The Science Behind the Particulate Matter (PM) Standards

George Thurston, Sc.D.
New York University School of Medicine
NYU-EPA PM Center, Deputy Director
Tuxedo, NY 10987

For Presentation at:
STAPPA AND ALAPCO
2005 FALL MEMBERSHIP MEETING
OCTOBER 22-26, 2005

Discussion Topics

- What's Been Learned Since the Last Standard Setting Process in 1997 regarding:
  - PM Health Effects Mechanisms
  - Epidemiological Bases of the $PM_{2.5}$ Short and Long-Term Standards
- The Health Benefits of Various Standards
- Implications to $PM_{2.5}$ Standard Setting

State of the Science in 1998

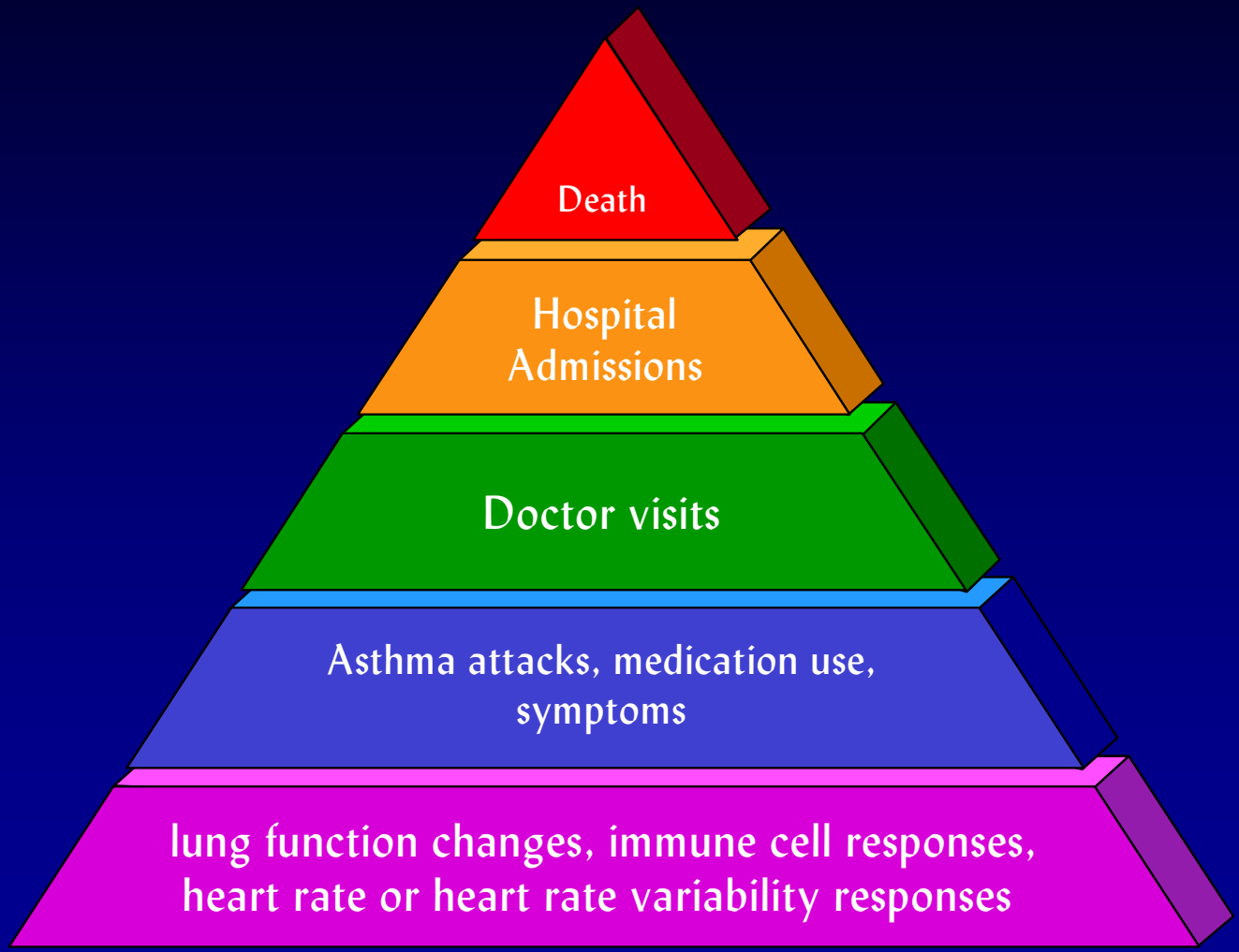
- Dozens of epidemiology studies from around the world reported associations between ambient PM and cardiac mortality and morbidity
- PM levels are very low compared with other particle exposures:

One cigarette = 10x more than typical 24 hour exposure to PM

- No widely accepted patho-physiological pathway or mechanism could explain how a person could die from exposure to PM at such low levels of air pollution.

EPA Particulate Matter Research Centers Program

The Epidemiological Pyramid of Air Pollution Effects

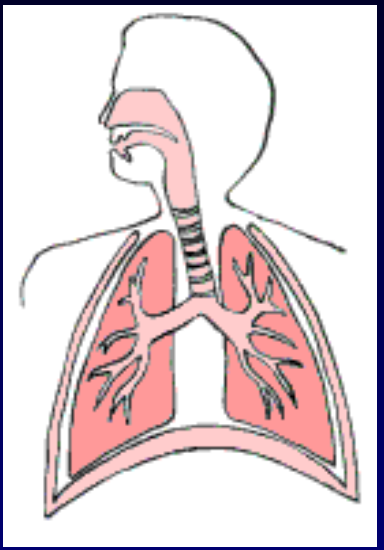


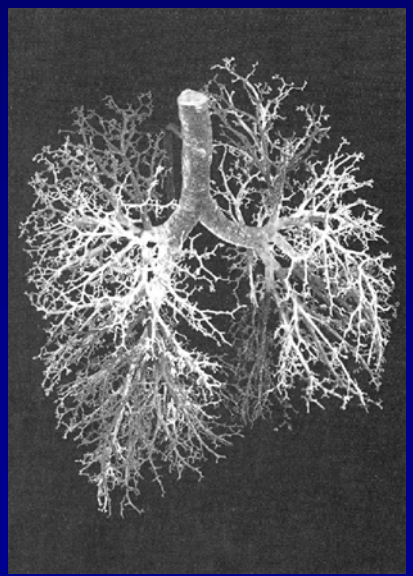
People Most Affected by Ambient Air Pollution

- Older Adults
- Persons with Pre-Existing Respiratory Disease (e.g., Chronic Obstructive Pulmonary Disease, COPD, such as emphysema, those with Cardiac problems)
- Children, especially those with Asthma.
- Healthy adults who work or exercise outdoors.
- Persons with inadequate health care, such as the poor and working poor.

Particle Deposition in the Lung

- Larger particles deposit in the upper airways (nose and throat) and are cleared out
- Smaller particles penetrate deep into the lungs and stay there longer



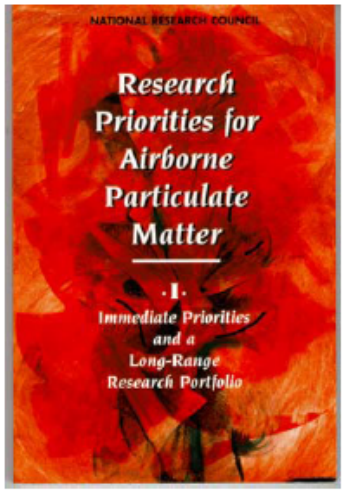


The very smallest (ultrafine) particles may enter the blood and travel throughout the body.

The First NRC Report

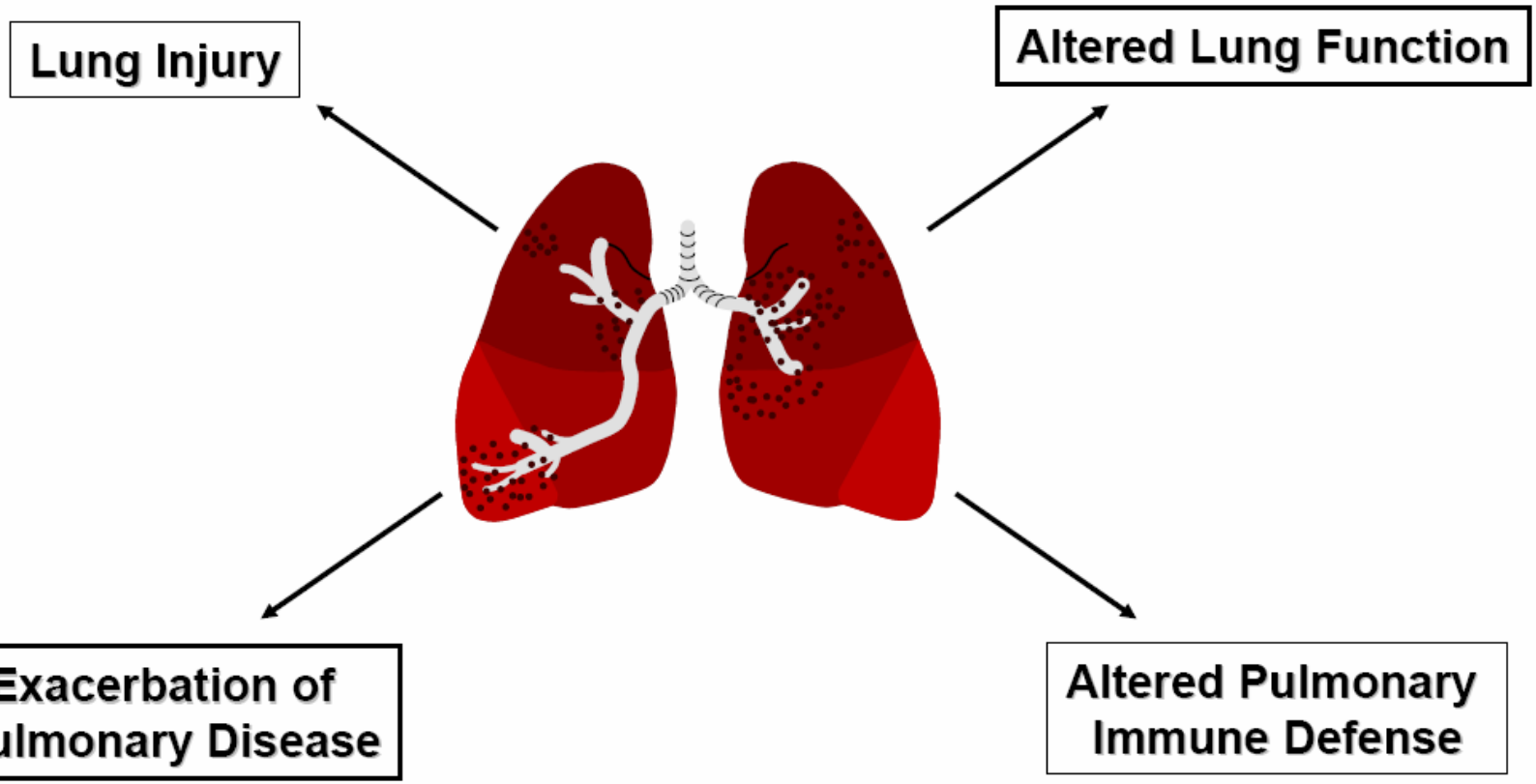
A Key Question in 1998:

What are the underlying mechanisms (pulmonary, vascular, cardiac) that can explain the epidemiological findings of mortality and morbidity associated with exposure to ambient particulate matter?



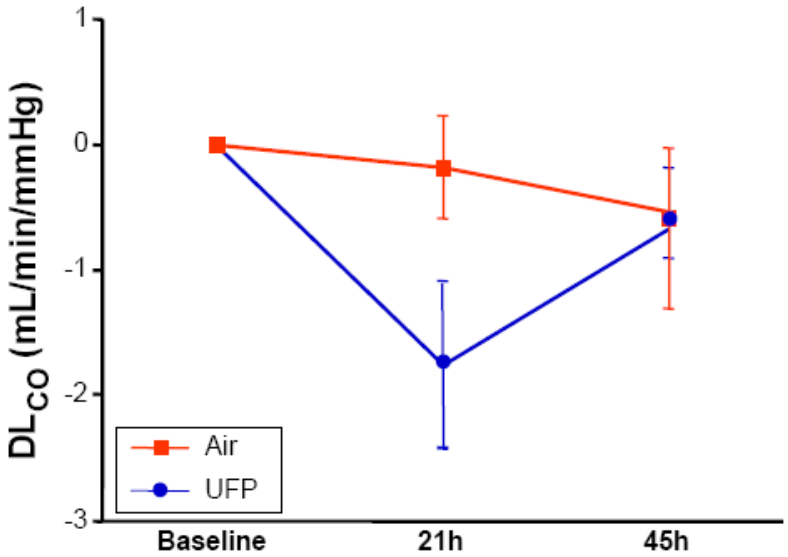
WHAT WE HAVE LEARNED IN RECENT YEARS

Potential Effects of PM on the Pulmonary System



PM Causes Changes in Lung Function

Humans exposed to ultrafine particles have decreased diffusing capacity.

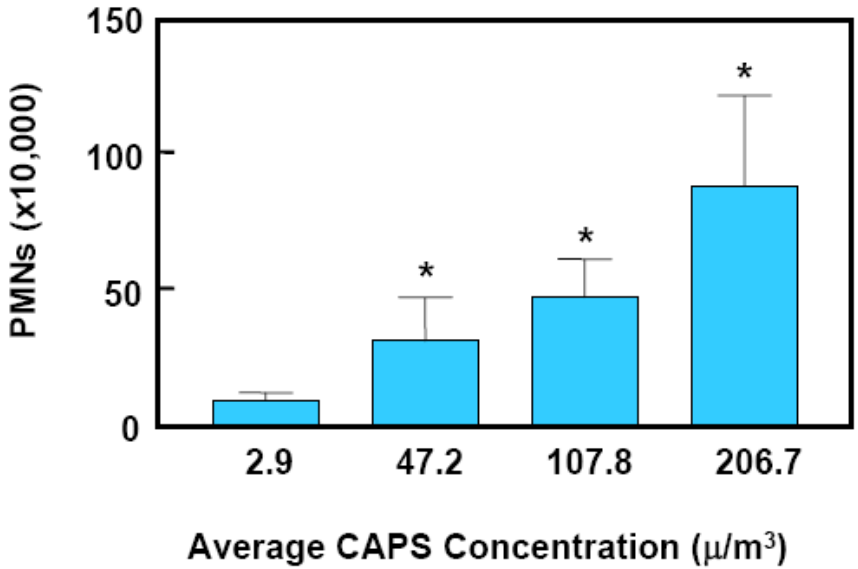


Diffusing capacity is a measure of oxygen transfer from the lungs to the blood

Pietropaoli, et al., 2004

PM Causes Lung Inflammation

Healthy young volunteers exposed to concentrated ambient air particles (CAPs) experience mild pulmonary inflammation

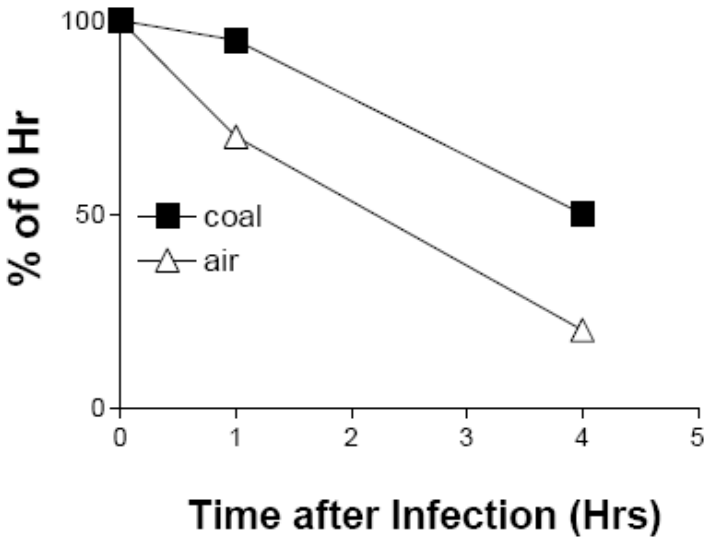


Ghio et al., 2001

PM Depresses Clearance and Inactivation of Bacteria

Epidemiology studies report associations between PM and increased incidence of hospitalization for respiratory infections.

Inactivation



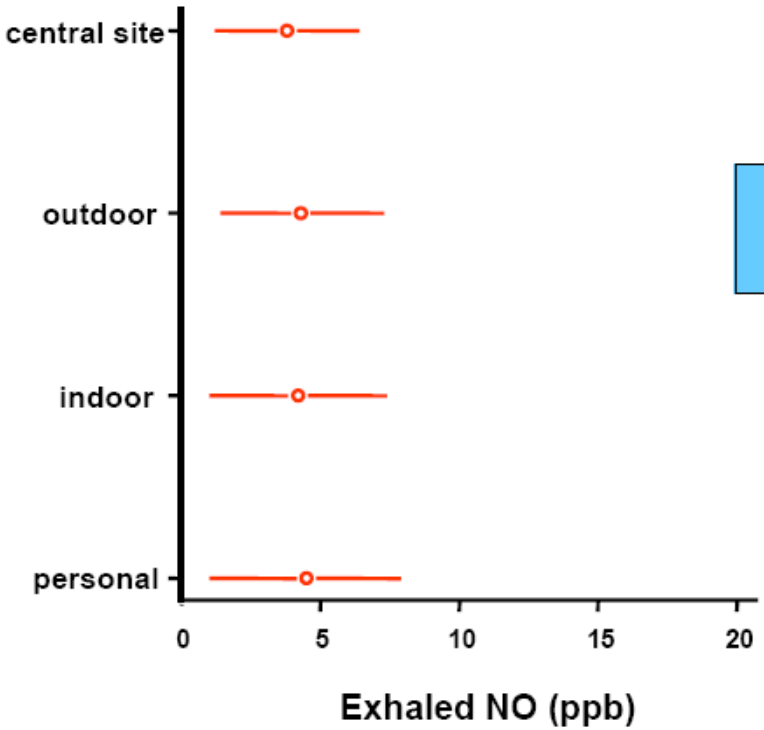
Host Resistance Model

	Control	Woodstove
% Mortality (Streptococcus)	0	21

Gilmour et al., 2002

PM Exposure Exacerbates Asthma

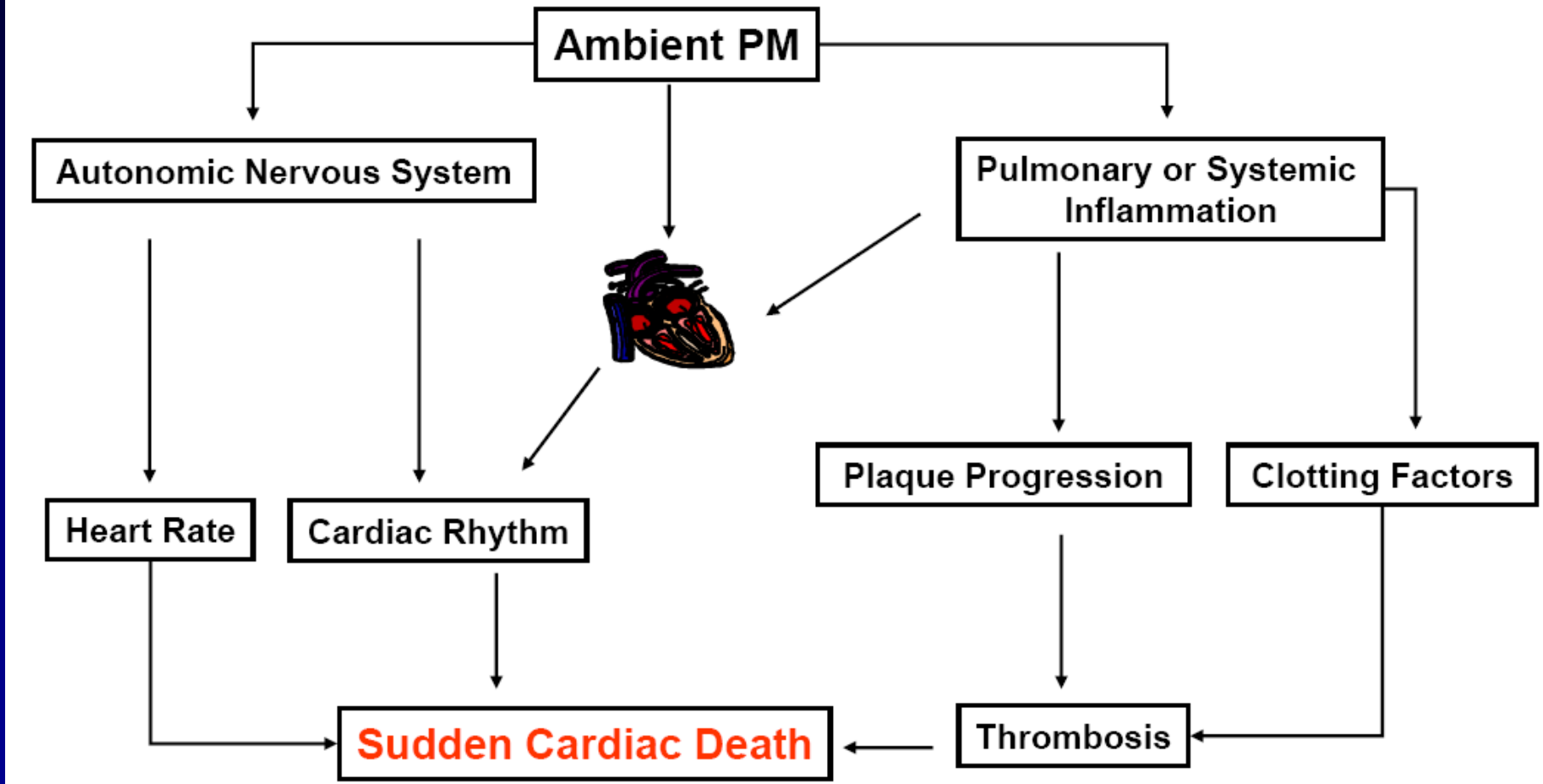
Change in exhaled nitric oxide per 10 μg/m^3 increase in $PM_{2.5}$ in children with asthma



NO is an indication of pulmonary inflammation

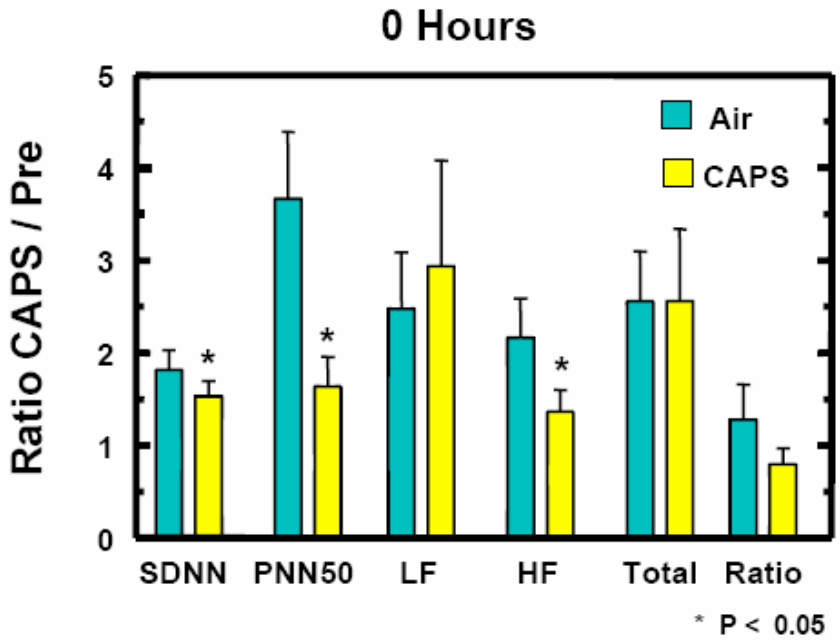
Koenig et al., 2003

Potential Effects of PM on the Cardiovascular System



PM Affects Autonomic Nervous System Control of the Heart

Elderly humans exposed to fine CAPS experience decreases in heart rate variability (HRV).



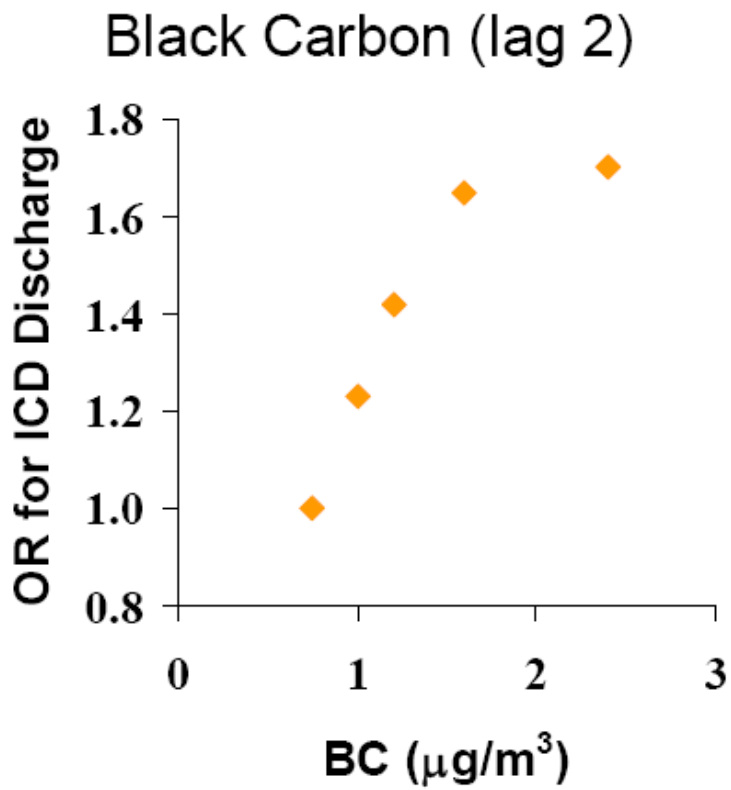
People with cardiovascular disease who have decreased HRV have a higher risk of getting a heart attack.

Devlin et al, 2003

PM Triggers Cardiac Arrhythmias in Humans

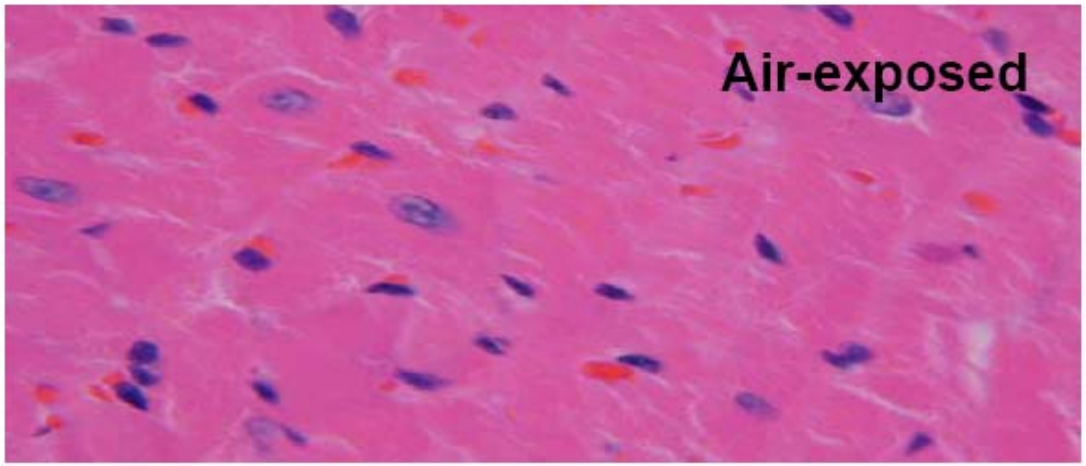
The number of times that implanted defibrillators discharged were related to prior days levels of PM and PM components

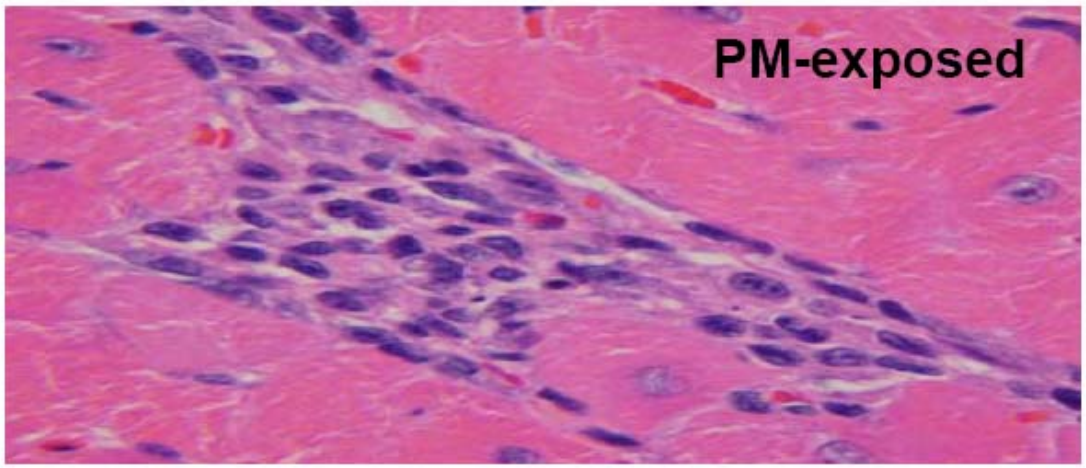
$PM_{2.5}$	1.22 (0.7,2.0)
BC	2.16 (1.0,4.9)



Peters et al, 2000

PM Causes Injury to Cardiac Cells



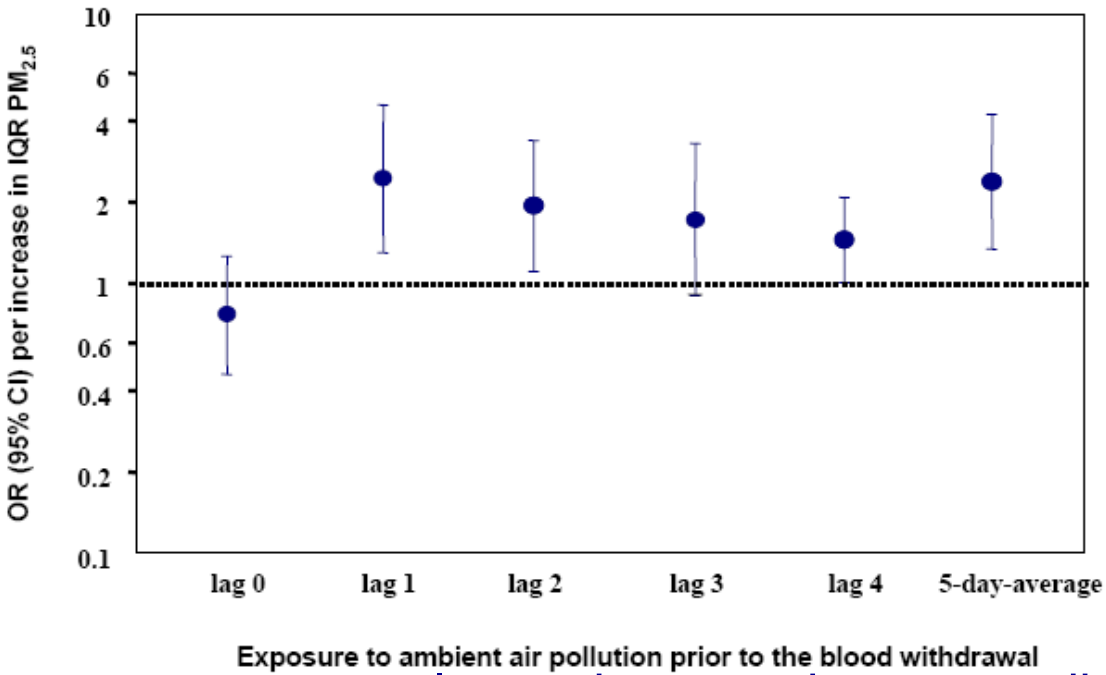


Rats exposed to ambient PM one day per week for 16 weeks

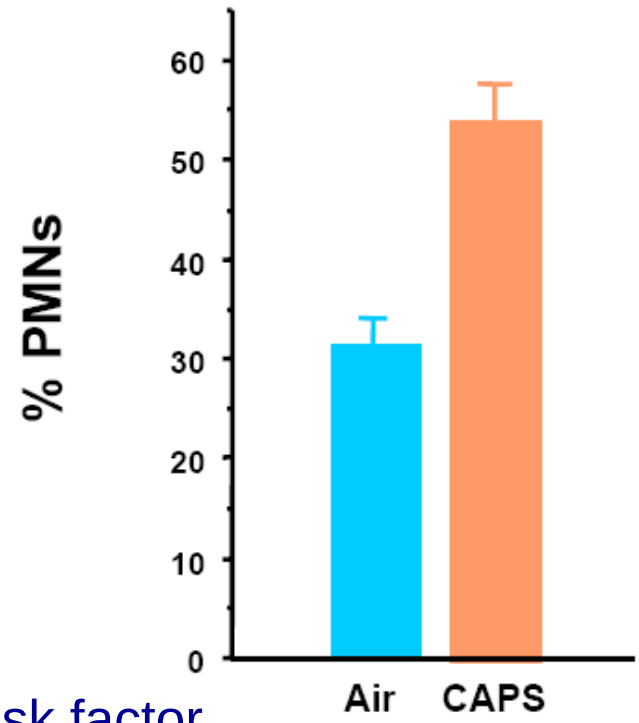
Kodavanti et al., 2003

PM Increases Vascular Inflammation

Increase in blood C Reactive Protein in Humans



Increase in blood PMNs in Rats Exposed to CAPS



Elevated CRP, a known cardiac risk factor, is associated with oxidative stress

Rueckerl et al., 2004

Gordon et al., 2000

Other Epidemiology Also Confirms a Rise in C-Reactive Protein (CRP) during Higher PM

(Source: Peters et al, EHJ, 2001)

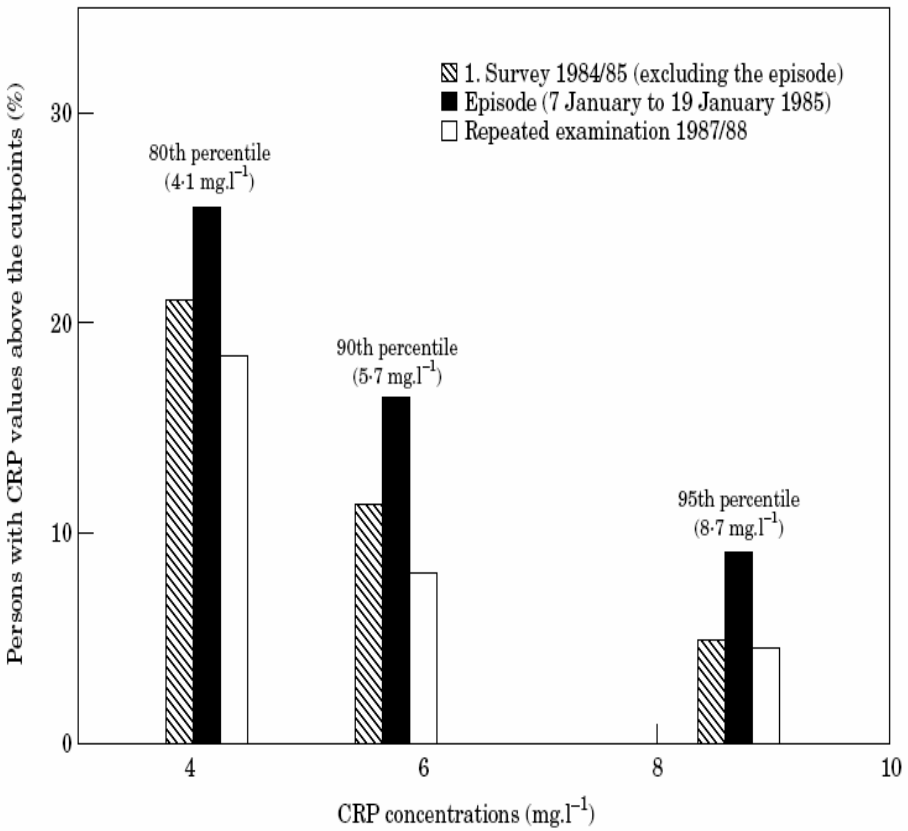


Figure 1 Influence of the air pollution episode 1985 on the distribution of elevated C-reactive protein (CRP) values.

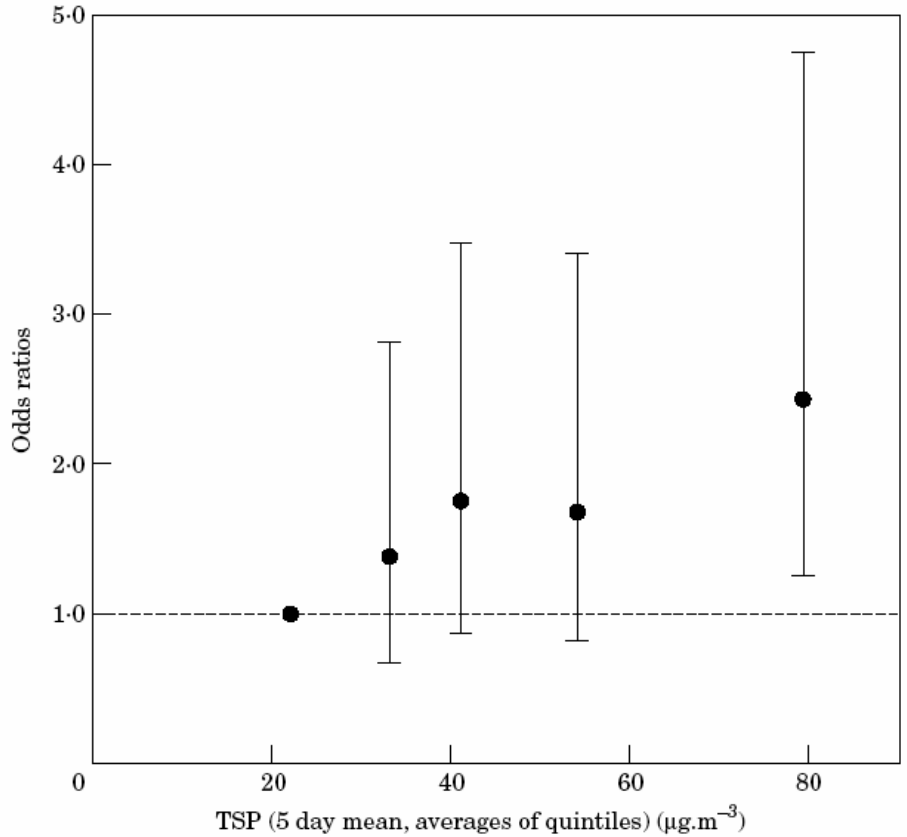


Figure 2 Multivariate regression results for quintiles of total suspended particulates (TSP) on C-reactive protein concentrations above 5·7 mg . l⁻¹ (90th percentile).

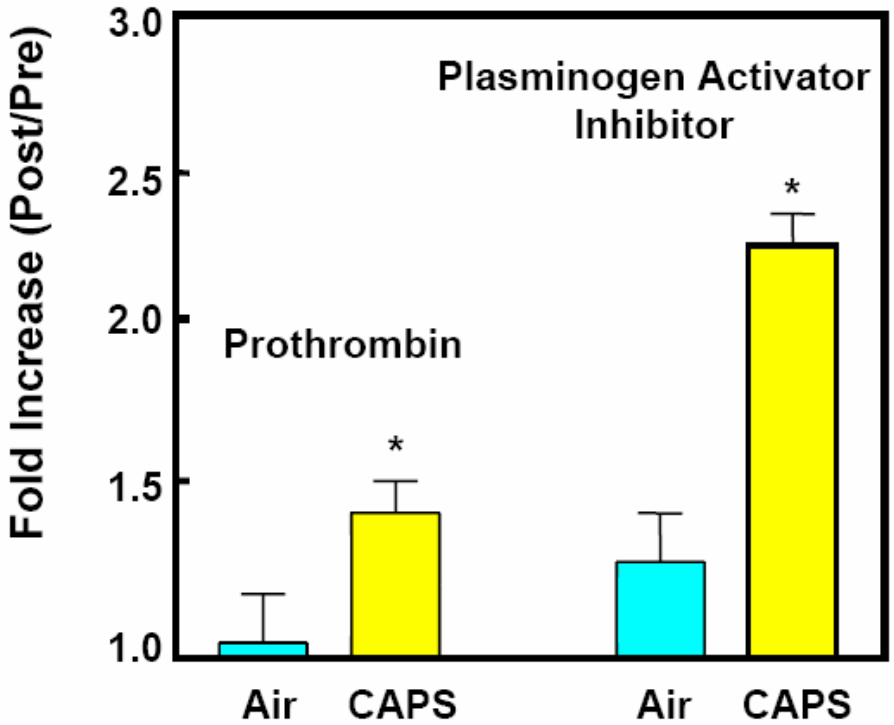
Acidic Sulfates, Transition Metals, and Oxidative Stress

- **Transition metals (e.g., Fe and V) can mediate electron transfer via Fenton Reactions causing oxidative stress.**
- **Oxidative Stress (OS) can lead to cellular damage:**
  - **OS is known to be involved in inflammation, tissue aging, cardiac ischemia, arthritis, cancer, and fibrosis (Mossman and Marsh, 1989, Janssen et al, 1993, Costa et al, 1989a, 1989b; Ewing, 1983; Slaga, 1983; Harman, 1981).**
- **The presence of acids in a particle greatly enhance the transition metals' solubility and, therefore, their bio-availability, increasing OS.**
  - **E.g., See Veronesi et al., 1999, Toxicol. Appl. Pharmacol., 155:106-115; Carter et al., 1997, Toxicol. Appl. Pharmacol., 146:180-188; and Chen et al. 1990, J. Toxicol. Environ. Hlth. 29:169-184.**

PM Increases Levels of Clotting and Coagulation Factors

Humans exposed to CAPS have changes in several blood factors which could potentially lead to a more pro-thrombogenic environment.

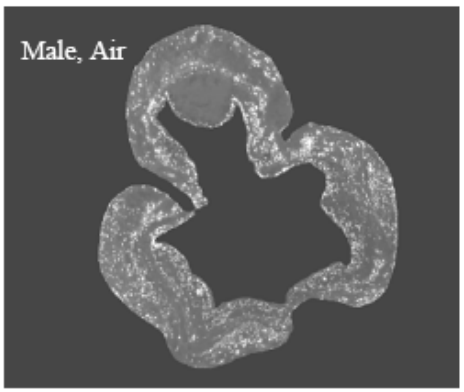
The net changes in these factors could potentially lead to an environment conducive to the formation of blood clots.

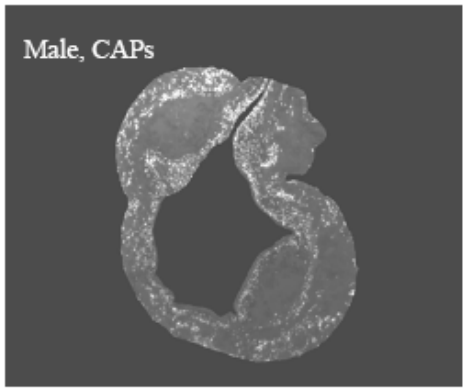


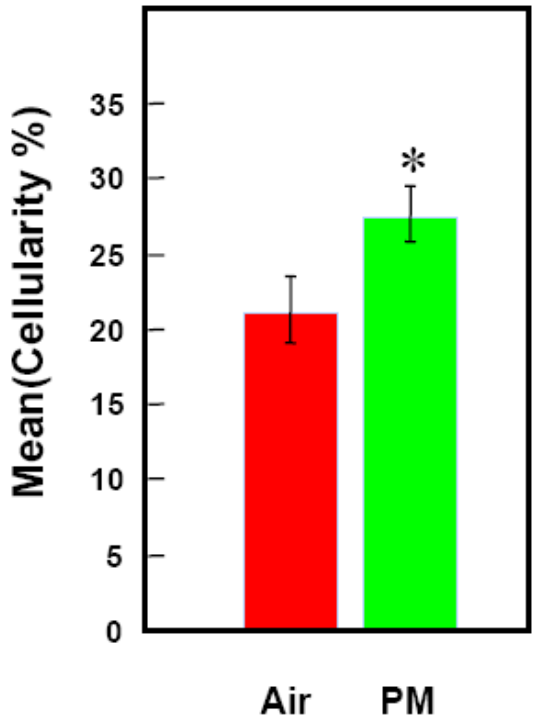
Devlin et al, 2004

PM Increases Arterial Plaque Thickness

Subchronic exposure of ApoE-/-LDLr-/- double knockout mice to CAPS for 6h/day, 5d/week, for 6 months (average of 110 μg/m^3) increases plaque cellularity.



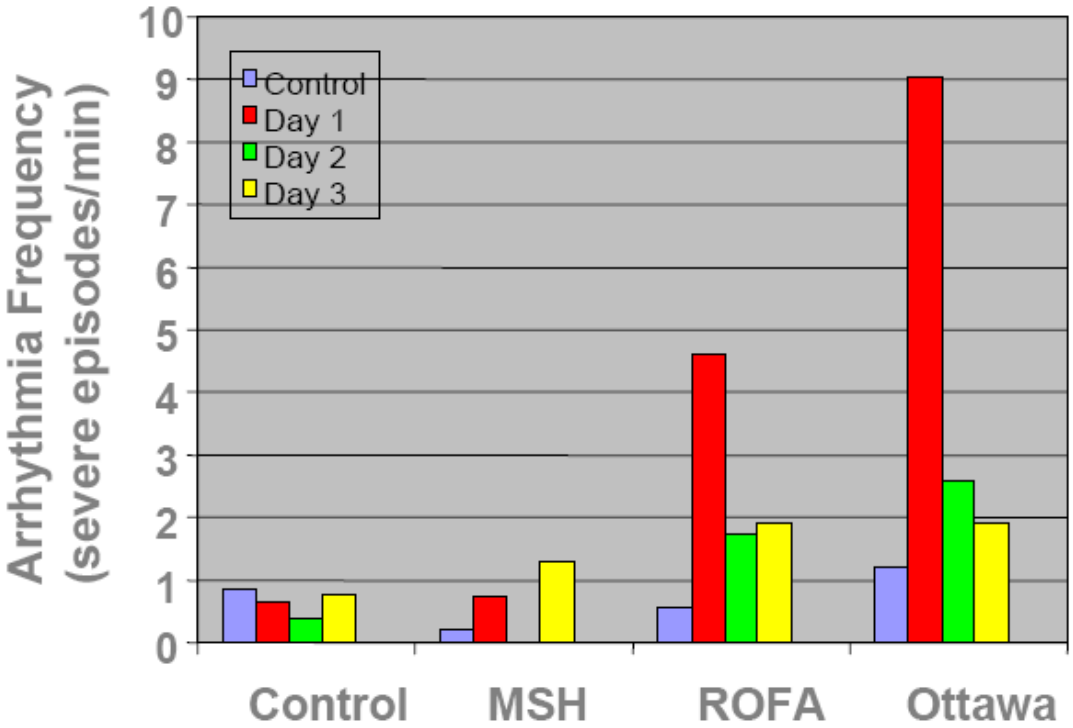


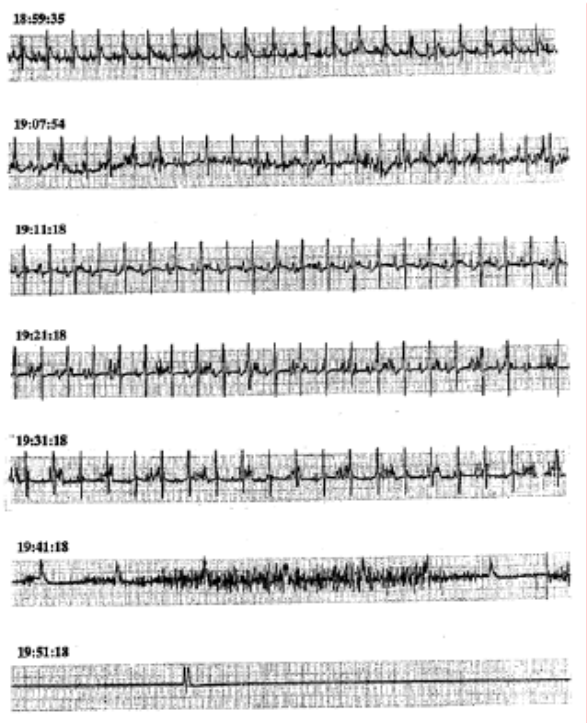


Chen et al., JAMA (in press), 2005

PM Causes Fatal Arrhythmias in Animals

Rats were treated with PM from various sources and arrhythmias measured for 3 days after exposure





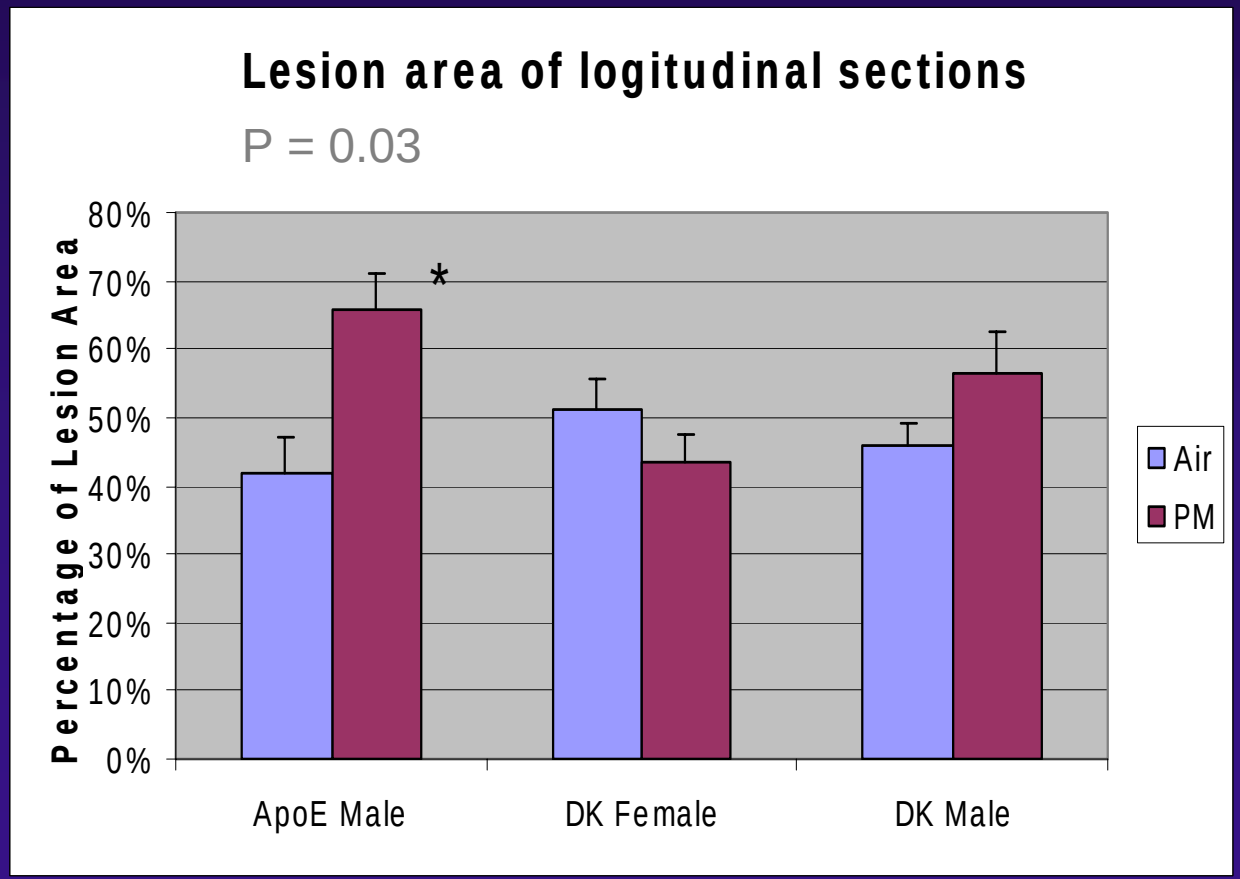
Watkinson et al., 2000

C57 Air

ApoE Air

ApoE PM

Effects of CAPs on aorta plaque size demonstrated in ApoE KnockOut Mice



Toxicology Progress Summary

Mechanistic Studies Have:

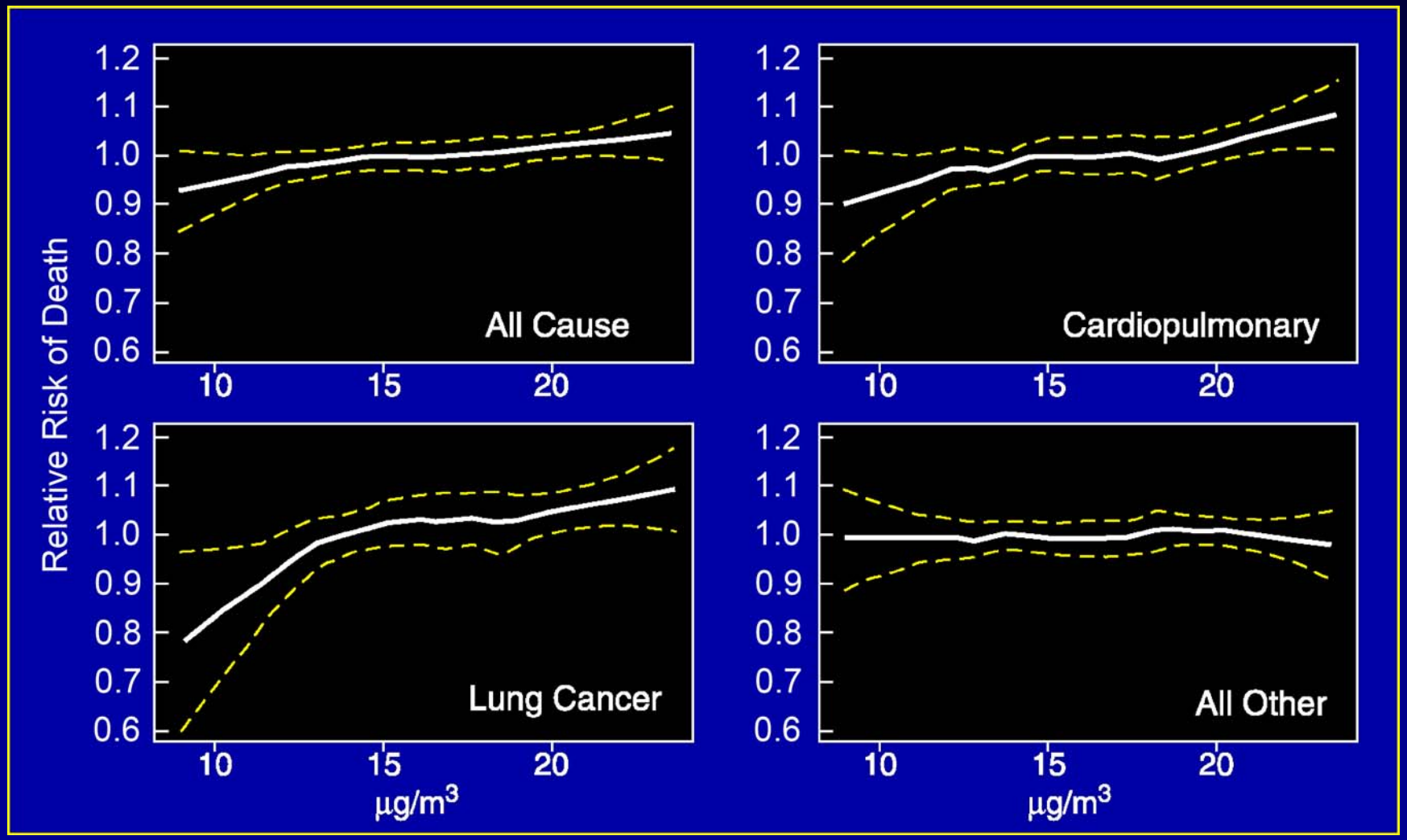
- **Defined several biologically plausible patho-physiological pathways by which PM can increase mortality and morbidity.**
- **Provided coherence to the epidemiology studies and extended their observations, thus strengthening the science in support of the PM standard.**

Epidemiologic Evidence Also Strengthened Since 1998

- More than 100 new short-term studies confirming the fine particle-mortality and morbidity associations.
- An extended analysis of the original American Cancer Society (ACS) prospective cohort study confirmed previous results, and found associations between long-term exposure and lung cancer.

Mortality Risk of Long-Term Fine PM Exposure Decrease with Exposure Down to *At Least* 7.5ug/m^3

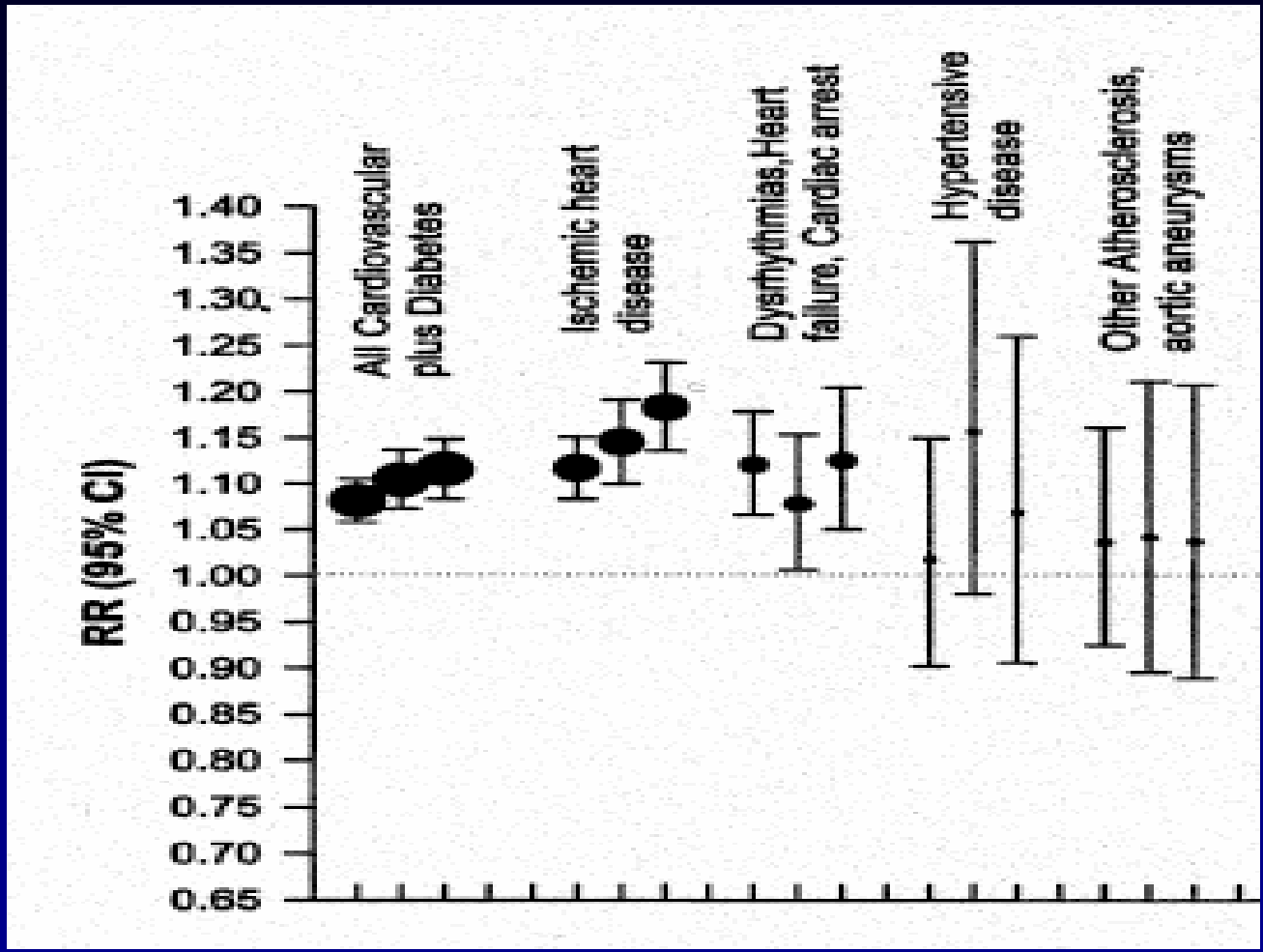
(Pope, Burnett, Thun, Calle, Krewski, Ito , and Thurston) (JAMA, 2002)



JAMA Study Conclusions

- Long-term exposure to fossil fuel combustion air pollution, and especially to fine particulate matter, is associated with increased annual risk of mortality.
- For lung cancer, living in a more polluted city is associated with approximately a 20% increase in residents' risks of dying from lung cancer.
- This is roughly comparable to the cancer risk of passive smoking exposure from living with a smoker.
- The cancer risk from air pollution appears greatest for non-smokers and those with lower socio-economic status.

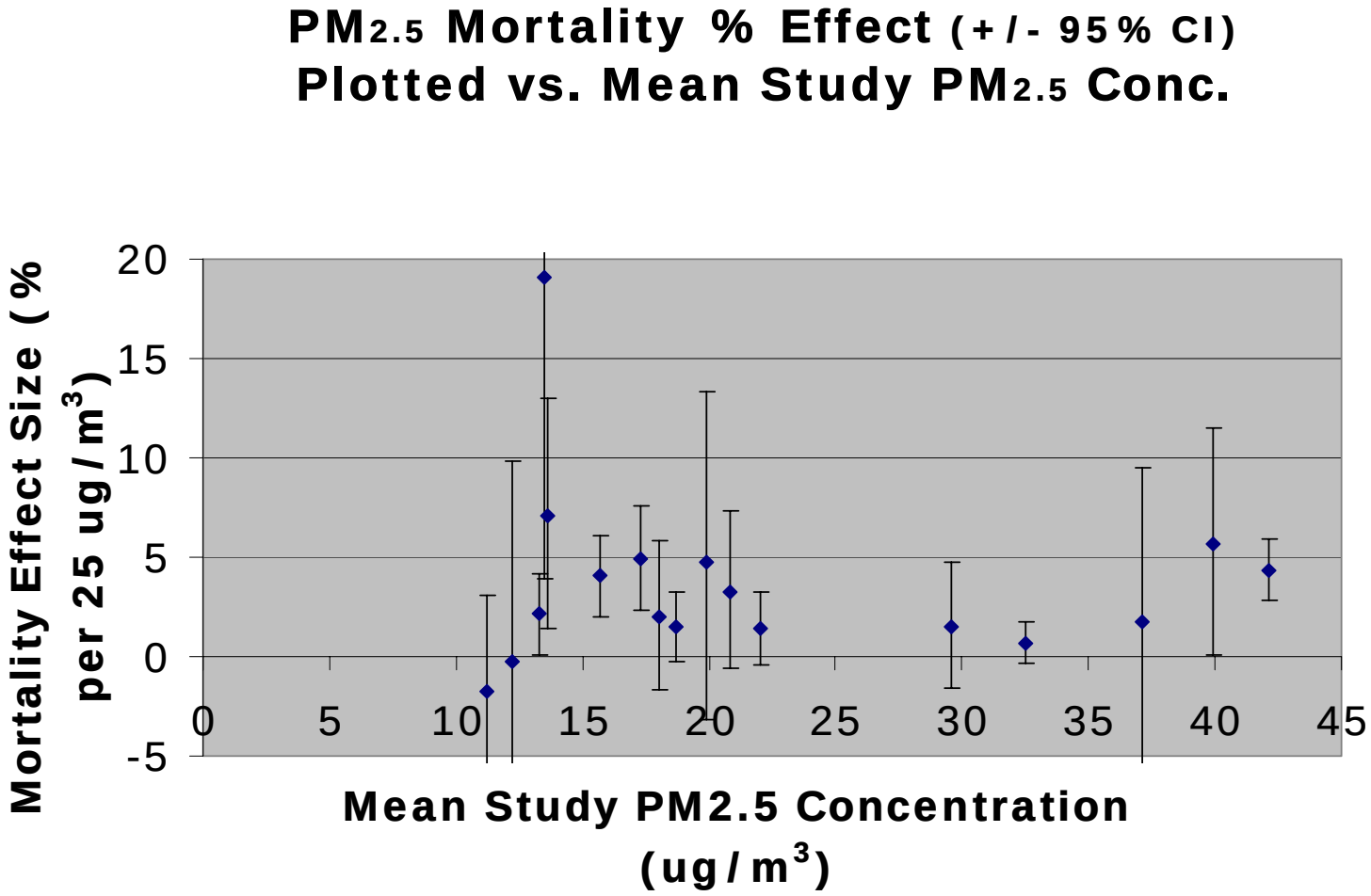
Cardiovascular Mortality Most Affected by Long Term Particulate Matter Air Pollution Exposures



Relative Risks and 95%ile CI's
for a 10 ug/m^3 increase in Annual $PM_{2.5}$ mass concentration

(SOURCE: Pope, Burnett, Thurston, Thun, Calle, Krewski, and Godleski, CIRCULATION, 2004)

New $PM_{2.5}$ Short-term Studies Indicate PM-Mortality Association Exists Below 15 ug/m^3 Mean Concentration



New $PM_{2.5}$ Short-term Studies Indicate that Co-Pollutants Do Not Modify the PM Effect

(Source: EPA PM Staff Paper, 2005)

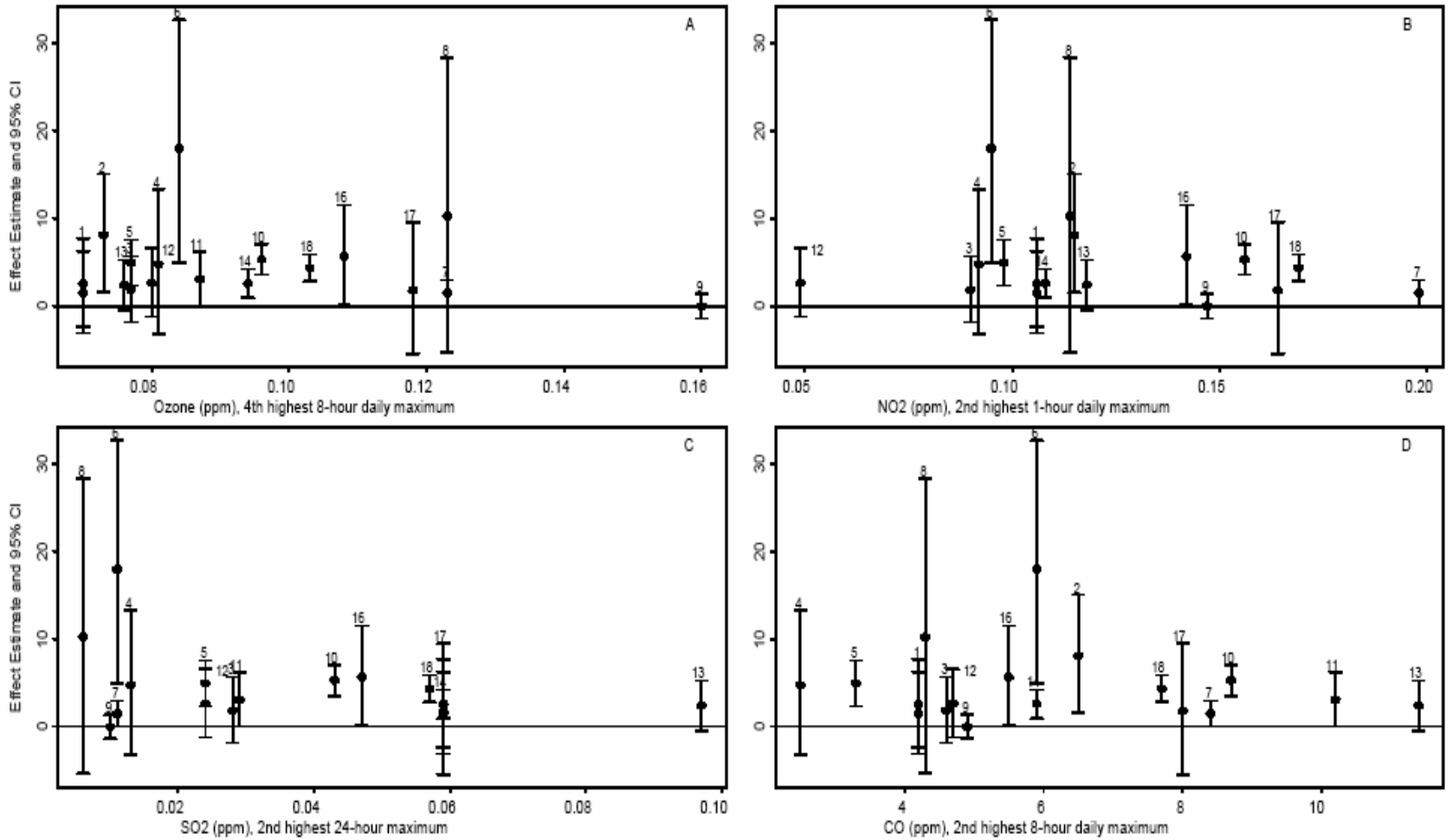
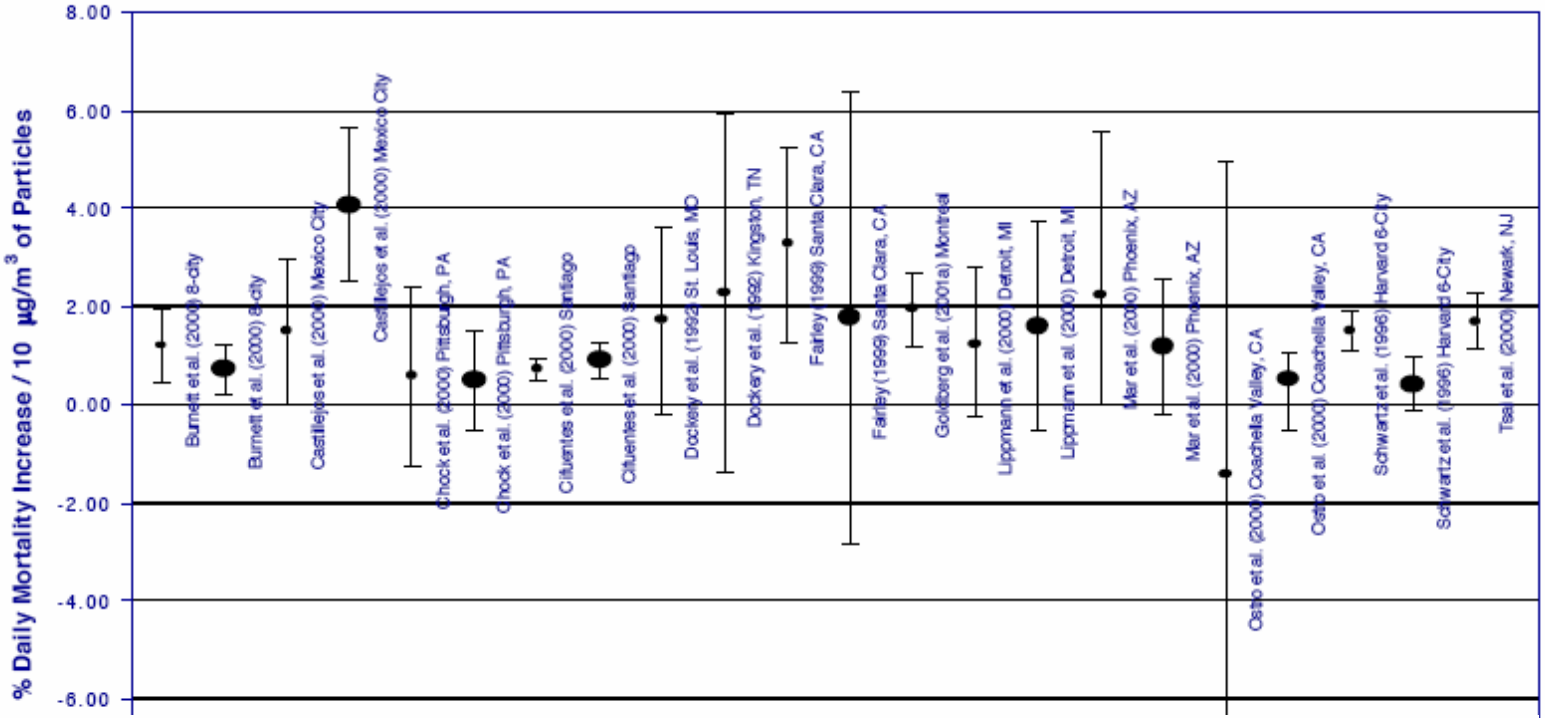


Figure 3-3. Associations between $PM_{2.5}$ and total mortality from U.S. studies, plotted against gaseous pollutant

New Size-Specific PM Studies Suggest That Urban Coarse Particles (PM_{10}-$PM_{2.5}$) May Also Associate With Acute Health Effects

(Source: CARB PM Report, 2002)

Figure 7.4 Daily Mortality Increases Associated with Fine and Coarse Particles



Note: Bar represents 95% confidence interval; small and large dots represent fine and coarse particles respectively.

EPA Staff Paper Benefit Analysis of Lowering the Short-Term PM Standard:

Annual Standard "Controls" Benefits > 30 ug/m^3

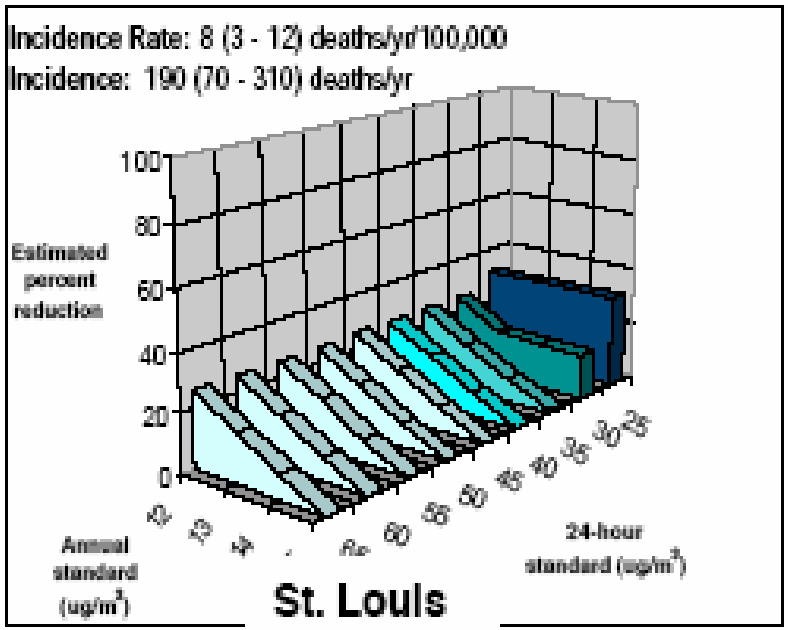


Figure 5-2(a) **Estimated percent reduction in $PM_{2.5}$-related short-term mortality risk for alternative standards *(98th percentile form)* relative to risk associated with meeting current standards (based on assumed cutpoint equal to policy-relevant background).** Risk associated with meeting current $PM_{2.5}$ standards, based on ACS extended study, is shown in figures in terms of estimated annual incidence rate and annual incidence (and 95% confidence ranges). Estimated policy-relevant background is 3.5 $\mu g/m^3$ in eastern cities and 2.5 $\mu g/m^3$ in western cities.

EPA Staff Paper Benefit Analysis of Lowering the Long-Term PM Standard: **More Deaths Avoided by Reducing Annual Avg.**

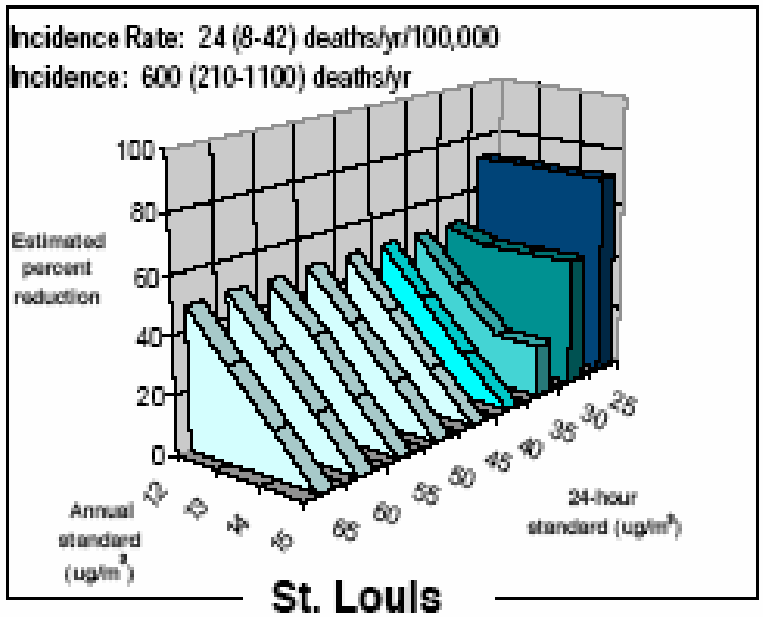
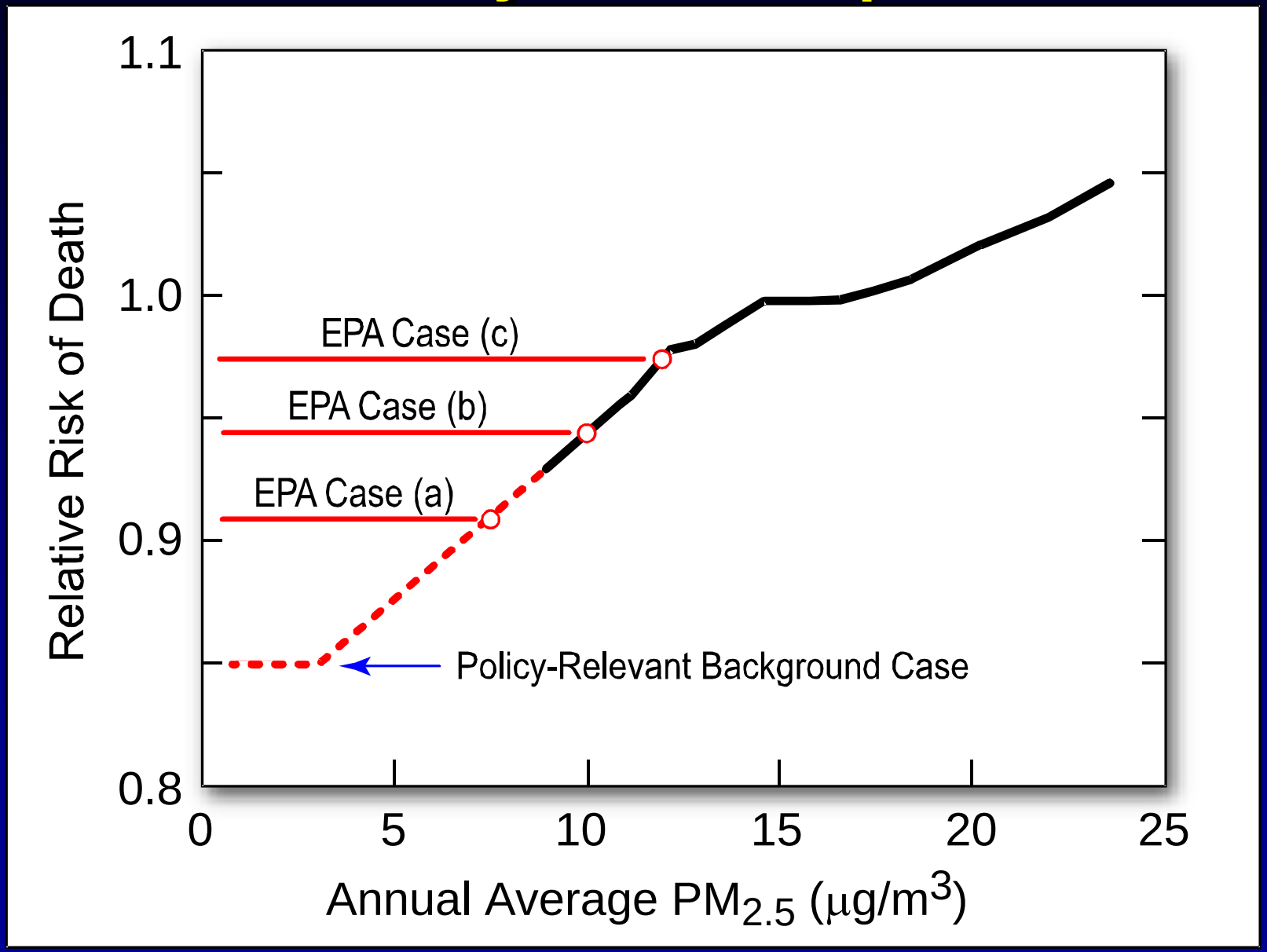
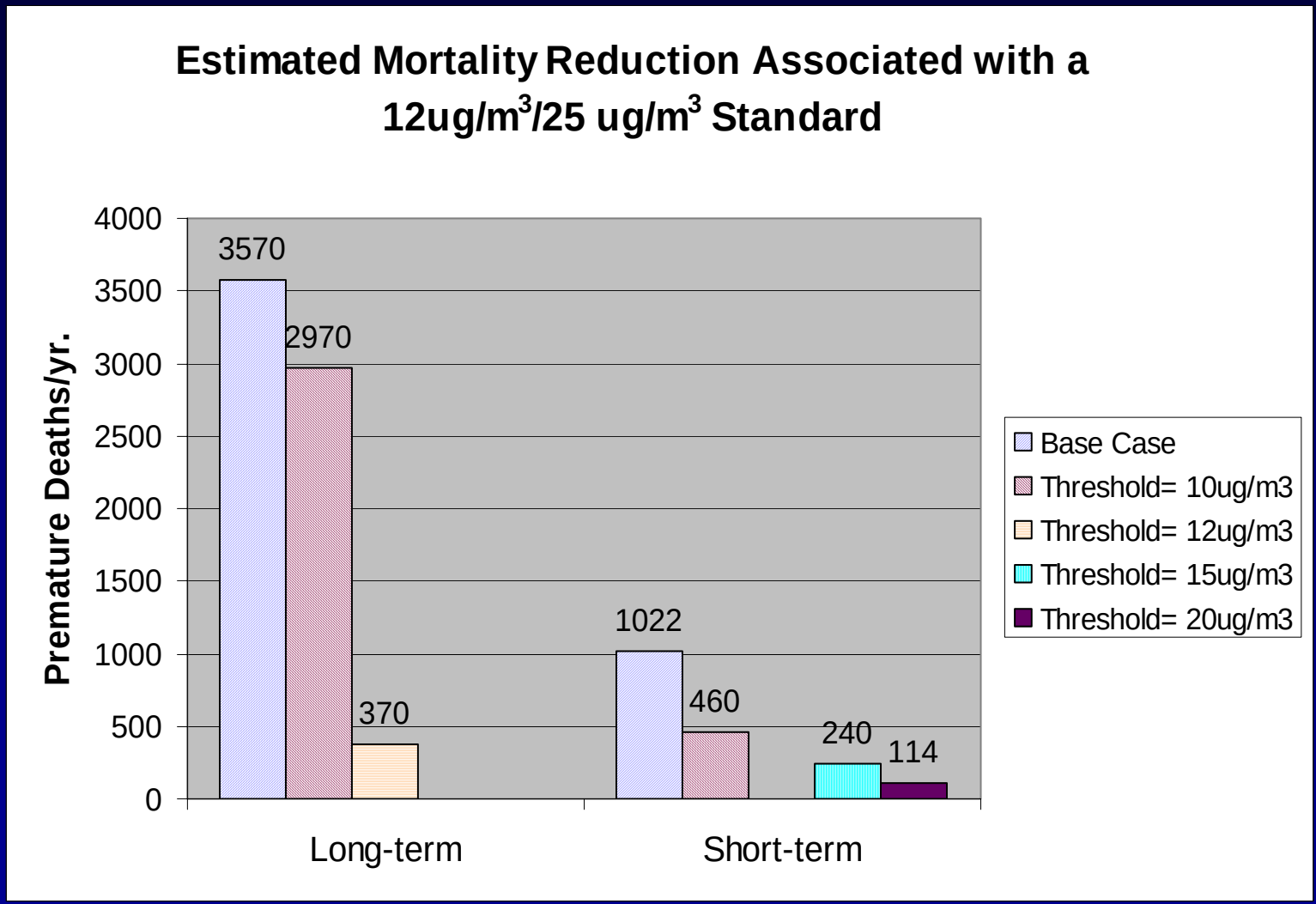


Figure 5A-1(a) **Estimated percent reduction in $PM_{2.5}$-related long-term mortality risk for alternative standards *(99th percentile form)* relative to risk associated with meeting current standards (based on assumed cutpoint of 7.5 $\mu g/m^3$).** Risk associated with meeting current $PM_{2.5}$ standards, based on ACS extended study, is shown in figures in terms of estimated annual incidence rate and annual incidence (and 95% confidence ranges).

Imposing a Threshold (Cutoff) of Effects on the PM Mortality Dose-Response Curve



Imposing a Threshold of Effects (Cutoff) on the Analysis Inappropriately Slashes Estimates of Clean Air Benefits: EPA Base Case Is Best Estimate



Implications

- New toxicological research has shown numerous effects and pathways of PM effects indicating that the epidemiological associations with morbidity and mortality are biologically plausible at ambient levels of $PM_{2.5}$.
- New epidemiological research has shown significant mortality and morbidity effects below the present $PM_{2.5}$ standards, supporting the setting of new U.S. standards at the lower end of the EPA Staff Paper's range of $PM_{2.5}$ standard options.

Acknowledgements

The Toxicology Progress portion of this presentation was based largely on progress reports presented at the most recent PM Center Directors' meeting in Washington, DC in October, 2004, including:

- Dr. Morton Lippmann, NYU
- Dr. Lung Chi Chen, NYU
- Dr. Robert Devlin, U.S. EPA