



Determining Which PM_{2.5} Species are Harmful: Can Differences in Study Methodologies Explain Differential Findings?

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Principles for Determining Which $PM_{2.5}$ Species Cause Health Effects

■ Problem:

- Why do some studies say that pollutant A is harmful, but pollutant B is not, while other studies say the opposite, for same or similar health endpoint (e.g., cardiovascular mortality)?

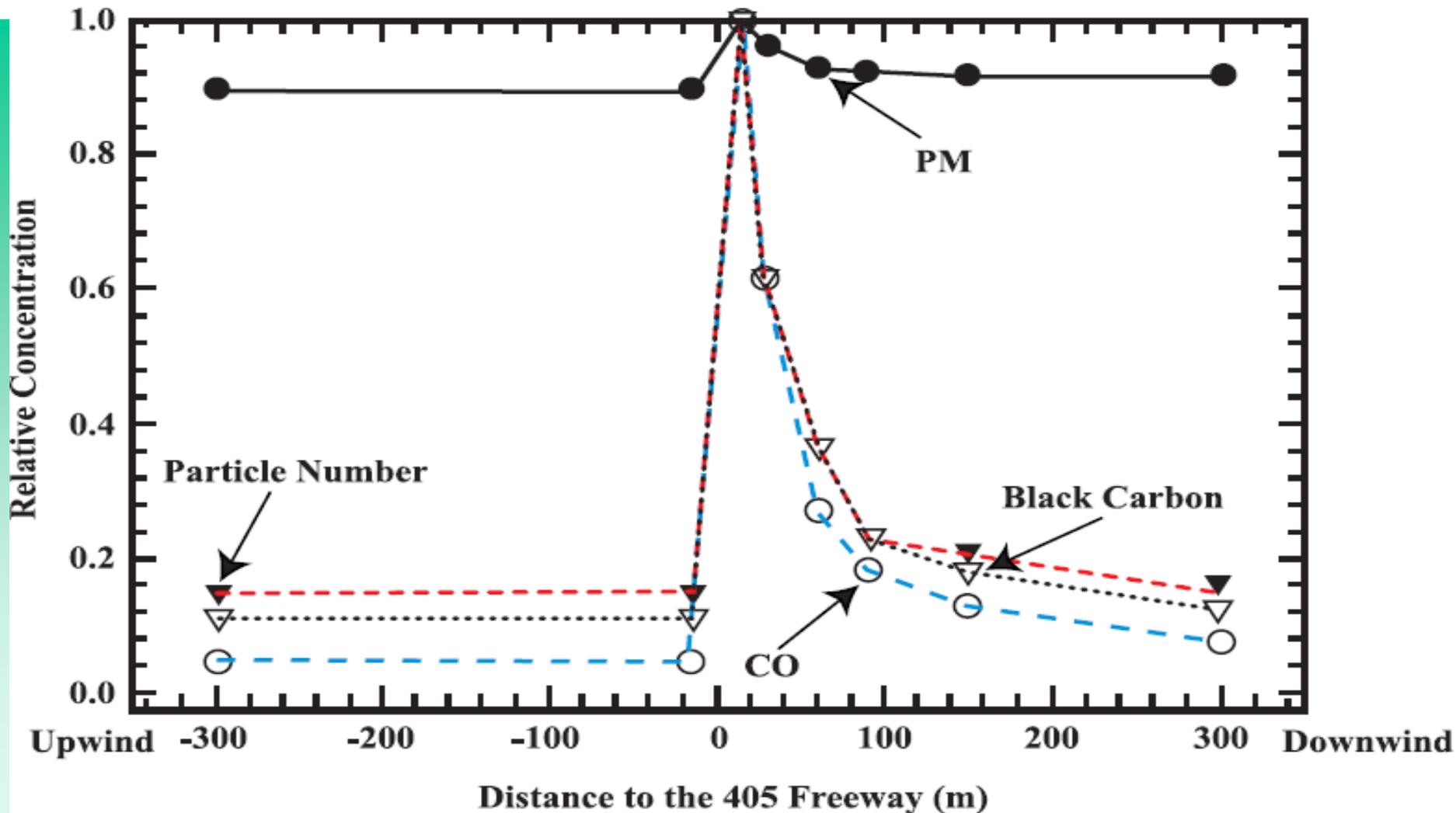
■ Over last 9 years, I've developed (and published) some ideas I'd like to share, to understand why these results can occur



Principles for Determining Which PM_{2.5} Species Cause Health Effects

- 1. Compare *many* PM_{2.5} species against same health endpoints in same studies
 - **Can't find associations for pollutant not included in model;**
 - **Association for a measured emission may exist only in absence of other emissions from model**
- 2. Epidemiology studies require accurate subject exposure information
 - **Effects of locally variable emissions understated, perhaps transferred, with poor exposure (e.g., black carbon!)**

How Variable is Black Carbon?





Principles for Determining Which $PM_{2.5}$ Species Cause Health Effects

- 3. Recognize and deal with fact that some $PM_{2.5}$ species are emitted from many sources
- Thus associations with one $PM_{2.5}$ species may reflect harm from one or more co-pollutants, often unmeasured



Principles for Determining Which $PM_{2.5}$ Species Cause Health Effects

- 4. Use information from several disciplines, combine toxicology (finding biological mechanisms for $PM_{2.5}$ species) and epidemiology with good subject exposure in comprehensive examination of effects of a particular $PM_{2.5}$ species (won't cover today unless there's a relevant question)



1. Compare many PM_{2.5} species against same health endpoints in same study

- Early studies (e.g., 6 Cities, ACS) included sulfate but no metals, no carbon species or elements among monitored PM_{2.5} species
 - Associations with sulfate
- New studies include 7 to 20 PM_{2.5} species, including metals, elements, and carbon species
 - Almost always find associations with black or elemental carbon (BC/EC), V, Ni, traffic density, vehicular emissions, but fewer associations with other PM_{2.5} species
- And yet...studies do not have good exposure info



Examples of findings of new studies (multi-county studies)

<i>Multi-County Studies</i>	<i>Geographic Area</i>	<i>Health Effect Studied</i>	<i>PM_{2.5} Species, Other Pollution Variables</i>
1. Peng et al., 2009	119 counties	Daily emergency CV, respiratory hospital admissions	7 largest PM _{2.5} components (sulfate, nitrate, silicon, BC, organic carbon, sodium and ammonium ions) <i>Associations with BC (CV), OC (respiratory)</i>
2. Bell et al., 2009	106 counties	Same day CV, respiratory hospital admissions	20 PM _{2.5} components (7 in Peng et al. (2009), plus 13 elements, mostly metals, incl. V and Ni) <i>BC, V, Ni associations</i>
3. Lipfert et al., 2009	206 rural and urban counties	Prospective cohort study, survival since enrollment	Twelve HAPs (incl. Ni but not V), sulfate, NO _x , BC, traffic density (surrogate for traffic emissions) <i>Associations with traffic density, benzene, formaldehyde, diesel particulate, NO_x, BC, Ni</i>
4. Lipfert et al., 2006	206 rural and urban counties	Prospective cohort study, survival since enrollment	15 elements (mostly metals, incl. V and Ni), BC, OC, nitrate, sulfate, PM _{2.5} , traffic density (surrogate for traffic emissions) <i>Associations with traffic density, BC, NO₃, V, Ni – traffic density most robust in multi-pollutant models</i>



Atlanta area studies

- Sulfate mainly from several nearby coal plants
 - **No steel mills, coke ovens, residual oil**
- Found three studies with six or more PM_{2.5} species
- Findings: mostly same as new multi-county studies, e.g., CVD associations with carbonaceous BC, OC



Atlanta Area studies (cont.)

<i>Atlanta Area Studies</i>		<i>Health Effect Studied</i>	<i>PM_{2.5} Species, Other Pollution Variables</i>
1. Metzger et al., 2004	31 hospitals in Atlanta area	Daily emergency department CV admissions	PM ₁₀ , PM _{2.5} , 10 to 100 nanometer particle count, water soluble metals, sulfate, acidity, OC, BC Associations with BC, OC
2. Tolbert et al., 2007	41 hospitals in Atlanta area	Daily emergency department CV, respiratory admissions	PM _{2.5} , sulfate, OC, BC, total carbon, water soluble metals (1998-2004 period of study) Associations with BC, OC, total carbon (CV admissions); no PM species associations (RD admissions)
3. Sarnat et al., 2008	27 hospitals in Atlanta area	Daily emergency department CV, respiratory admissions	EC, OC, Se, nitrate, sulfate, K and Zn Associations with BC, OC, K, Zn (CV admissions); sulfate (RD admissions)



How interpret these new studies with multiple PM_{2.5} species?

■ No firm conclusions

- Need to confirm using studies with better exposure to locally variable emissions (BC) to understand how associations for several PM_{2.5} species might change
- If hospital admissions or deaths associated with BC go up, they have to go down for other PM_{2.5} species
- Need toxicology for toxicity, biological mechanisms of different air parcels, PM_{2.5} species (much action)

■ Yet conclusions move in new direction

- Consistent associations now are with BC, Ni, traffic variables, fewer with other PM_{2.5} species – *if and only if* many “suspect” PM_{2.5} species are included



2. Epidemiology studies require accurate subject exposure information

- Principle in epidemiology literature:
 - With inaccurate exposure for spatially variable emission, pollutant association will be understated, may be transferred to pollutant with less exposure error
- Can we illustrate *understatement* and *transference* by comparing studies with good exposure to locally variable emission (BC) vs. those without?



Studies of Heart Rate Variability (HRV) Changes

- Illustrate with HRV changes
- Variability in heart rate is normal
- HRV *reduction* appears to be caused by oxidative stress in heart
 - Thus is a marker for oxidative stress
 - Also may predict MI (heart attack) for those with CVD
- So changes in HRV are important....



Studies of Heart Rate Variability (HRV) Changes

- Most epidemiological studies use readings from a central monitor as a proxy for what people are actually exposed to
- BC can vary from about 0.1 to 1.0 $\mu\text{g}/\text{m}^3$ across a city, but central monitor reading will imply that everyone exposed to one concentration
- Thus for emissions with large local variability – such as BC/EC – exposures and thus health effects will likely be underestimated



Importance of Accurate Exposure Information

- What happens with good vs. poor exposure info?
 - Suh and Zanobetti (2010), “Exposure Error Masks the Relationship Between Traffic-Related Air Pollution and Heart Rate Variability”
- Using central monitor data, *no* statistical associations between five measures of HRV and four different pollutants, including BC
- Using personal monitors, *statistically significant associations between BC and all five measures of HRV, risk estimates increase by between 3 and 45 times, but no associations with other PM_{2.5} species, including sulfate and PM_{2.5}*



Studies of Heart Rate Variability (HRV) Changes

- When subject exposure to black carbon (BC) is accurate, monotonic decrease in HRV measures with increasing BC exposure (2 examples)
 - [St. Louis bus study](#): monitor followed subjects (Adar, 2007); HRV falls with increasing BC, and falls the most with the highest BC exposure
 - Similar results in [Boston study](#): monitor next to same road as residences ([Schwartz et al., 2005](#)), ensuring good BC exposure measurements
 - In both studies, almost every BC association is statistically significant



St. Louis Bus Study (Adar et al., 2007) – HRV reduction related to increased BC

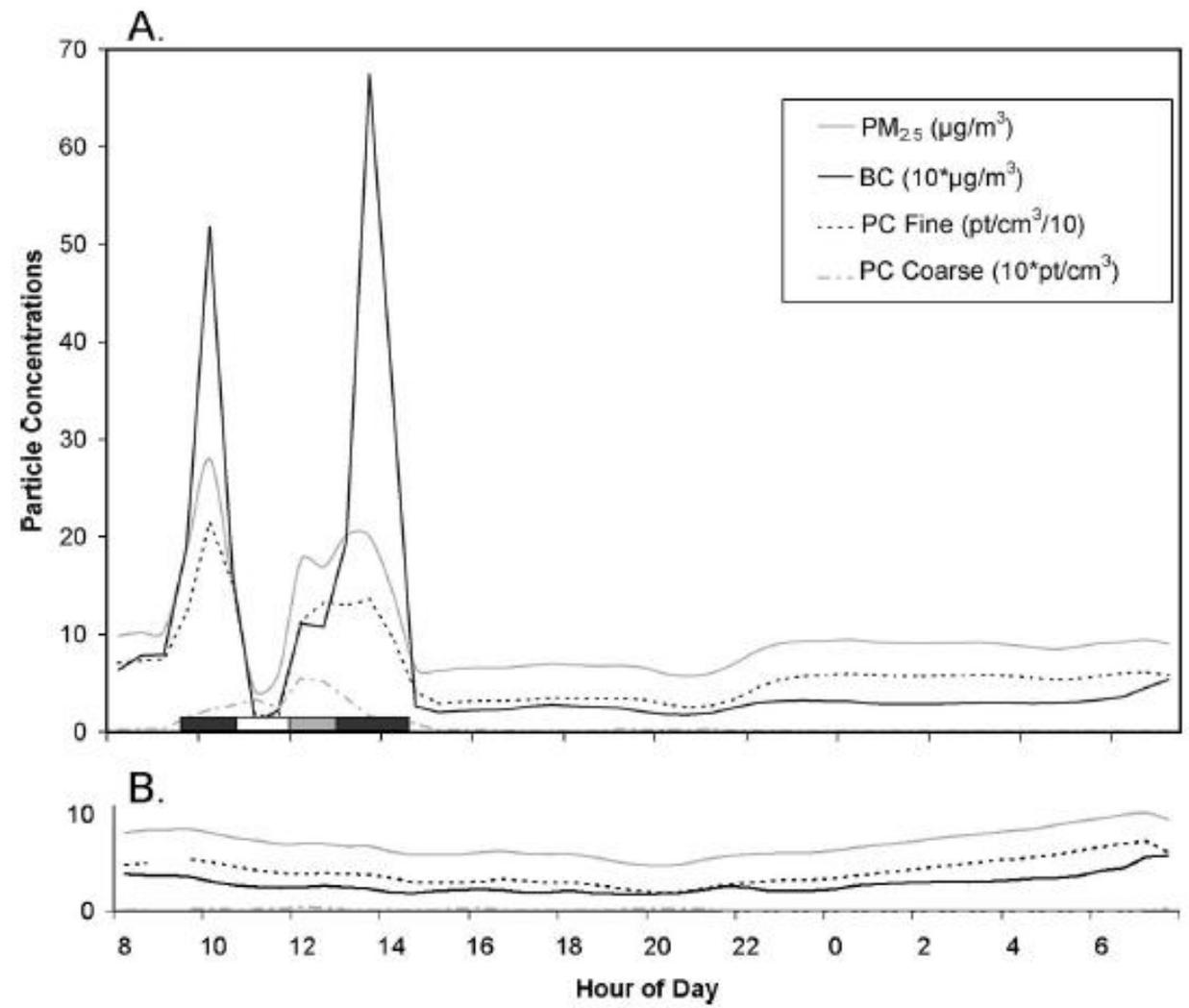


FIGURE 1. Particulate concentrations during (A) a sample trip day and (B) the previous nontrip day. Dark boxes at bottom of graph A represent any time periods during which the one-hour bus trips occurred. Lunch was demarcated using a light shaded box, whereas the activity (an Omni movie) was highlighted with the clear box.

St. Louis Bus Study – Relationship Between BC and reduced HRV

	Black Carbon			
	Effect Estimate	<i>P</i> Value of Interaction	% Change Per IQR (95% Confidence Interval)	
SDNN				
Bus	-0.0052	-0.02	-4.6 (-6.1 to -3.0)	
Nonbus	-0.00093	0.003	-0.1 (-0.3 to 0.1)	
RMSSD				
Bus	-0.005	-0.01	-2.6 (-4.2 to -0.9)	
Nonbus	-0.0013	-0.01	0.64	-0.3 (-0.5 to -0.1)
pNN50 + 1				
Bus	-0.0066	-0.008	-2.0 (-4.5 to 0.5)	
Nonbus	-0.0015	-0.02	0.34	-0.5 (-0.8 to -0.1)
LF				
Bus	-0.0073	-0.02	-6.0 (-9.3 to -2.5)	
Nonbus	0.0011	-0.006	0.028	-0.2 (-0.7 to 0.3)
HF				
Bus	-0.011	-0.02	-5.8 (-9.1 to -2.3)	
Nonbus	-0.0013	-0.03	0.50	-0.9 (-1.4 to -0.4)

Monotonic decrease in HRV with increase in BC (Schwartz et al., 2005)

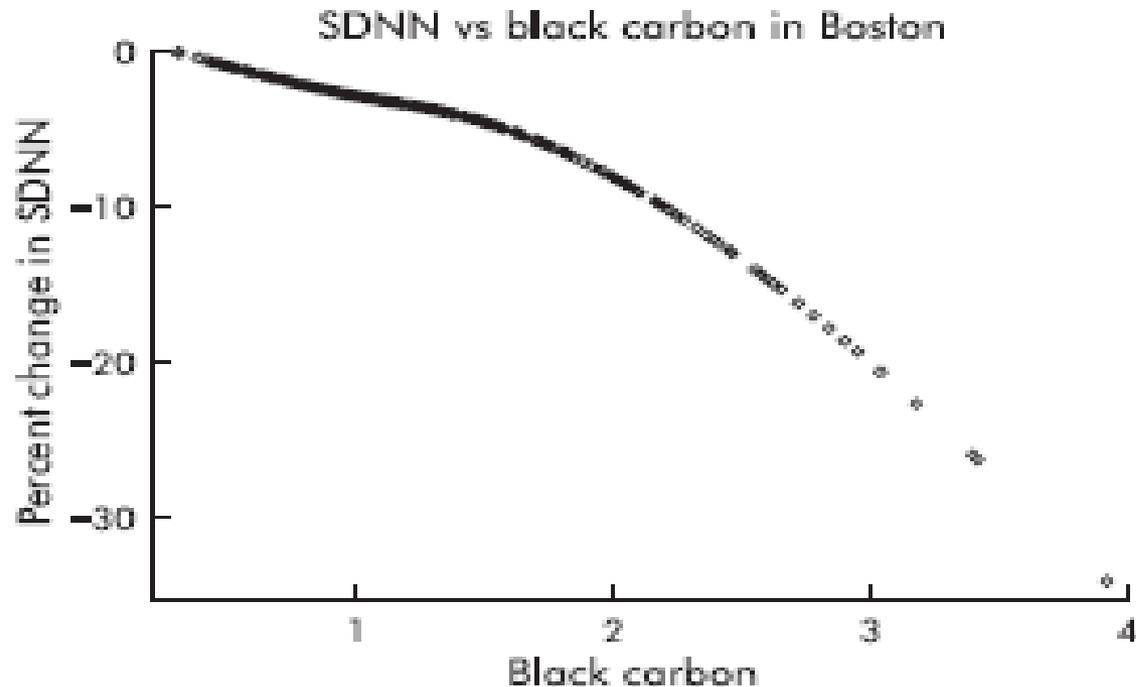


Figure 2 Smoothed plot of the percentage deviation from predicted SDNN (based on the model with all other covariates) versus black carbon concentrations in Boston. The association is nearly linear, despite being fit with about 3 degrees of freedom.



With poor exposure, BC associations weaken

- In contrast, when BC exposure is not well characterized (one central monitor reading for people across a metro area), then associations with BC are few or non-existent
 - Few: Wheeler (2006), Park (2005)
 - Non-existent: Luttman-Gibson (2006)



Transference?

- When BC or urban exposure is well characterized, BC or urban emissions are associated with HRV changes, but regional emissions containing sulfate and/or secondary organic aerosol are not associated
 - Schwartz, 2005;
 - Creason, 2001;
 - Ebel, 2005)
- Illustrations (next slide) from Schwartz (2005)
[Creason (2001) similar findings]

No HRV associations with regional $PM_{2.5}$ with accurate BC exposure

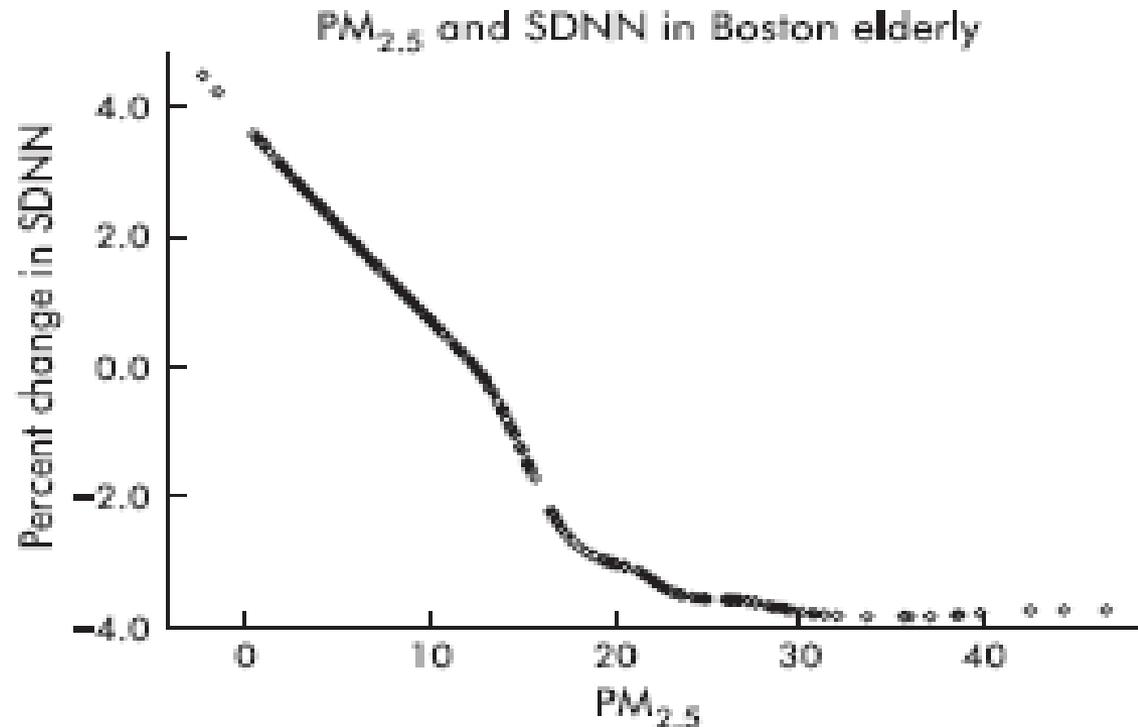


Figure 3 Smoothed plot of the percentage deviation from predicted SDNN (based on the model with all other covariates) versus $PM_{2.5}$ concentrations in Boston. The association flattens out at high concentrations where the correlation between $PM_{2.5}$ and black carbon disappears.

No HRV associations with regional PM_{2.5} with accurate BC exposure, but limited PM_{2.5} associations due to BC

Table 3 Percentage change in heart rate variability associated with an interquartile range increase in particle exposure

Variable	SDNN (ms)	r-MSSD (ms)	PNN ₅₀ (%)	LFHFR
BC*	-4.6 (-2.0 to -7.2)	-6.1 (0 to -11.9)	-9.4 (-0.1 to -17.8)	1.8 (-3.0 to 7.0)
BC†	-5.1 (-1.5 to -8.6)	-10.1 (-2.4 to -17.2)	-16.9 (-6.0 to -26.6)	7.2 (7 to 14.1)
PM _{2.5} *	-3.4 (0.6 to -7.3)	-7.4 (1.6 to -15.5)	-12.9 (0 to -24.2)	1.4 (-5.5 to 8.8)
PM _{2.5} †	-2.6 (0.8 to -6.0)	-10.1 (-2.8 to -16.9)	-12.7 (-1.6 to -22.5)	0.2 (-4.6 to 5.2)
Secondary PM*	-0.5 (2.8 to -3.7)	-3.0 (4.8 to -10.3)	-6.6 (-16.9 to 5.0)	1.4 (-4.1 to 7.2)
Secondary PM†‡	-0.9 (2.5 to -4.1)	-6.4 (0.6 to -12.9)	-5.8 (-15.6 to 5.1)	-2.4 (-7.6 to 3.1)

All models control for subject, temperature, day of week, hour of day, medication use on that day, and time trend.

*1 hour average.

†24 hour average.

‡Residuals of PM_{2.5} controlling for black carbon (BC).



Is There Evidence that Transference Occurs?

- Where BC exposure is *least* well characterized (monitor a mile from residences, *and* 400 feet in air), no BC associations, but strong sulfate associations (Luttmann-Gibson, 2006)
 - Other explanations aside from transference possible
- Reference: Grahame, 2009: “Does improved exposure information for PM_{2.5} constituents explain differing results among epidemiological studies?”



3. Some PM_{2.5} species are emitted from many sources, thus associations may reflect harm from co-pollutants, often unmeasured

- More prevalent issue from 1980s to mid 2000s
 - Sulfate gradients away from major roads
 - Near-highway monitor mixes regional secondary sulfate with vehicular primary sulfate correlated with EC, vehicular HAPs
 - Residual oil combustion, steel and coke operations emitted sulfate plus metals, PAHs,
 - Need to separate effects of regional sulfate from effects of residual oil, steel, and coke sulfate emissions, with their V and Ni, metal and PAH co-emissions respectively

■ References

- Grahame and Hidy, 2007: “Pinnacles and Pitfalls for Source Apportionment of Potential Health Effects From Airborne Particle Exposure”
- Grahame and Hidy, 2004: “Using Factor Analysis to Attribute Health Impacts to Particulate Pollution Sources”



Example: Laden et al, 2000 (sulfates from different sources are present)

- Study examines associations with daily mortality in six cities of markers for:
 - vehicular emissions (Pb)
 - dust (Si)
 - coal combustion (Se)
- For Se, and separately for sulfate as S, findings are counterintuitive –
 - Only Boston (city with lowest Se, and near lowest S) had significant mortality associations for either Se or S
 - Localities with considerably higher Se and S (St. Louis, Steubenville, Knoxville) had no Se or S mortality associations



Laden et al (2000) Se and S findings

Percent increase in daily deaths and 95% CIs for Se (coal tracer) and S (from Laden et al., 2000)^a

	Boston	St. Louis	Knoxville	Madison	Steubenville	Topeka	Combined
Se factor	2.8% 1.2–4.4	0.3% –1.1–1.6	0.8% –2.7–4.3	0.9% –2.5–4.2	1.1% –1.2–3.5	–3.9% –11.2–3.5	1.1% 0.3–2.0
Sulfur	7.9% 3.9–12.1	0.8% –2.4–4.2	1.0% –6.8–9.4	4.6% –3.0–12.7	0.5% –6.8–8.3	–10.3% –23.1–4.6	3.0% 0.9–5.2

^aFor Se, percent increase is for a 10- $\mu\text{g}/\text{m}^3$ increase in mass concentration from the coal source; for S, percent increase is for an increase from the 5th to the 95th percentile.

Levels of PM_{2.5} and selected elements in the six cities (from Laden et al., 2000), with standard deviations in parentheses

	Boston	St. Louis	Knoxville	Madison	Steubenville	Topeka
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	16.5 (9.2)	19.2 (10.1)	21.1 (9.3)	11.3 (7.5)	30.5 (22.4)	12.2 (7.1)
Sulfur (ng/m^3)	1922 (1392)	2350 (1583)	2556 (1491)	1482 (1327)	4248 (3185)	1368 (1169)
Selenium (ng/m^3)	0.7 (0.9)	2.2 (1.9)	1.9 (1.5)	0.9 (0.8)	5.2 (4.2)	0.8 (0.7)



Example: Laden et al., 2000

- Why the “reverse dose response function”?
- Long story short:
 - **Residual oil as burned contains traces of Se**
 - Using EPA data source for ratio of V to Se in as-burned residual oils, **over 2/3rds of Se in Boston air from local residual oil (1,700 MW) in 1980s**
 - Calculated that **about half Boston sulfate was also from residual oil combustion, mostly primary V sulfates, with Ni as well**
 - **Residual oil emissions are very toxic relative to secondary sulfate, coal fly ash**



Conclusions re Laden et al (2000) findings

- Se and S were significantly associated with daily mortality only in Boston, **because only in Boston was residual oil an important source of each in ambient air**
- Se and S were not associated with daily mortality in localities with higher levels of each, because in those localities, **there were no residual oil emissions**
- Associations *per se* don't necessarily point to harm – have to understand toxicity of different co-emissions, in this case V and Ni from residual oil
 - Reference: Grahame and Hidy, 2004



Conclusions

- 1. **Number of PM_{2.5} species monitored**
 - If an epidemiology study doesn't include many PM_{2.5} species, it must fail to find associations with important missing species
 - **likely to make findings with whatever limited species are monitored**
 - New studies with up to 20 PM_{2.5} variables, even without good exposure information, mostly find vehicular emissions, V, and Ni associations
 - **This is new**



Conclusions (cont.)

■ 2. **Accurate subject exposure**

- If exposure is accurate, more likely to get *larger, more consistent and robust* associations with pollutant likely to cause harm
- With less accurate exposure, *weaker associations, perhaps even transfer of associations from more harmful pollutant, to pollutant with more accurate exposure information*



Conclusions (cont.)

- **3. Separating effects of different sources, when each source emits a common pollutant, but different co-emissions**
 - Separate effects of regional rural air masses, high in PM, from urban air masses, enriched in BC, for more different health endpoints
 - If V, Ni emissions are present, need to separate these as well



Conclusions (cont.)

- Black carbon and some highly correlated emissions are very likely to be causally related to many cardiovascular mortality and morbidity outcomes (Grahame and Schlesinger, 2010; many other publications, such as Janssen et al., 2011)
 - Toxicology
 - Human panel studies
 - Population based epidemiology
- V and Ni may well be so associated, but need to corroborate toxicology and limited population based epidemiology with human panel studies



Conclusions (cont.)

- Sulfate – despite over 20 years of press releases from environmental groups and others – does not yet appear to be shown causally related to mortality
 - “Perception is reality”
 - Early sulfate mortality associations were in studies such as 6 Cities (1993) and ACS (1995), which included only sulfate, not BC, V, Ni, or other important PM_{2.5} species
 - Toxicology – sulfates and acidity at ambient levels not harmful
 - Theories for how other PM_{2.5} species can be made harmful by sulfate haven’t yet been shown harm in real world
 - “Acid catalysis” – but large rural air masses often NOT associated with harm, as shown in some of today’s slides
 - Make metals harmful by making them soluble – but in many studies, some reviewed today, metals other than V, Ni not associated with harm



Conclusions (cont.)

- In its Integrated Science Assessment, EPA has developed criteria for assessing whether PM_{2.5} is causally related to various mortality and morbidity endpoints
 - *Consistent* results among different studies, study designs
 - *Coherence* between toxicology and epidemiology
 - *Dose-response function*: more adverse effects at higher doses
- These are good criteria, but they are being used to assess PM_{2.5}, not PM_{2.5} species
 - Artifact of 1970 Clean Air Act, when pollution levels were much worse, we knew little about components?



Conclusions (cont.)

- In on-the-record comments of March 12, 2009, DOE suggested to EPA that instead of assessing $PM_{2.5}$, which differs in composition and thus toxicity at different times and places, EPA should instead assess the major $PM_{2.5}$ species according to these criteria



Conclusions (cont.)

- Need to assess *each PM_{2.5} species of interest* – not PM_{2.5} *per se*, as if it were similar everywhere in the US – *against criteria for determining causality*
- In so doing, emphasize studies with methodologies discussed:
 - Include many PM_{2.5} species of interest
 - Use studies with good subject exposure
 - Separate effects of sources with common PM_{2.5} emissions
 - Use toxicology to establish biological mechanisms, and thus biological plausibility, for each species



References

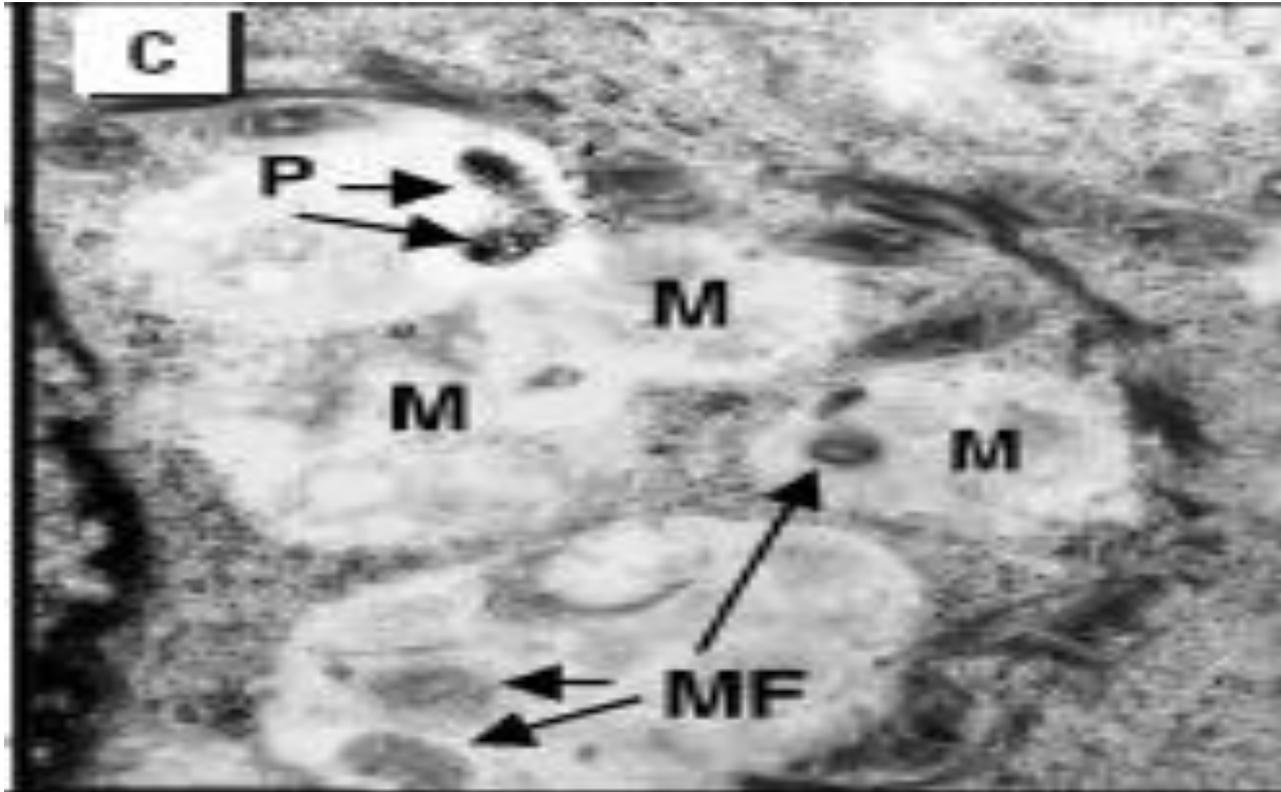
- Grahame, T., and Hidy, G. 2004. Using factor analysis to attribute health impacts to particulate pollution sources. *Inhal. Toxicol.* 16 (suppl.1):143–152.
- Grahame TJ. 2009. Does improved exposure information for PM_{2.5} constituents explain differing results among epidemiological studies? *Inhal. Toxicol.* 21: 381-393
- Grahame T, and Hidy GM. 2007. Pinnacles and Pitfalls for Source Apportionment of Potential Health Effects From Airborne Particle Exposure. *Inhal. Toxicol.* 19: 727-744
- Grahame TJ, and Schlesinger RB. 2010. Cardiovascular health and particulate vehicular emissions: a critical evaluation of the evidence. *Air Qual. Atmos. Health.* online Jun 30, 2009
<http://www.springerlink.com/content/671125671x133314/fulltext.html>



Appendix: Toxicology of BC

- Studies by UCLA and USC researchers have examined cellular effects in human lung cells of ultrafine PM near freeways, a major fraction of which is BC
- Ultrafine PM enters cells more easily than larger PM
- When in the cell, ultrafines lodge in the mitochondria, cause oxidative stress (next slides), likely due to PAHs
 - From Li et al. (2003) “Ultrafine Particulate Pollutants Induce Oxidative Stress and Mitochondrial Damage

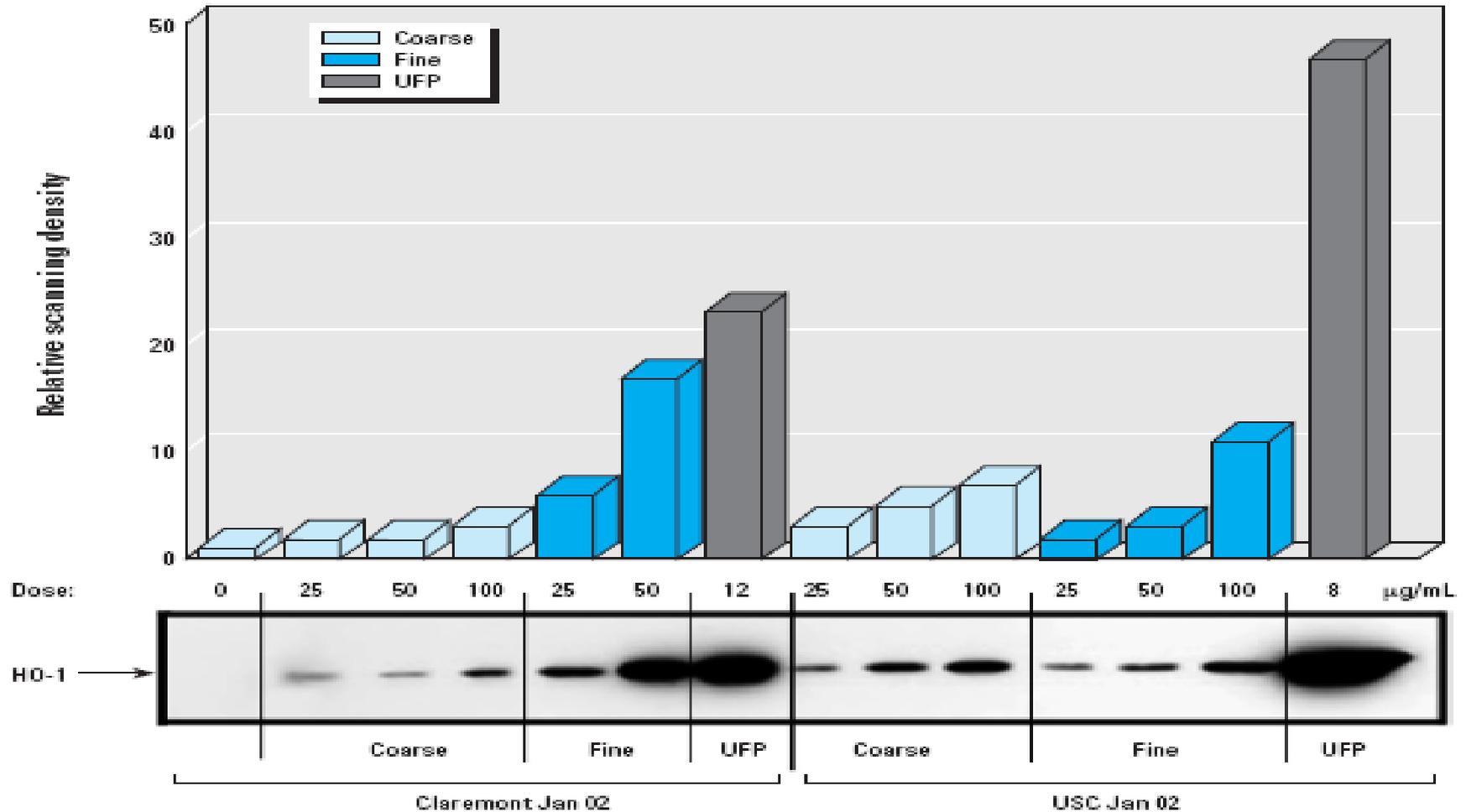
Oxidative Stress from Ultrafine PM/BC



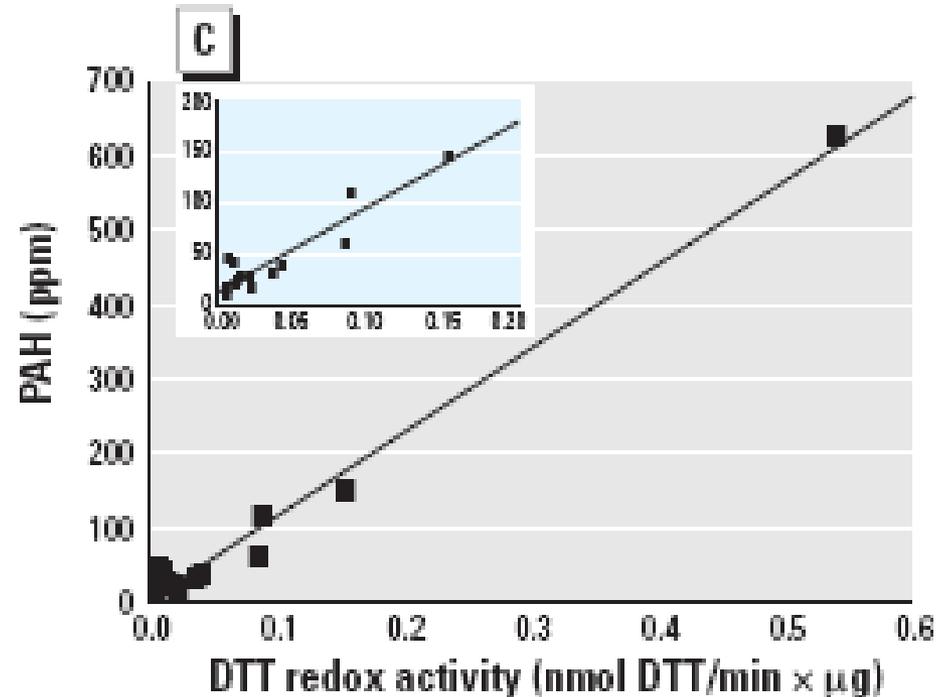
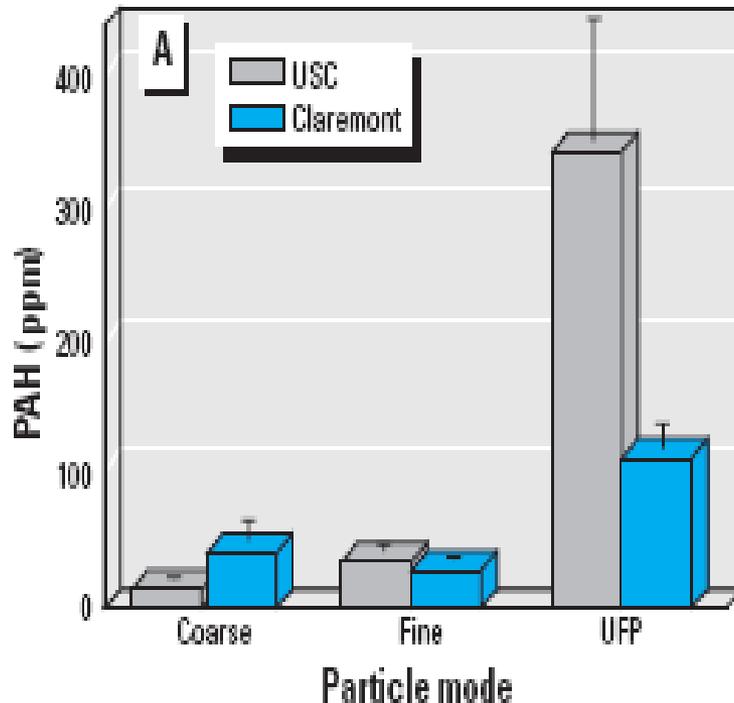
Electron micrographs demonstrating mitochondrial destruction in BEAS-2B cells treated with 8.4 $\mu\text{g}/\text{mL}$ of USC-Jan 02 UFPs for 16 hr; UFP-treated cells; magnification $\times 26,300$ (P = uf particles, M = mitochondria)

Oxidative Stress from Ultrafine PM/BC

A



Ultrafine PM, PAH content, oxidative stress related



(A) PAH content for each set of CAPs; (C) Linear regression analysis demonstrating the correlation between PAH content and 15 DTT data points

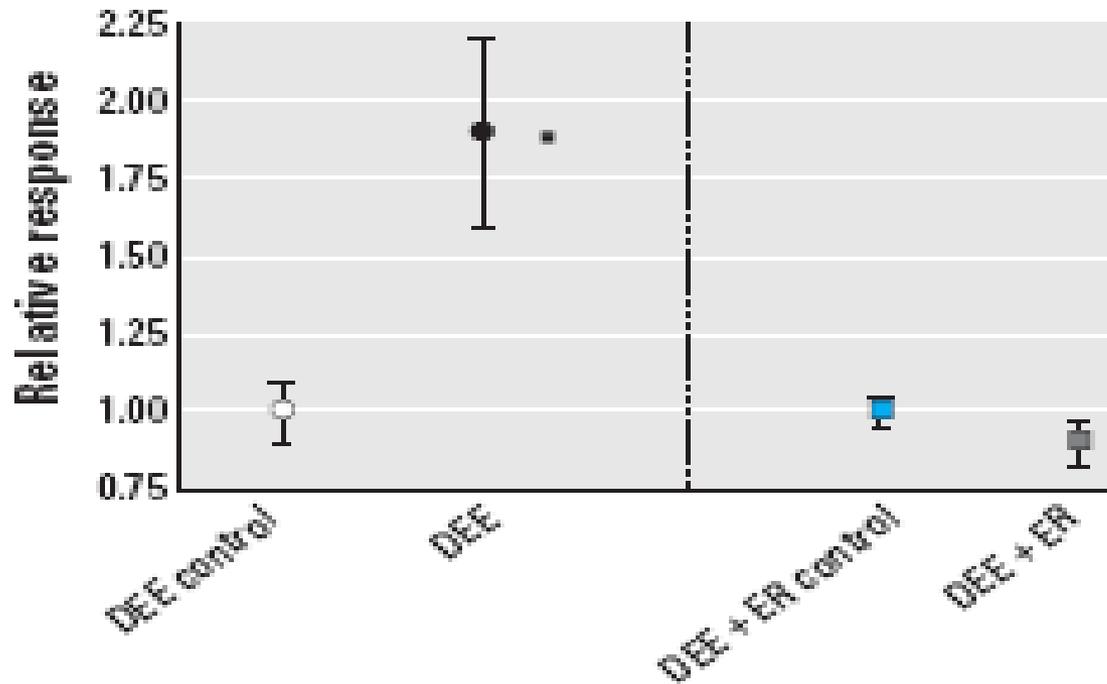


Animal Tests Confirm Health Effects (McDonald et al., 2004)

- Study examined inflammatory, oxidative stress, and resistance to virus in rodents exposed to either 2002 diesel exhaust or filtered air
- Then examined these effects in diesel exhaust using new catalyzing particle trap
- Found that all adverse health effects associated with diesel exhaust were abrogated by the catalyzing trap

Animal Tests Confirm Health Effects (McDonald et al., 2004)

- Won't walk you through all five results, but this one (oxidative stress) is typical (DEE + ER is Diesel Engine Exhaust plus Emissions Reduction, control is filtered air):





Animal Tests Confirm Health Effects (McDonald et al., 2004)

- Also showed that 100% of BC, large percentage of most carbonaceous compounds were eliminated by catalyzing trap (next slide)



Animal Tests Confirm Health Effects (McDonald et al., 2004)

Table 4. Comparative composition of DEE, DEE + ER, and control (clean air) exposure chambers.

Analyte or chemical class	Control	DEE	DEE + ER	DEE vs. DEE + ER (percent decrease)
Particle composition				
Black (elemental) carbon ($\mu\text{g}/\text{m}^3$)	0.0	200.3	0.0	100
Organic carbon ($\mu\text{g}/\text{m}^3$)	4.5	39.9	4.2	90
Sum of other SVOC PAHs ($\mu\text{g}/\text{m}^3$)	0.4	1.7	0.6	65
Sum of particle PAHs (ng/m^3)	0.0	23.0	0.0	100
Sum of Oxy-PAHs ($\mu\text{g}/\text{m}^3$)	0.05	1.29	0.08	94
1,3-Butadiene ($\mu\text{g}/\text{m}^3$)	0.0	2.2	0.0	100
Benzene ($\mu\text{g}/\text{m}^3$)	0.4	4.5	0.2	95
Pyrene ($\mu\text{g}/\text{m}^3$)	0.03	0.34	0.02	93
Benzo[a]pyrene (ng/m^3)	0.00	0.08	0.00	100