feet of a home per day	Odds Ratio (95% CI)
	(n=4,346; 26,606)
≥ 13,290 trucks	1.23 (1.06-1.43)
≥ 8,684 heavy-duty diesel vehicles	1.18 (1.02-1.37)

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)

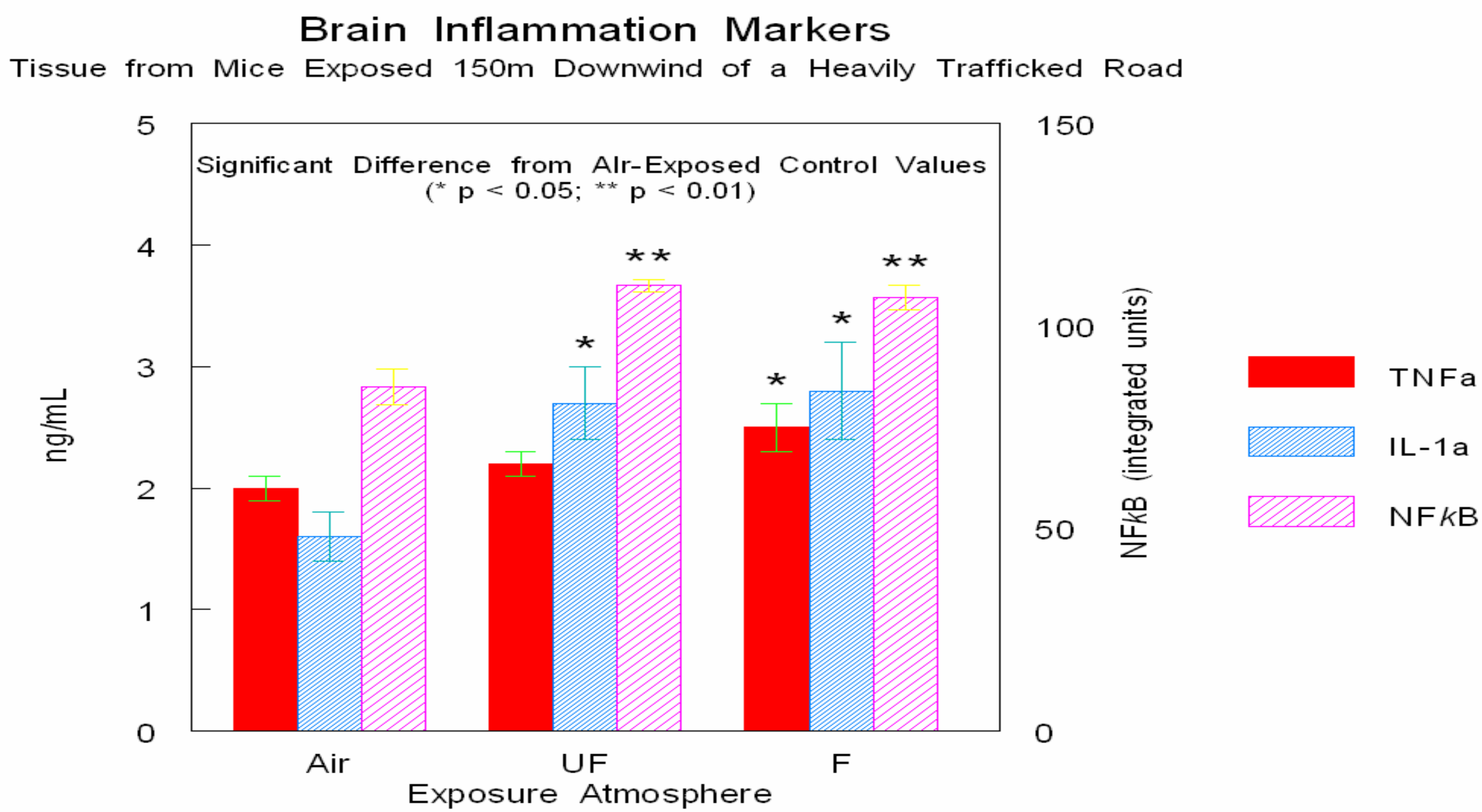




Wilhelm M, Ritz B. Residential Proximity to Traffic and Adverse Birth Outcomes in Los Angeles County, California, 1994-1996. Environ Health Perspect 2003 Feb;111(2):207-16.

Recent Studies of Freeway Exposures and Mobile Source Effects: **Central Nervous System**

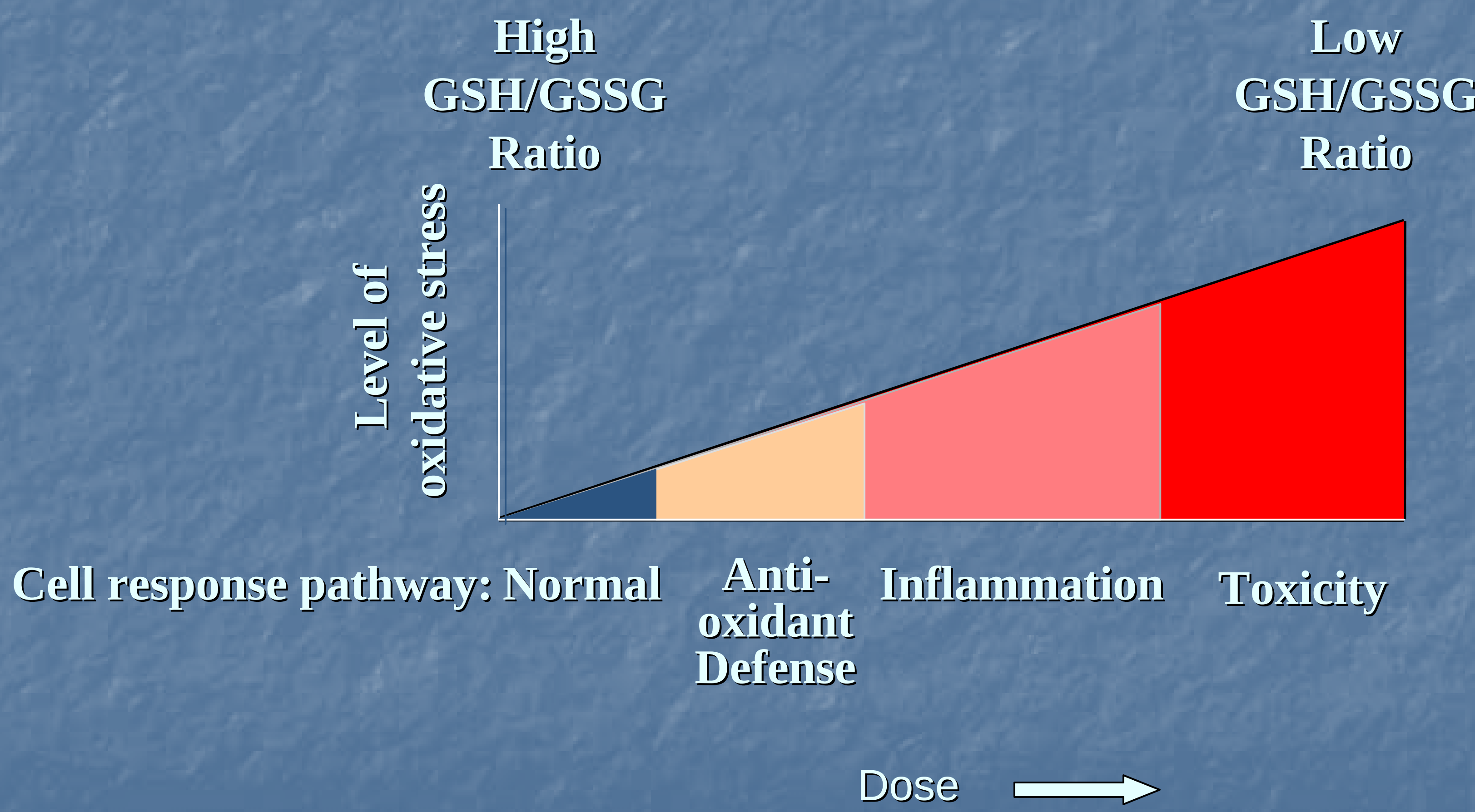
Kleinman et al., in preparation, 2004



Mechanistic Hypotheses as a Basis for Studying PM Toxicity and Health Effects

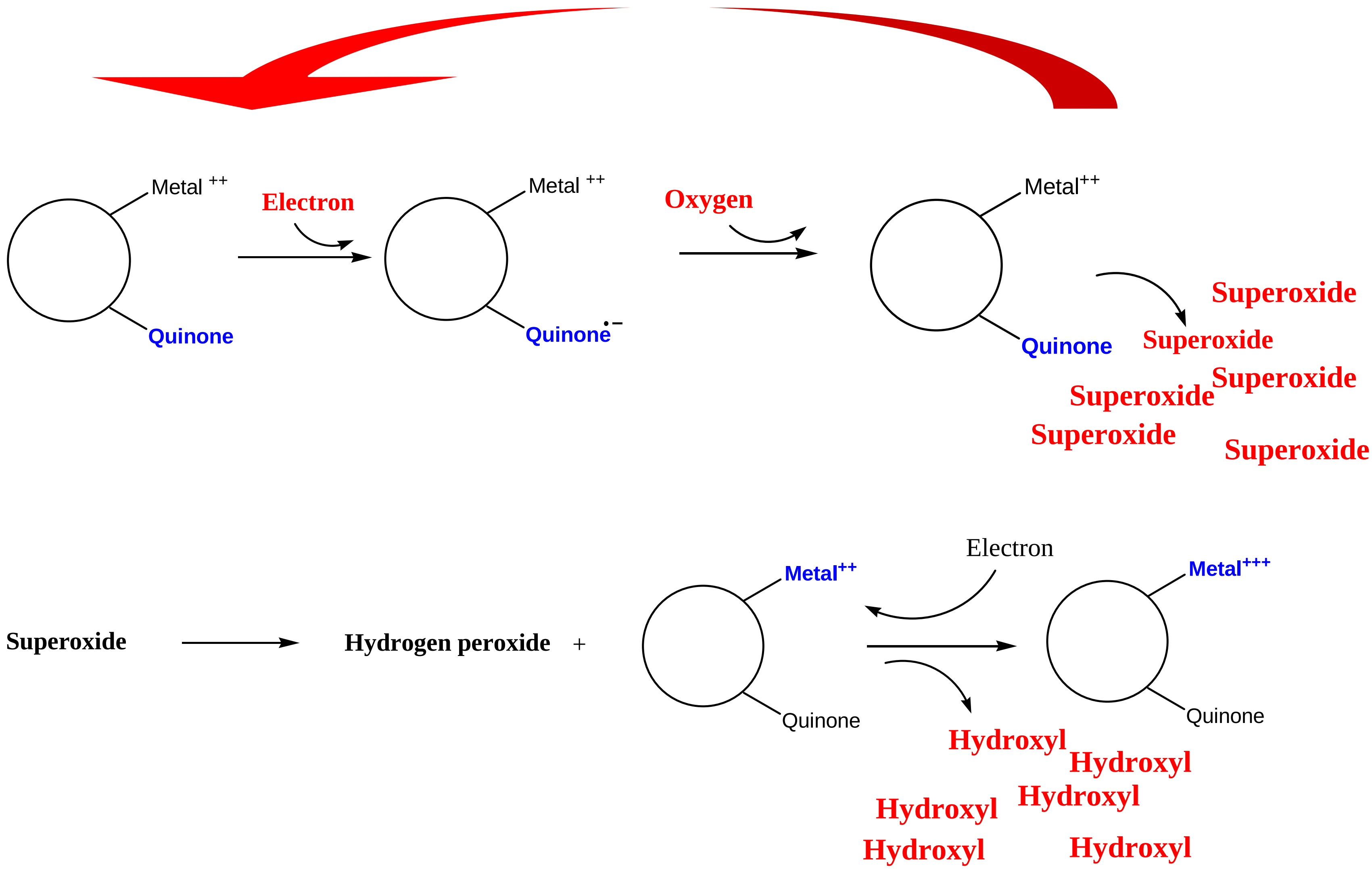
- PM contains pro-oxidative chemicals
- Organic chemicals and metals located on the PM matrix are responsible for toxicity
- PM generates reactive oxygen species → oxidative stress
- Oxidative stress → pro-inflammatory effects
- Inflammation → adjuvant effects in asthma, cardiovascular disease and other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

Pathways of Oxidative Stress



Xiao, et al.

Compounds Capable of Catalytic Redox Activity and Oxidative Stress Production



Particle Size and Composition: Relation to Toxicity

Table 5
Contrasting features of coarse, fine, and ultrafine particles[a]

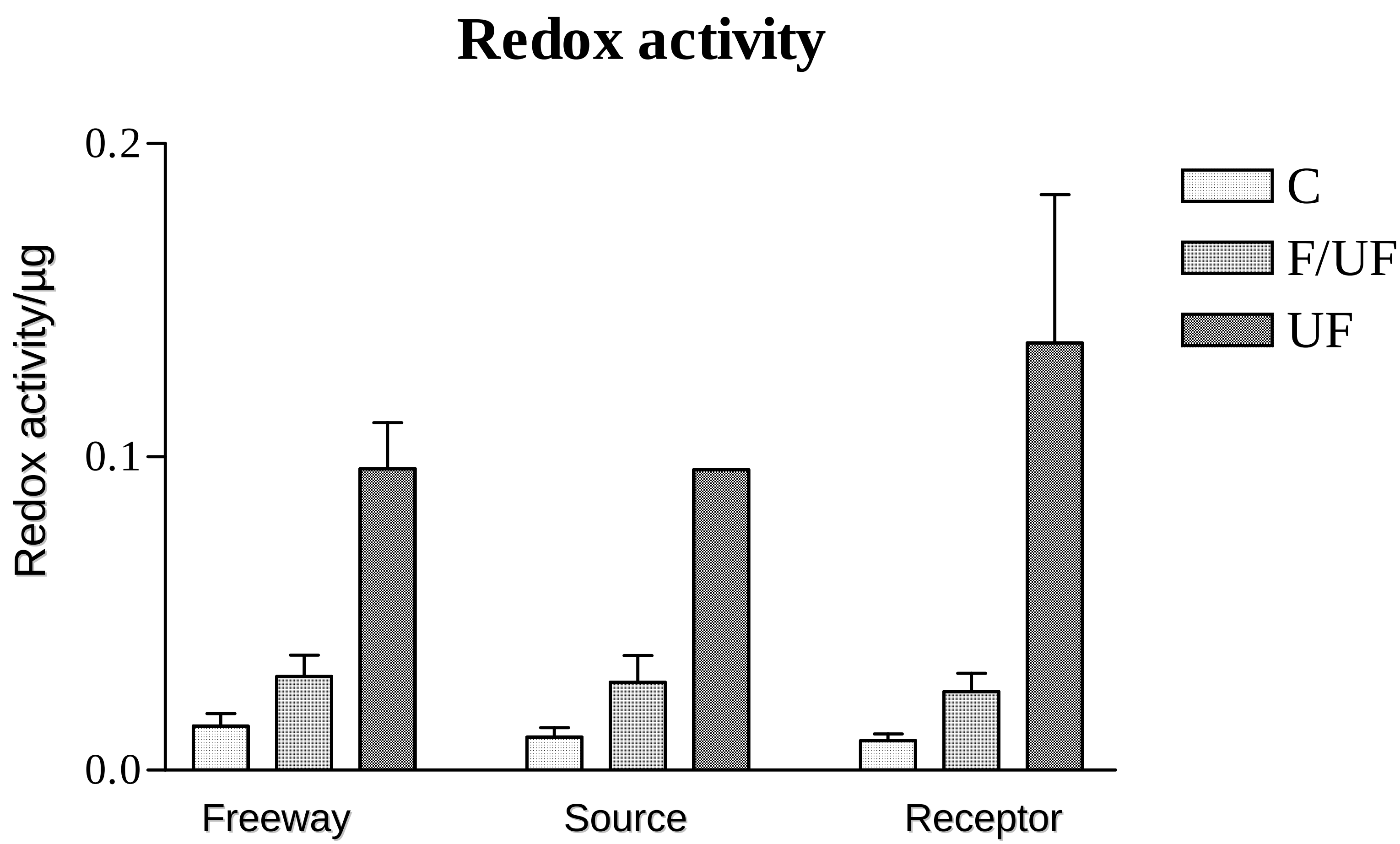
Parameters	Particle mode		
	Coarse (PM_{10})	Fine ($PM_{2.5}$)	Ultrafine
Size	2.5–10 μm	2.5–0.15 μm	<0.15 μm
Organic carbon content	+	++	+++
Elemental carbon content	+	++	+++
Metals as % of total elements	+++	++	+
PAH content	+	+	+++
Redox activity (DTT assay)	+	++	+++
HO-1 induction	+	++	+++
GSH depletion	+	+++	+++
Mitochondrial damage	None	Some	Extensive

[a] [85].

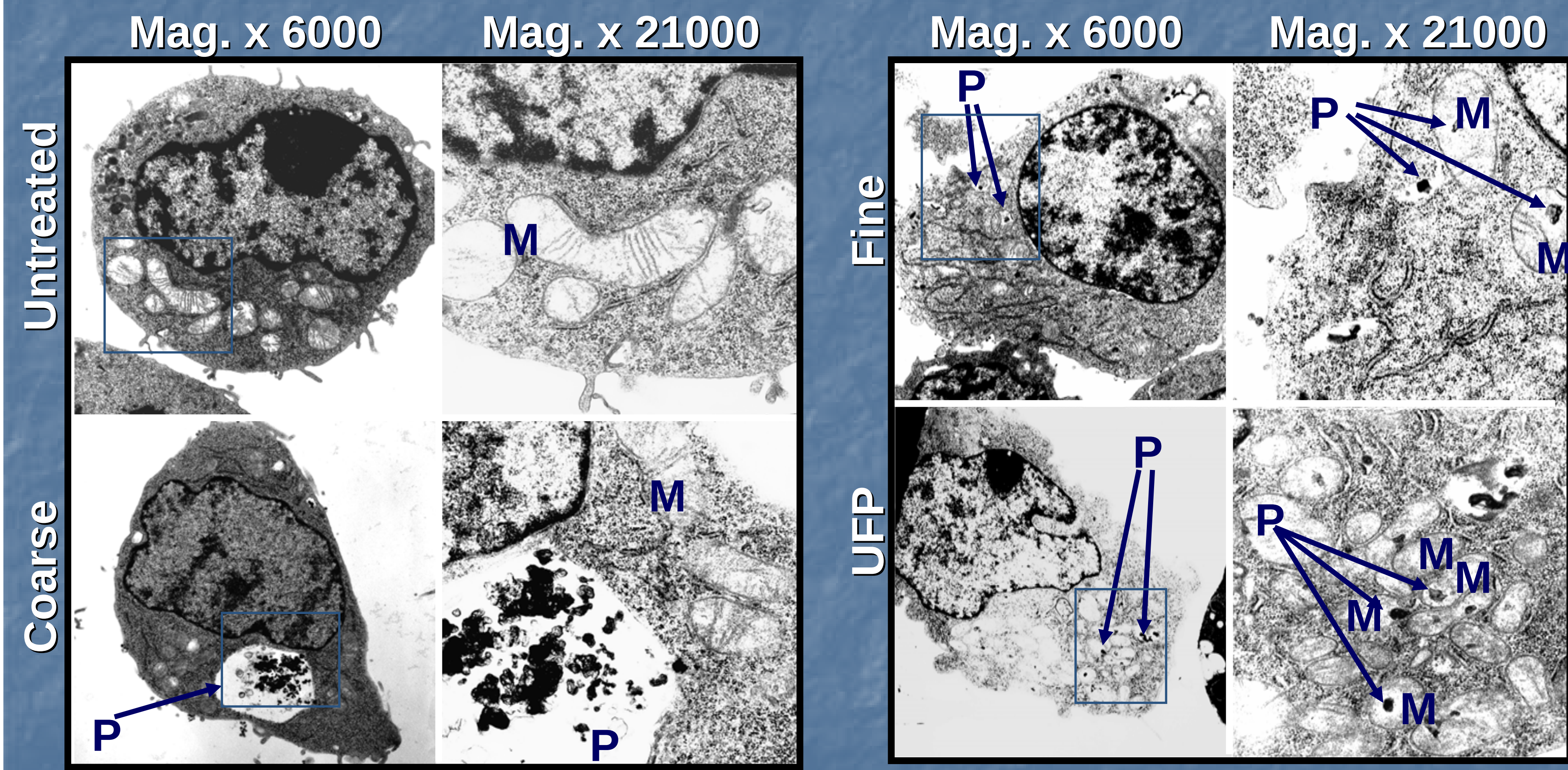
(sampled at source site)

From: Li, N., Hao, M., Phalen, R., Hinds, W., Nel, A. (2003). "Particulate air pollutants and asthma: A paradigm for the role of oxidative stress in PM-induced adverse health effects." Clinical Immunology 109: 250-265.

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



Mitochondria: An Important Subcellular Target of PM and a Source of ROS Generation



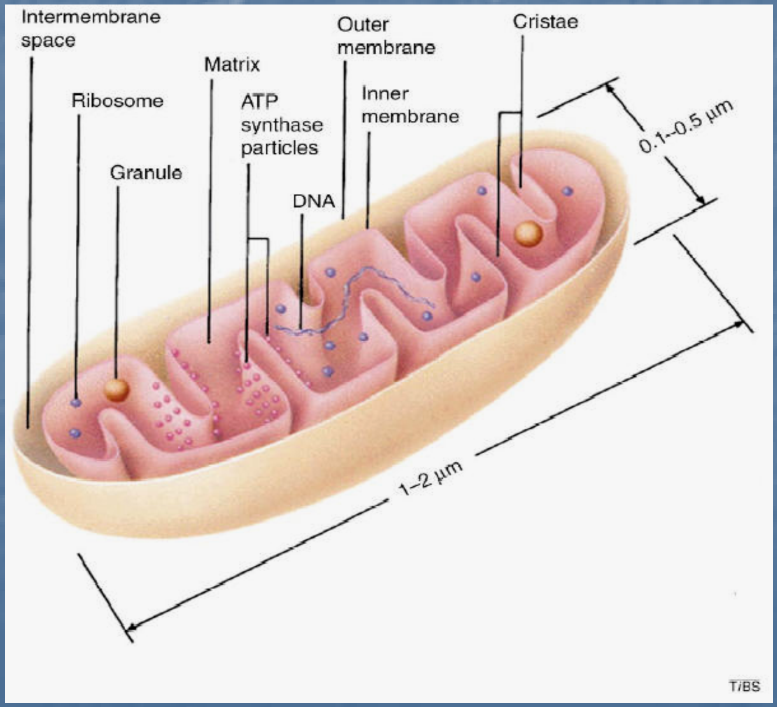
RAW 264.7

Li, N., Sioutas S, Cho A, Schmitz D, Misra C, Sempf J, Wang M, Oberly T, Froines J, Nel A (2003). "Ultrafine Particulate Pollutants Induce Oxidative Stress and Mitochondrial Damage." Environmental Health Perspectives 111(4): 455-460.

Hypothesis:

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

DEP, ultrafine PM fractions → Mitochondrial functional assays → Cell death



- 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
  - Mitchondrial 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