# The Science Behind the Particulate Matter (PM) Standards

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# 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

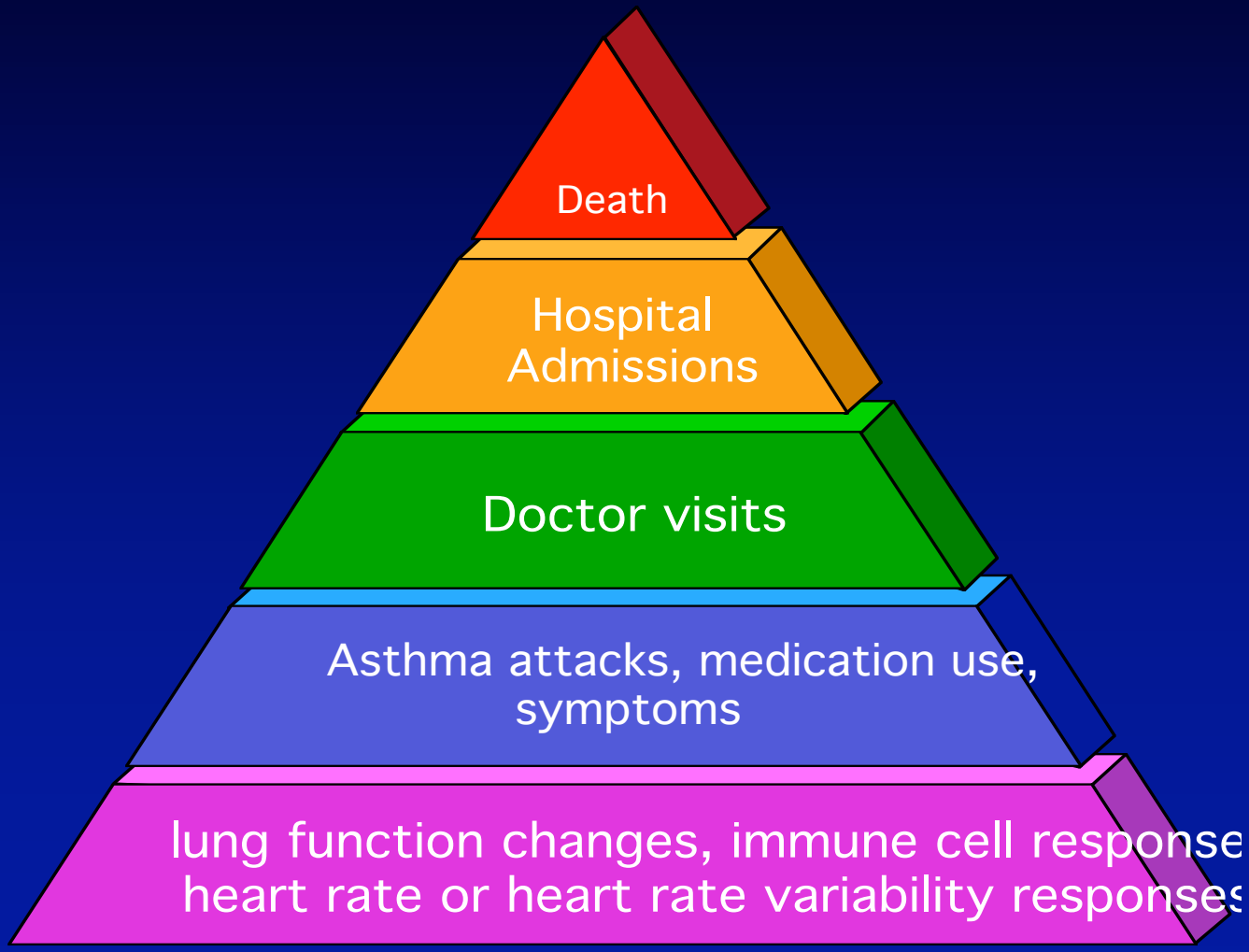
# State of the Science in 1998

- 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 = 10 x 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

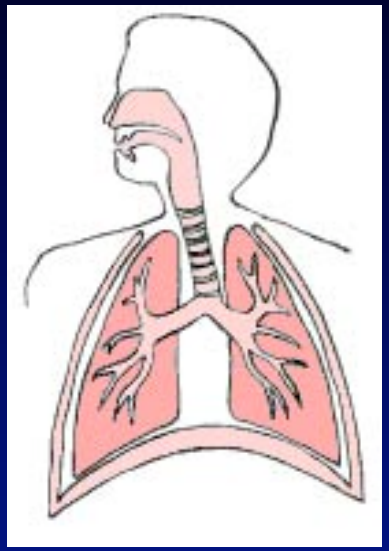


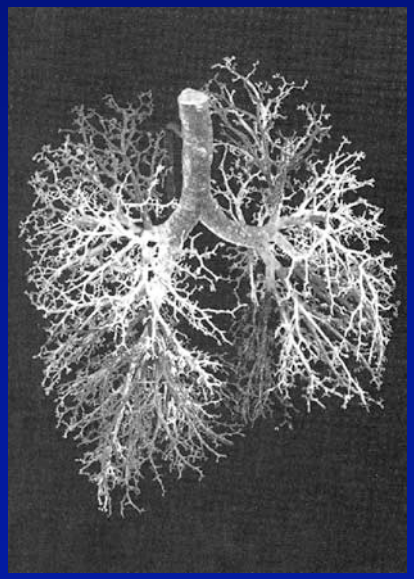
# People Most Affected by Ambient Air Pollution

- 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.

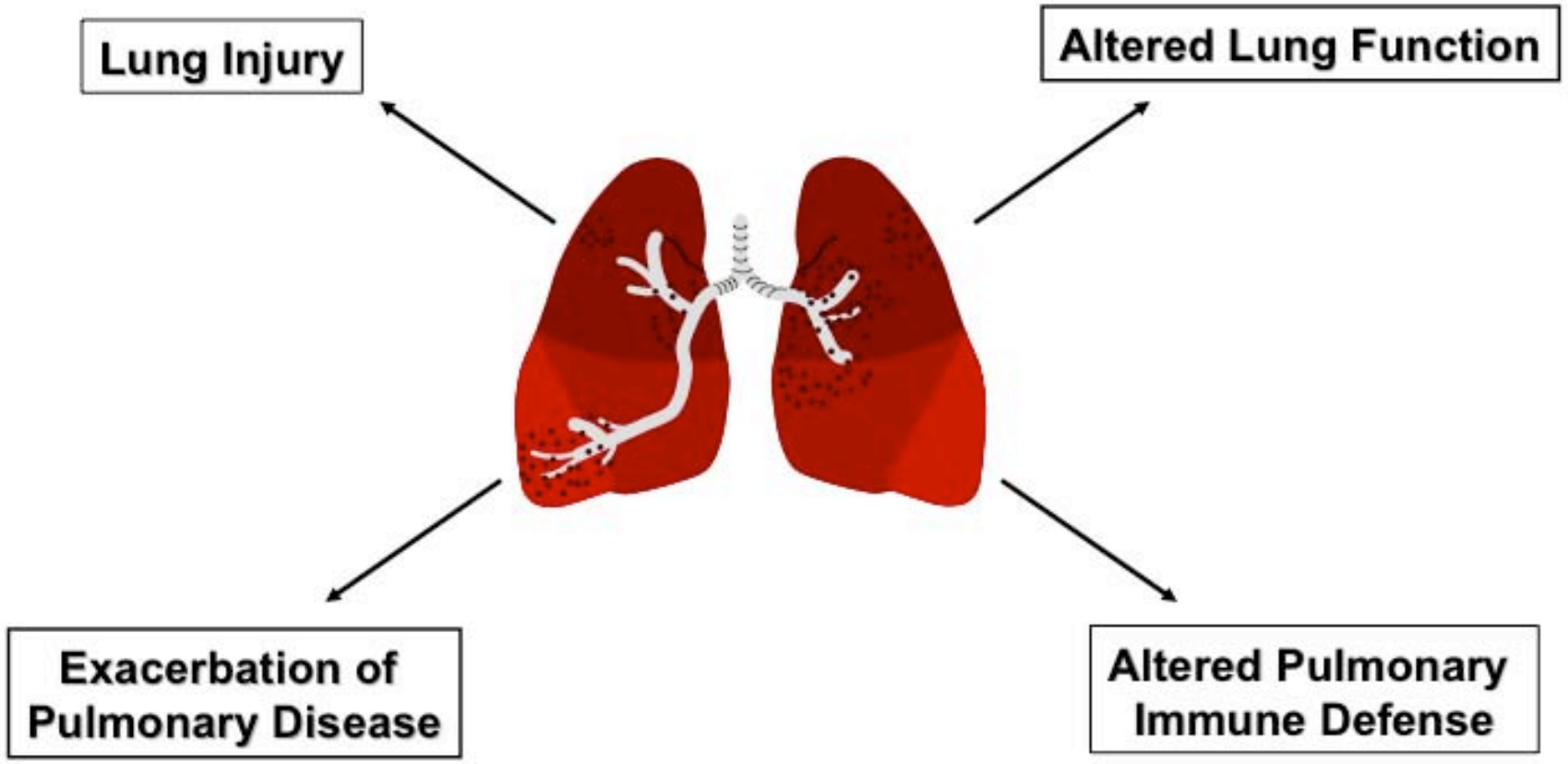
# The First NRC Report

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

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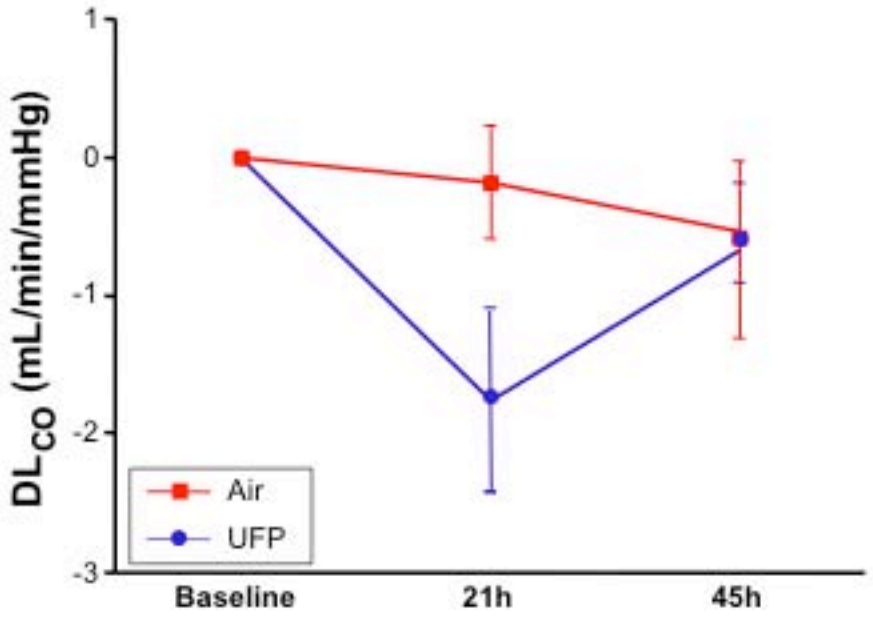
# PM Causes Changes in Lung Function

**Humans exposed to ultrafine particles have decreased diffusing capacity.**

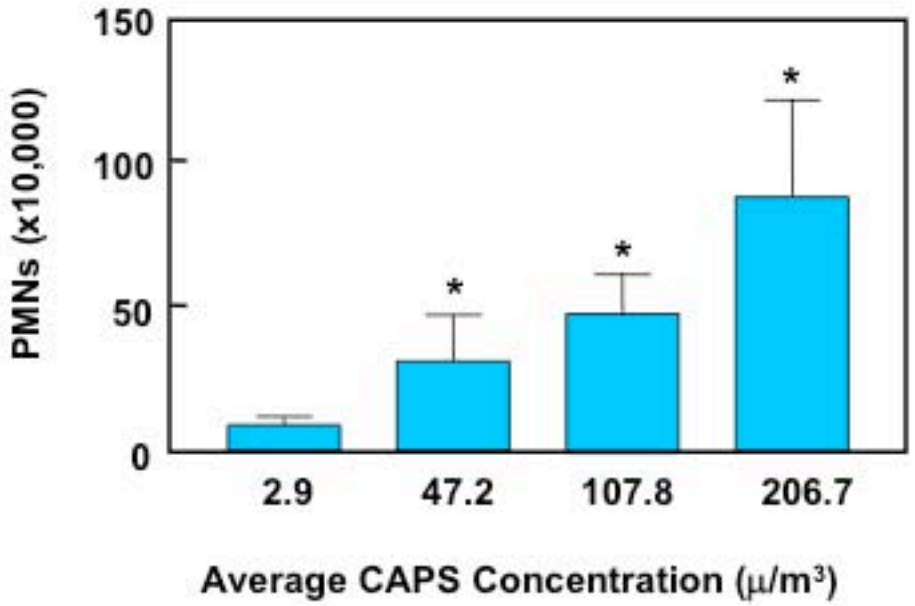



**Diffusing capacity is a measure of oxygen transfer from the lungs to the blood**

Pietropaoli, et al., 2004

# PM Causes Lung Inflammation

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

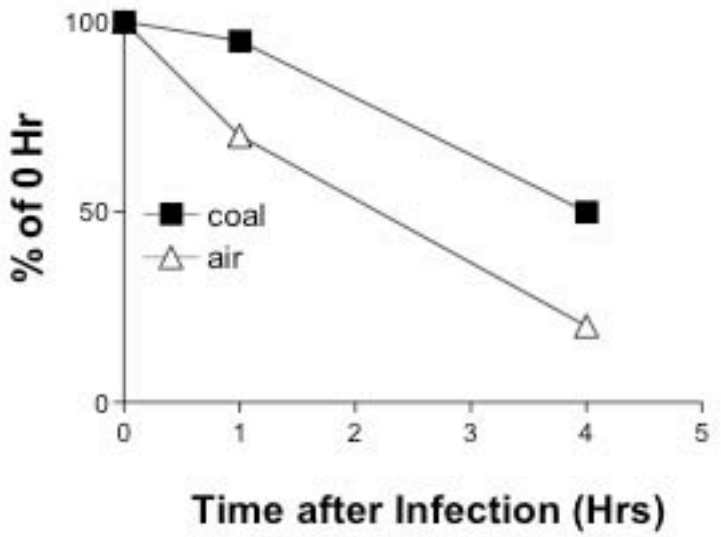



Ghio et al., 2001

# PM Depresses Clearance and Inactivation of Bacteria

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

## Inactivation



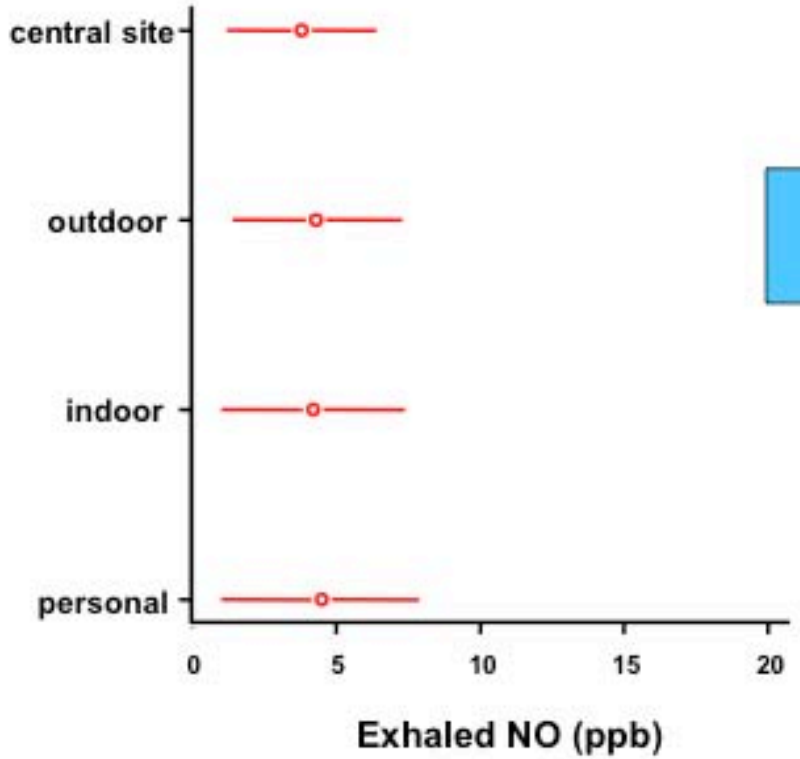

## Host Resistance Model

| | Control | Woodstove |
|---|---|---|
| % Mortality (Streptococcus) | 0 | 21 |

Gilmour et al., 2002

# PM Exposure Exacerbates Asthma

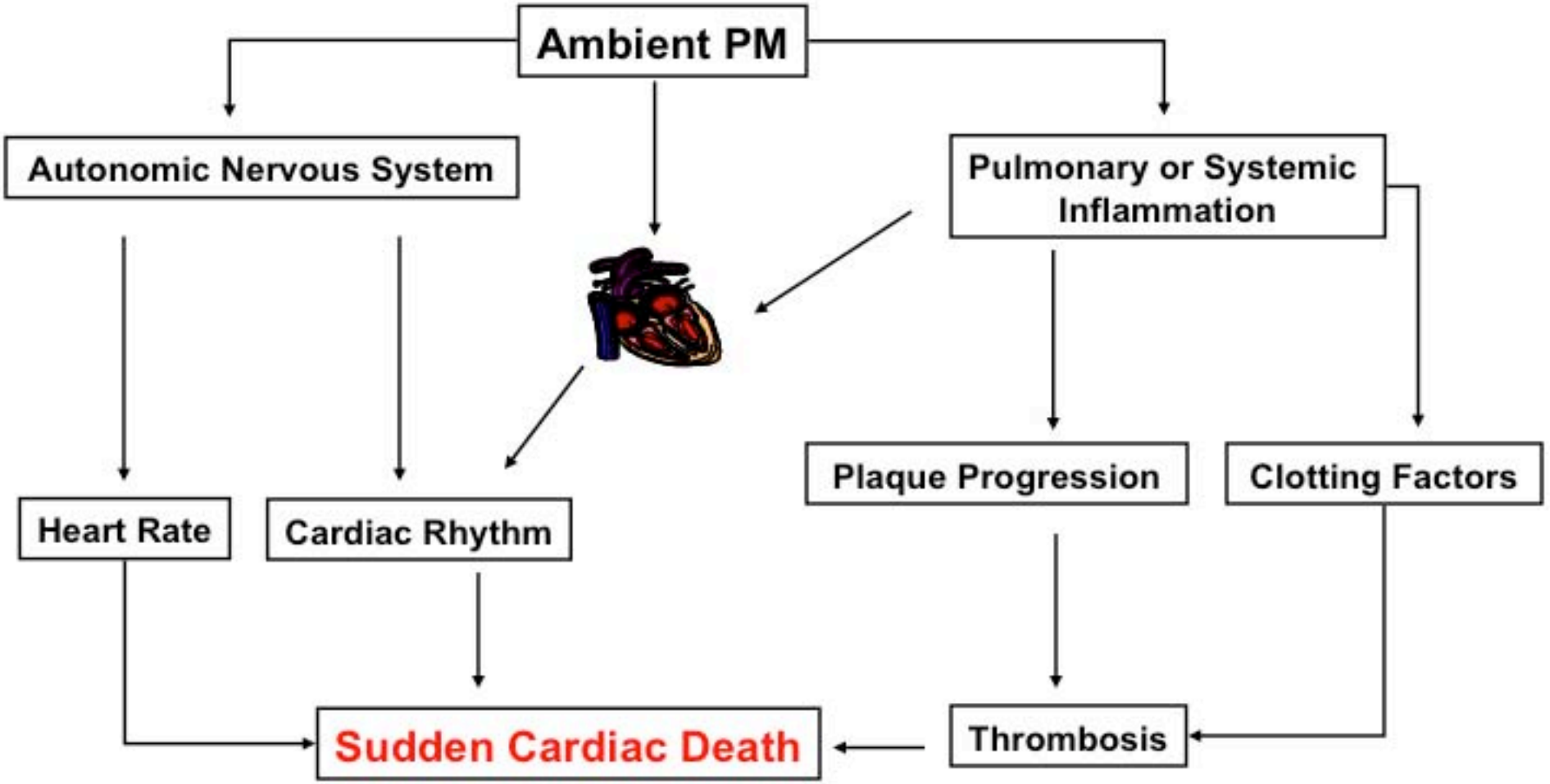
**Change in exhaled nitric oxide per 10 μg/m$^3$ increase in $PM_{2.5}$ in children with asthma**




NO is an indication of pulmonary inflammation

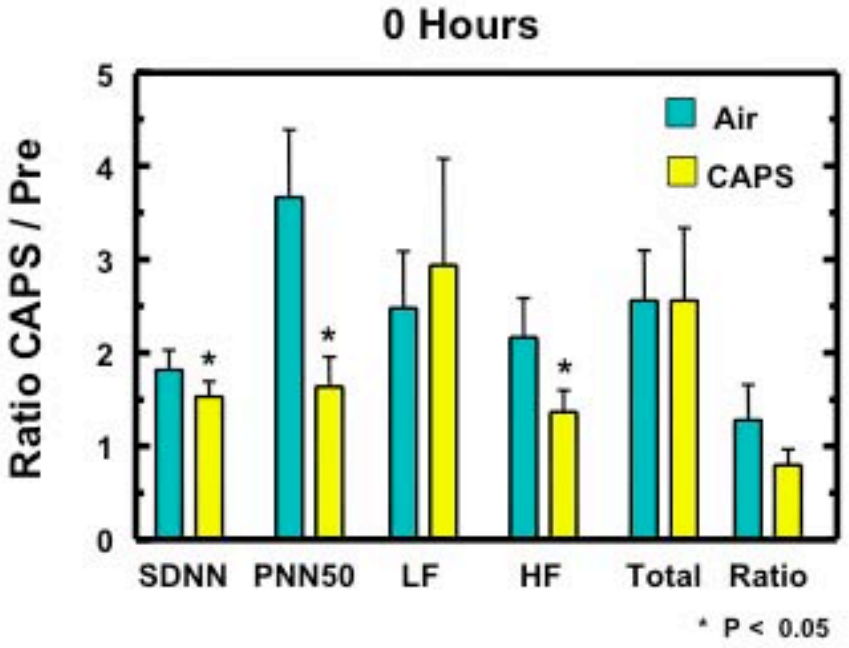
Koenig et al., 2003

# 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).**



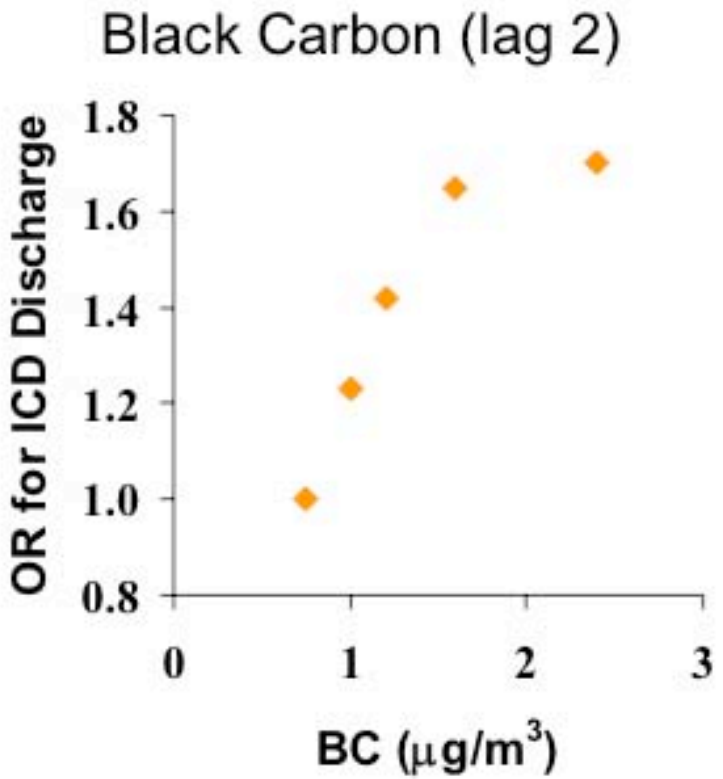

**People with cardiovascular disease who have decreased HRV have a higher risk of getting a heart attack.**

Devlin et al, 2003

# PM Triggers Cardiac Arrhythmias in Humans

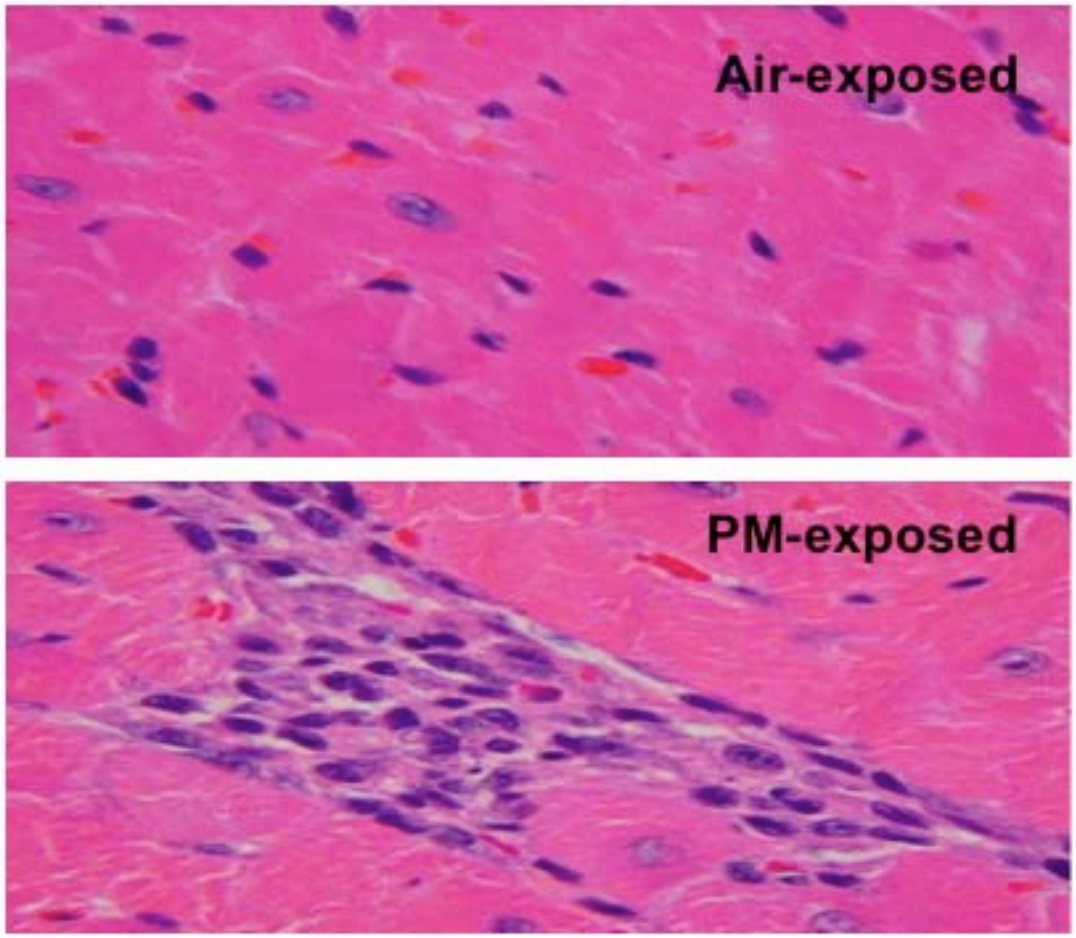
**The number of times that implanted defibrillators discharged were related to prior days levels of PM and PM components**

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




Peters et al, 2000

# PM Causes Injury to Cardiac Cells

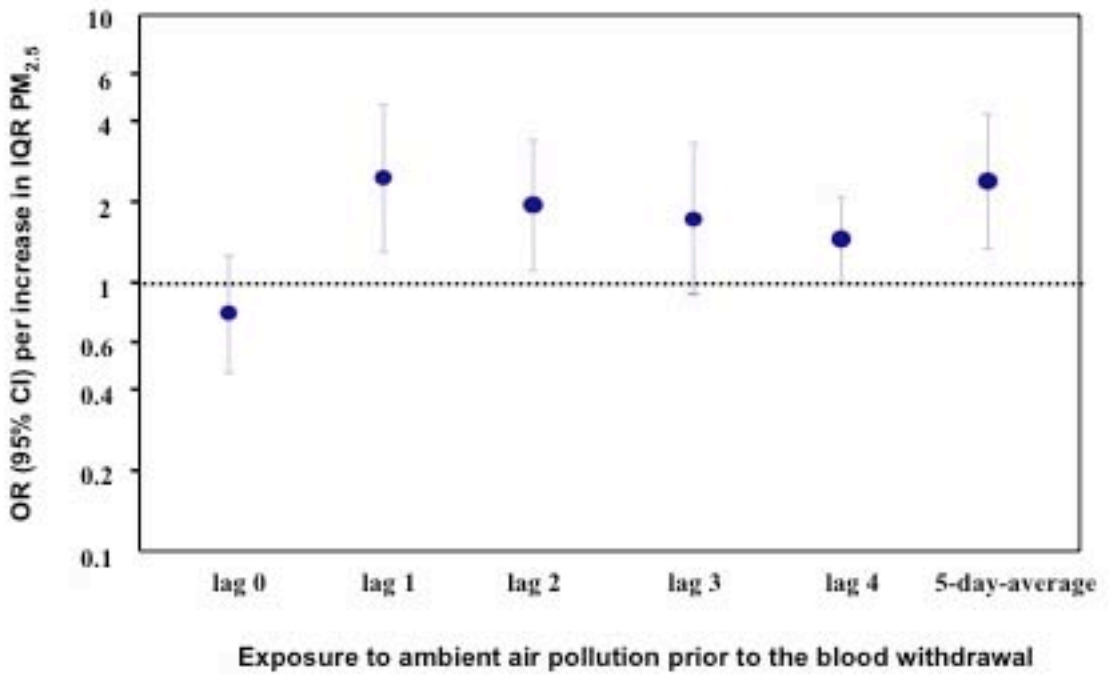



Rats exposed to ambient PM one day per week for 16 weeks

Kodavanti et al., 2003

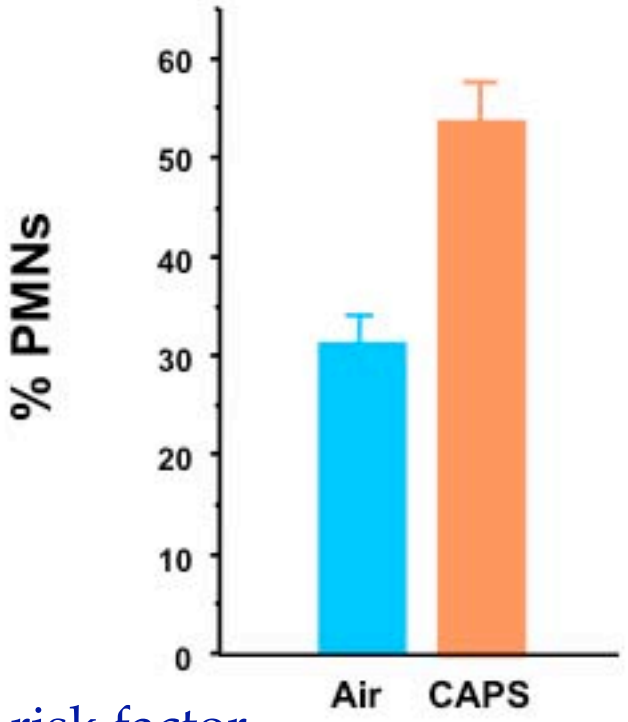
# PM Increases Vascular Inflammation

**Increase in blood C Reactive Protein in Humans**




Rueckerl et al., 2004

**Increase in blood PMNs in Rats Exposed to CAPS**




Gordon et al., 2000

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

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

(Source: Peters et al, EHJ, 2001)

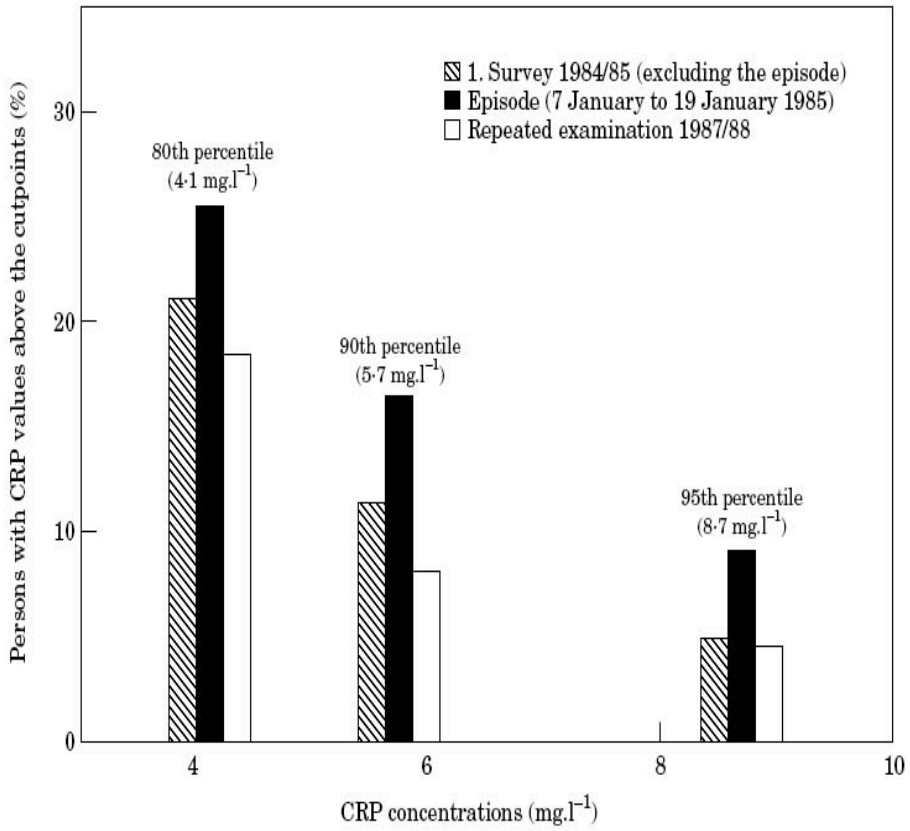



*Figure 1* Influence of the air pollution episode 1985 on the distribution of elevated C-reactive protein (CRP) values.

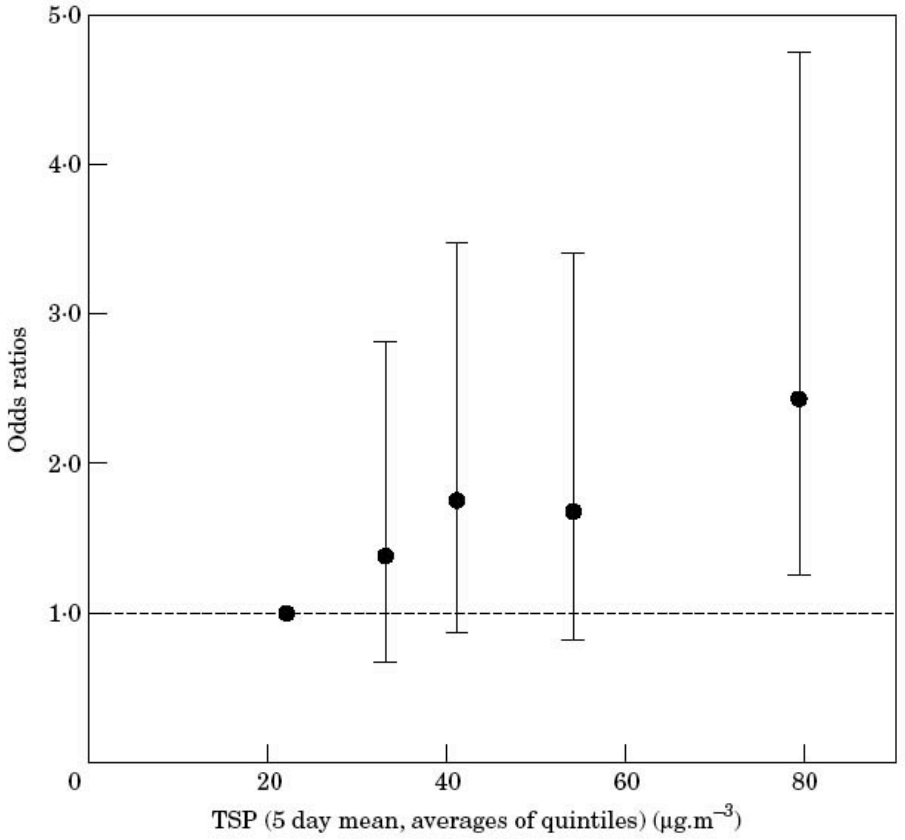



*Figure 2* Multivariate regression results for quintiles of total suspended particulates (TSP) on C-reactive protein concentrations above 5·7 mg . l$^{-1}$ (90th percentile).

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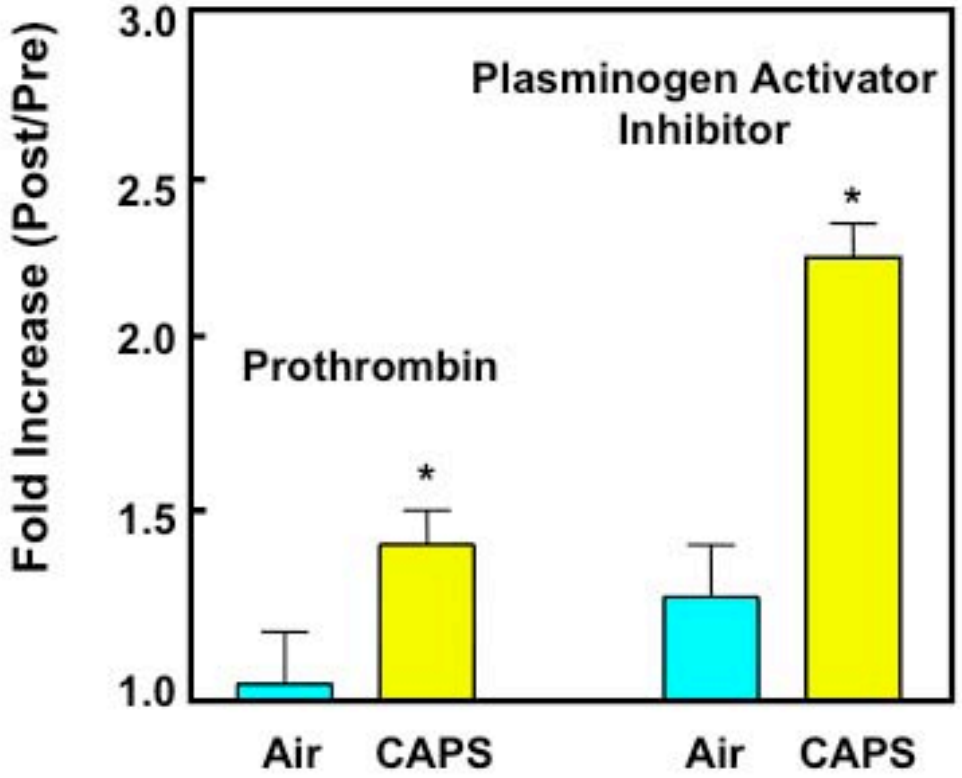
# Acidic Sulfates, Transition Metals, and Oxidative Stress

- **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.

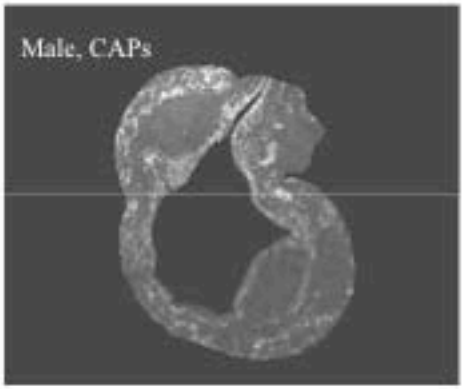
The net changes in these factors could potentially lead to an environment conducive to the formation of blood clots.

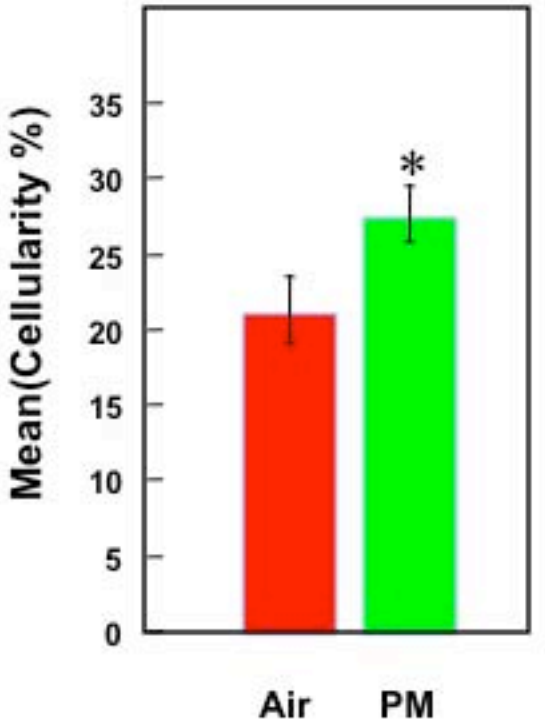



Devlin et al, 2004

# 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/m³) increases plaque cellularity.**

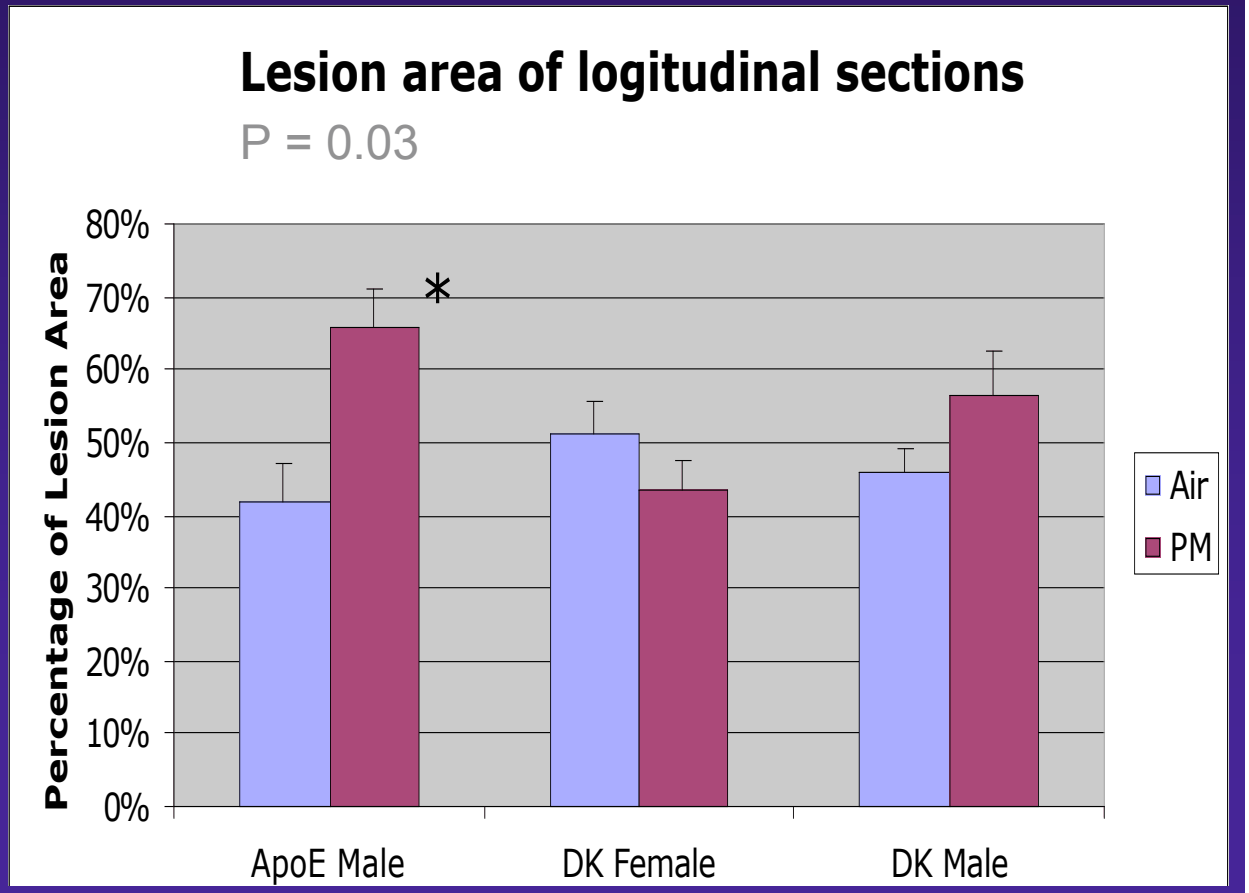




Chen et al., JAMA (in press), 2005

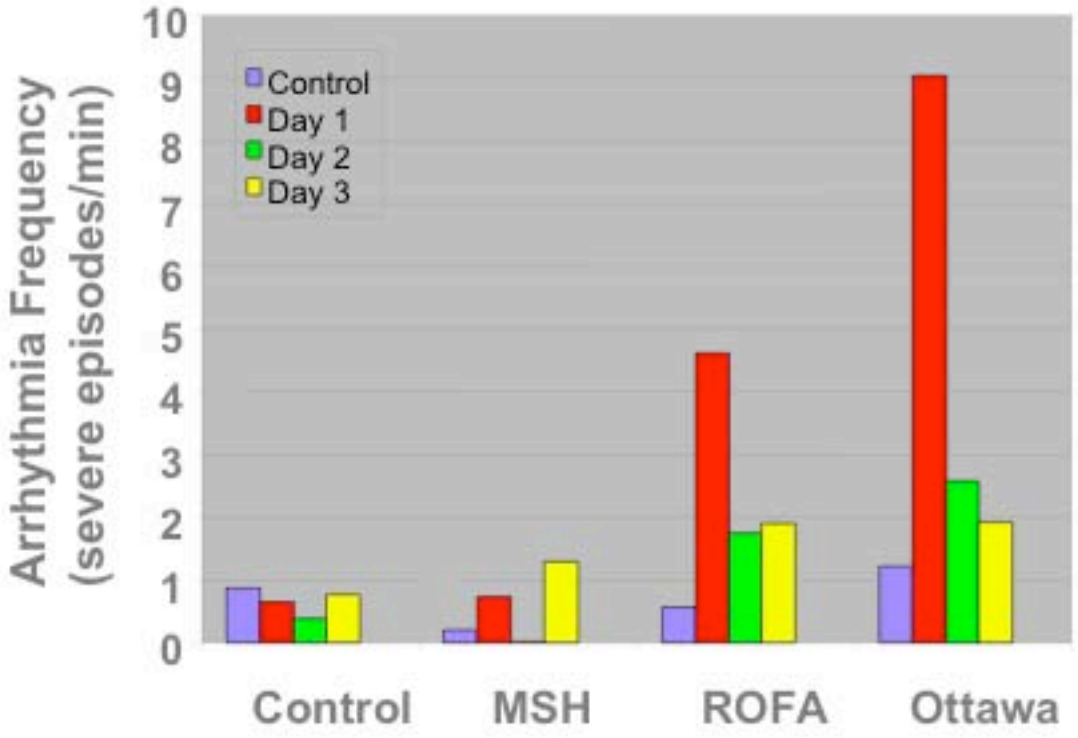
C57 Air | ApoE Air | ApoE PM

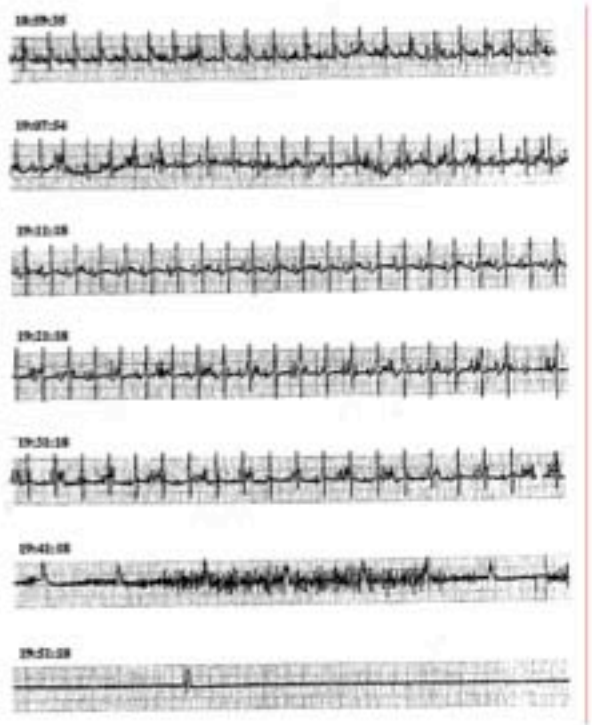
# Effects of CAPs on aorta plaque size demonstrated in ApoE KnockOut Mice



# 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*

# Toxicology Progress Summary

## Mechanistic Studies Have:

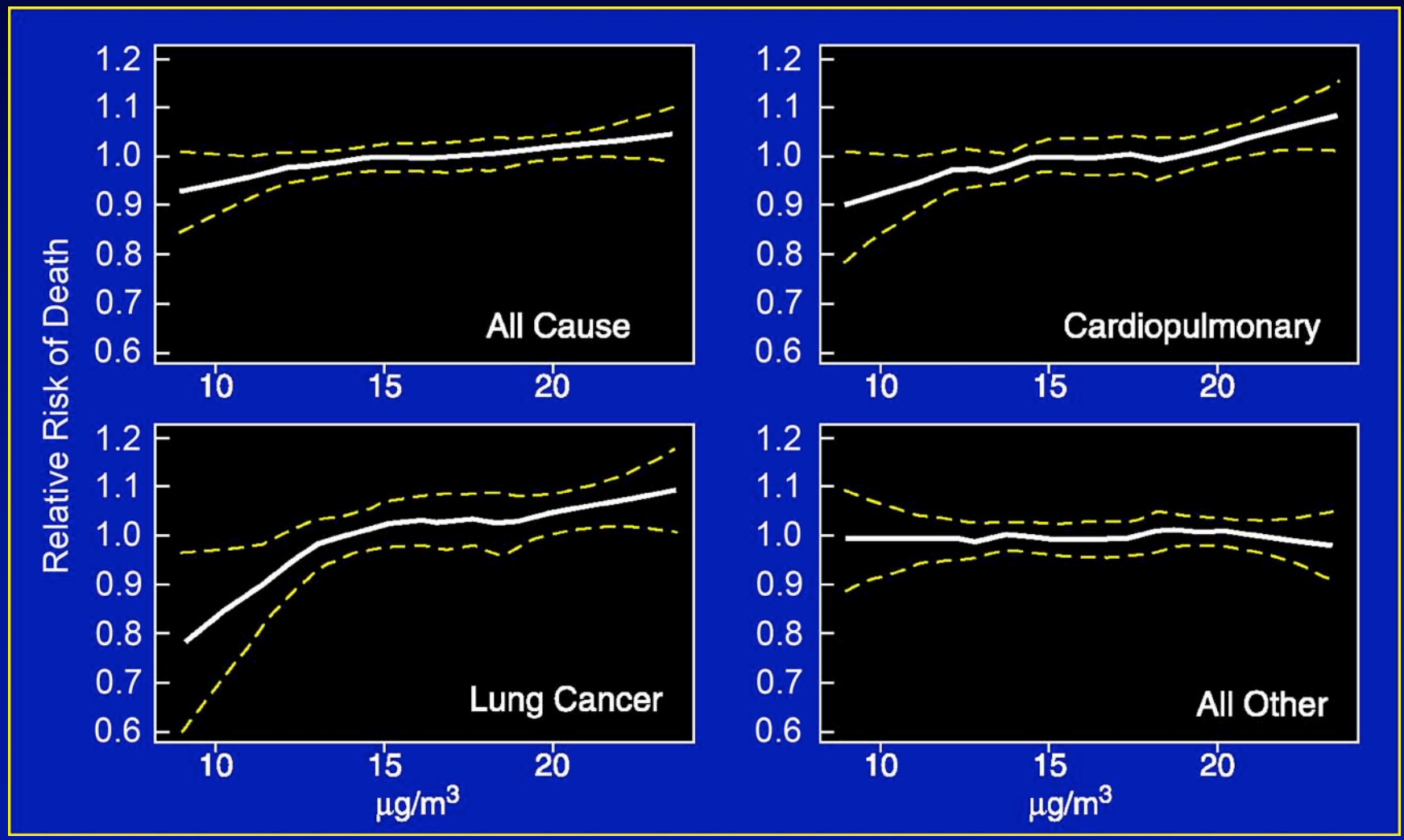
- Defined several biologically plausible patho-physiological pathways by which PM can increase mortality and morbidity.
- Provided coherence to the epidemiology studies and extended their observations, thus strengthening the science in support of the PM standard.

# Epidemiologic Evidence Also Strengthened Since 1998

- Dozens of 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 Below 10 ug/$m^3$

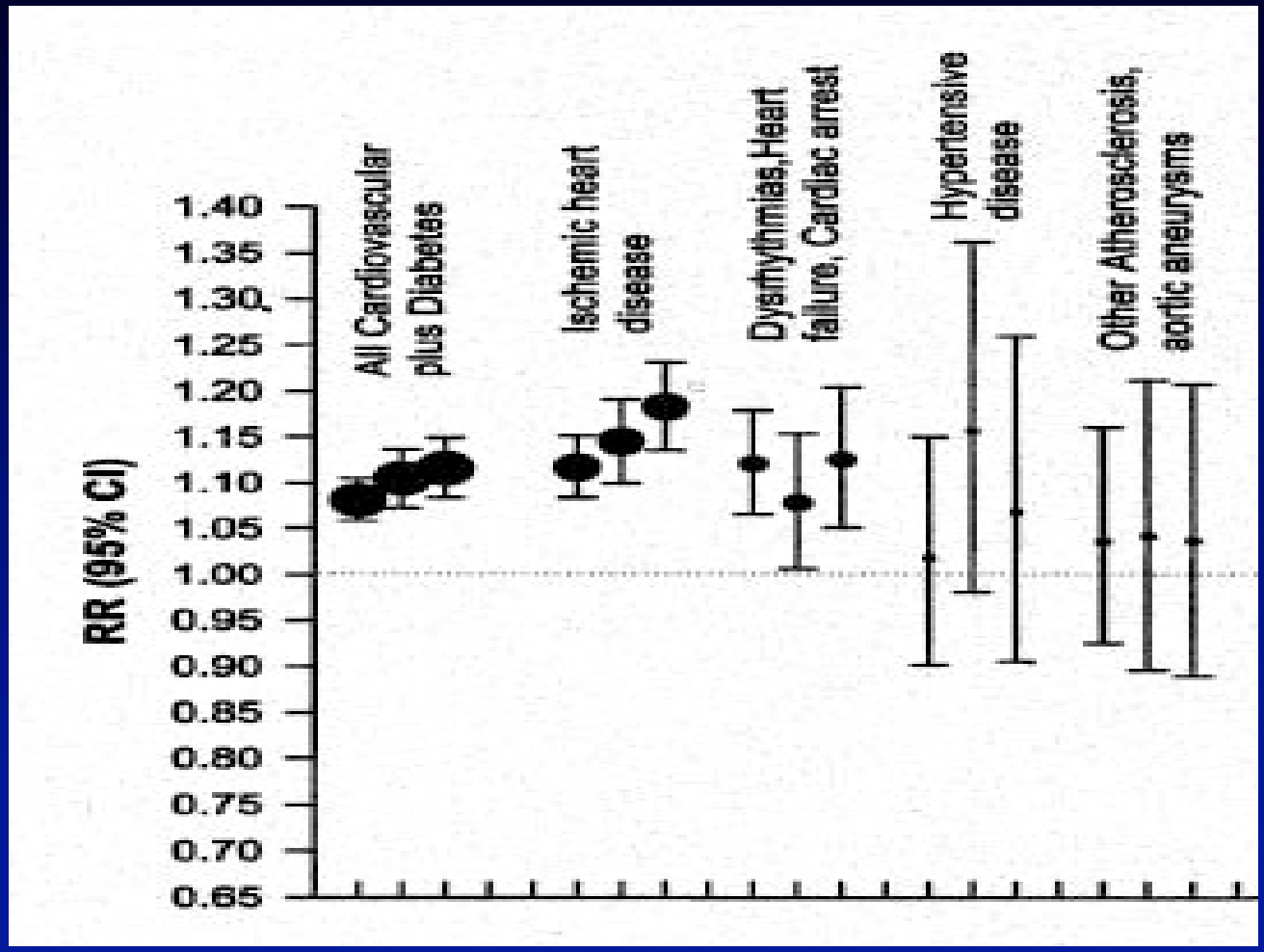
(Pope, Burnett, Thun, Calle, Krewski, Ito , and Thurston) (JAMA, 2002)



# 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.

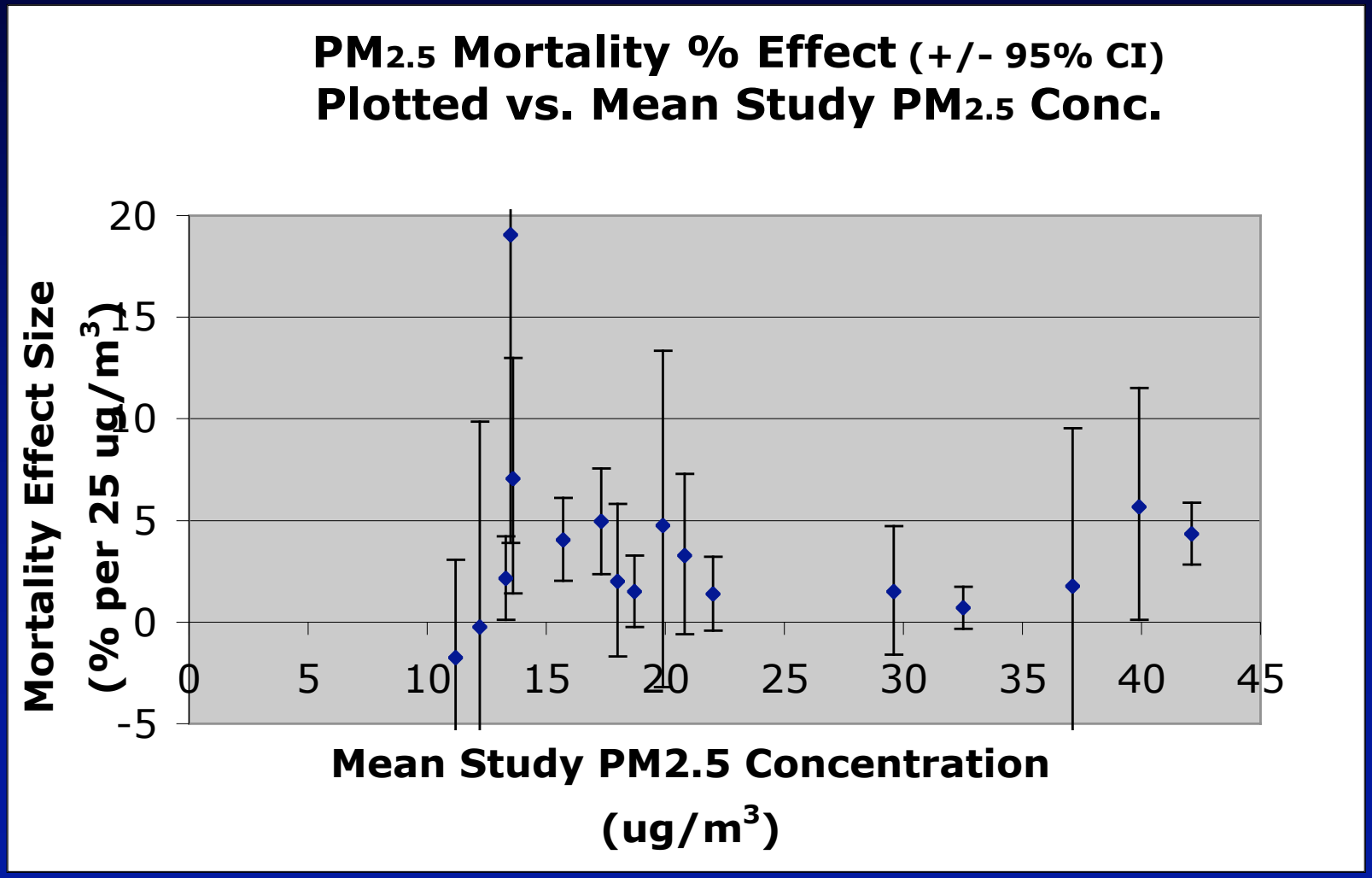
# Cardiovascular Mortality Most Affected by Long Term Particulate Matter Air Pollution Exposures




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)

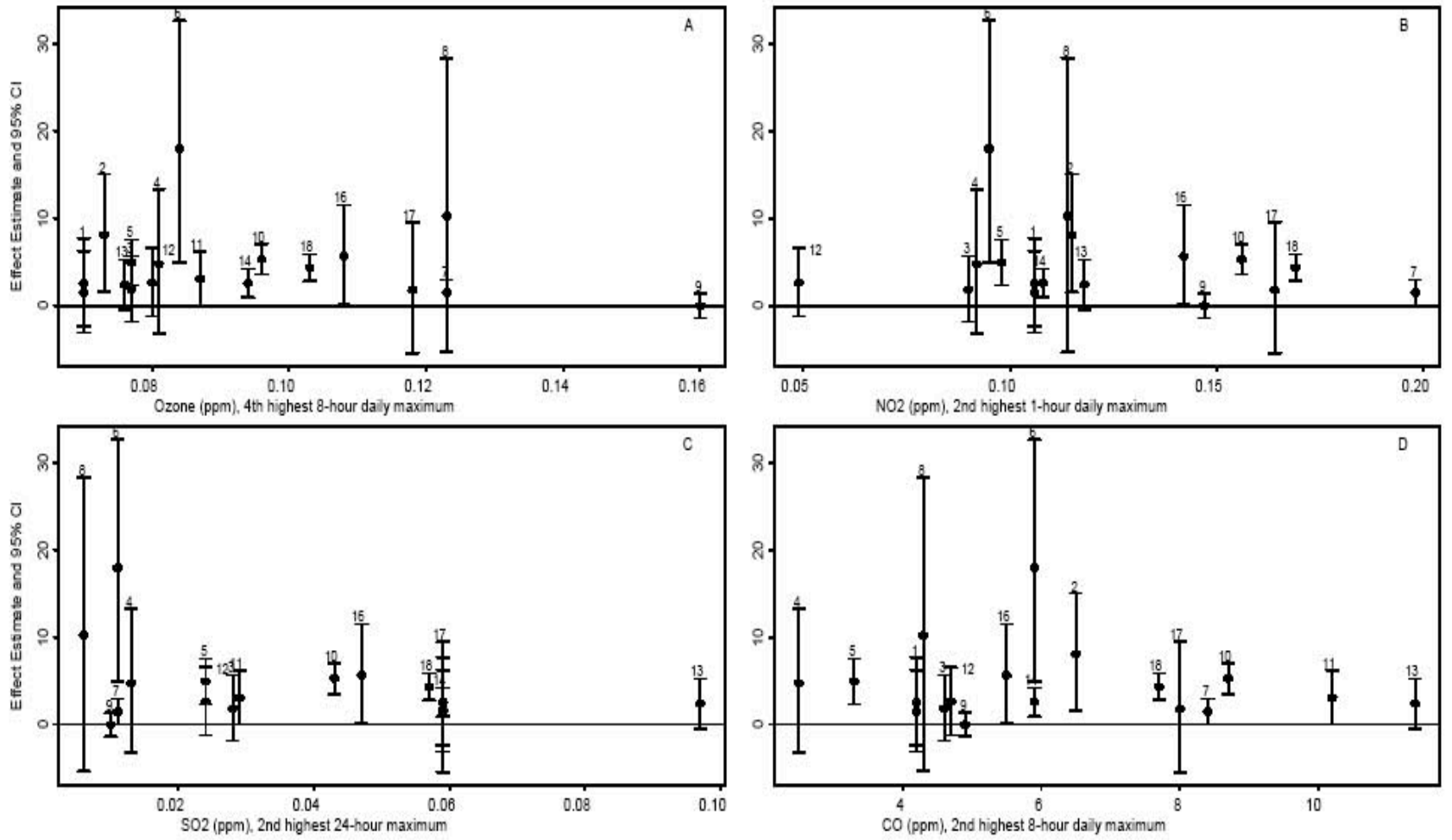
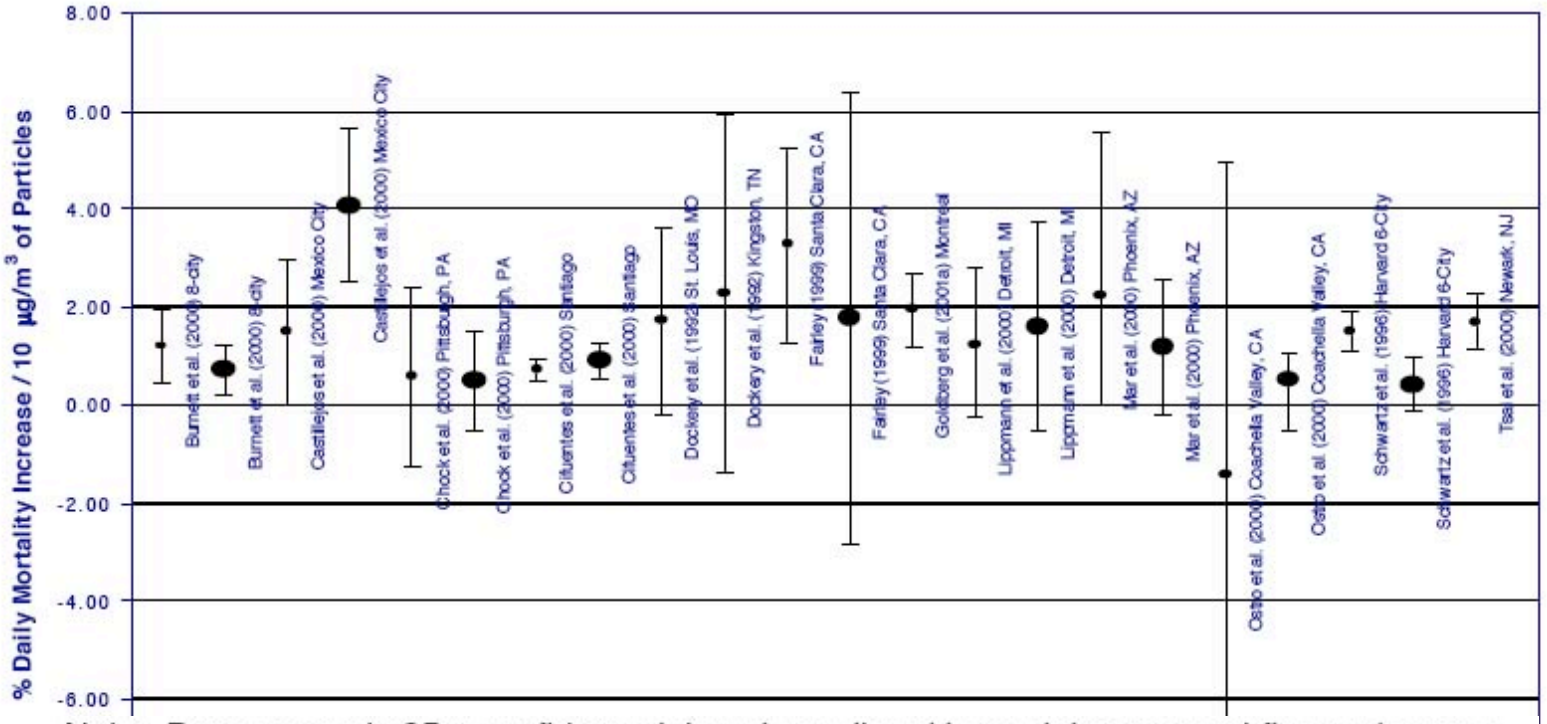



**Figure 3-3. Associations between $PM_{2.5}$ and total mortality from U.S. studies, plotted against gaseous pollutant**

# 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$^3$

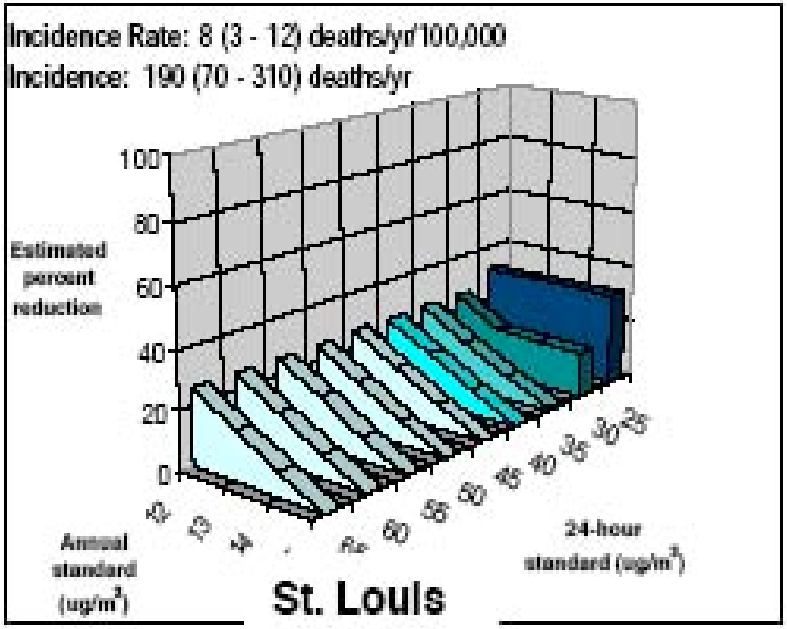



**Figure 5-2(a)** **Estimated percent reduction in $PM_{2.5}$-related short-term mortality risk for alternative standards *(98th percentile form)* relative to risk associated with meeting current standards (based on assumed cutpoint equal to policy-relevant background).** Risk associated with meeting 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.**

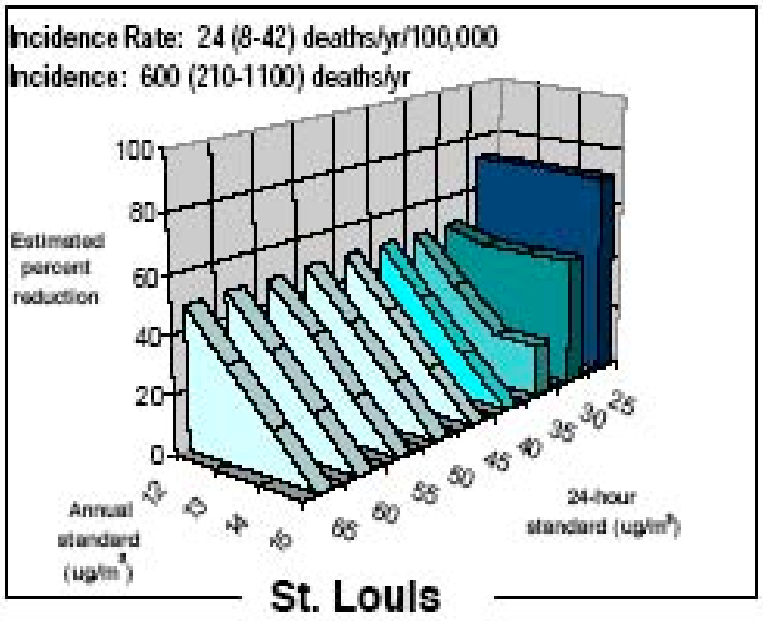
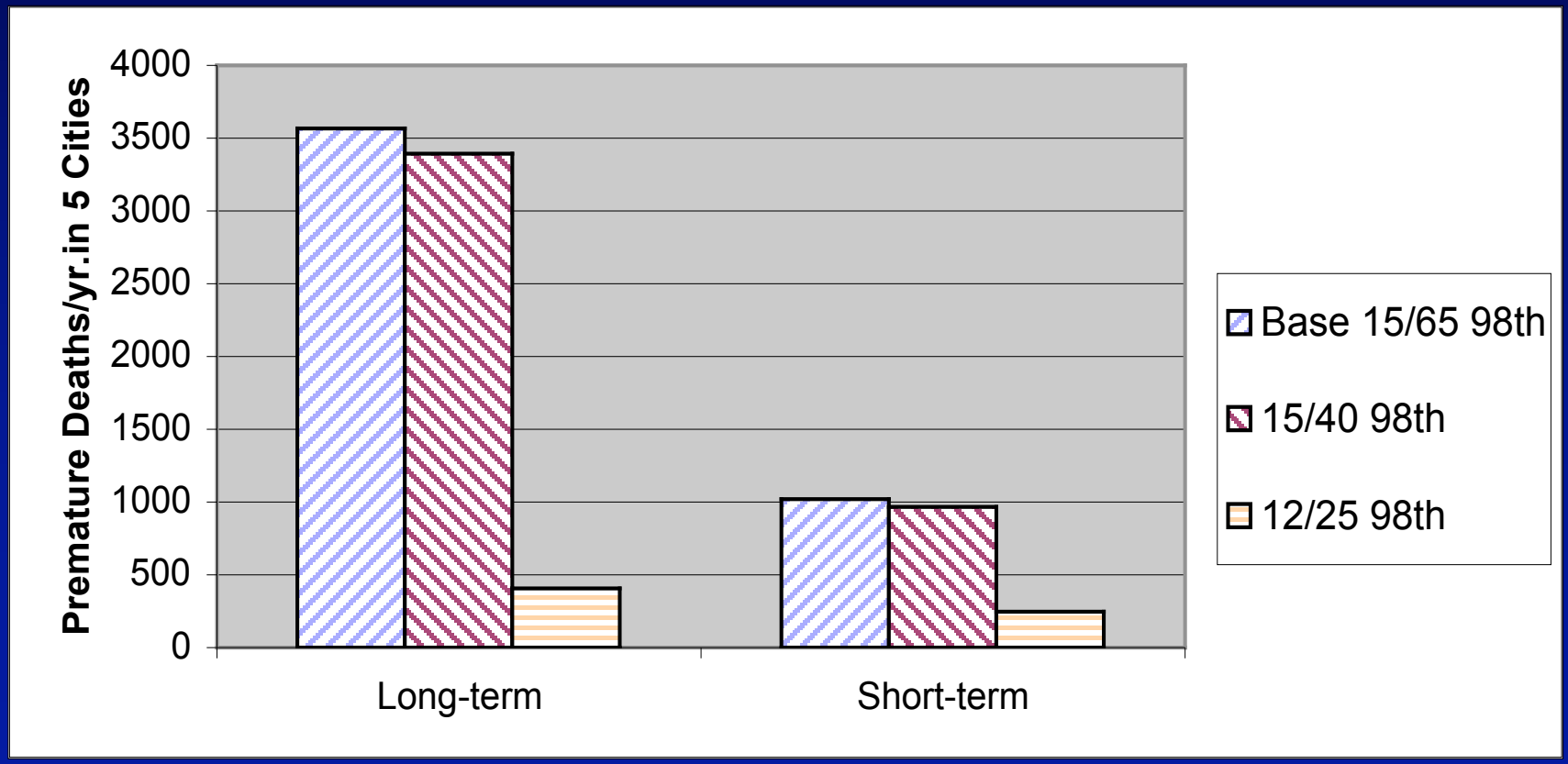


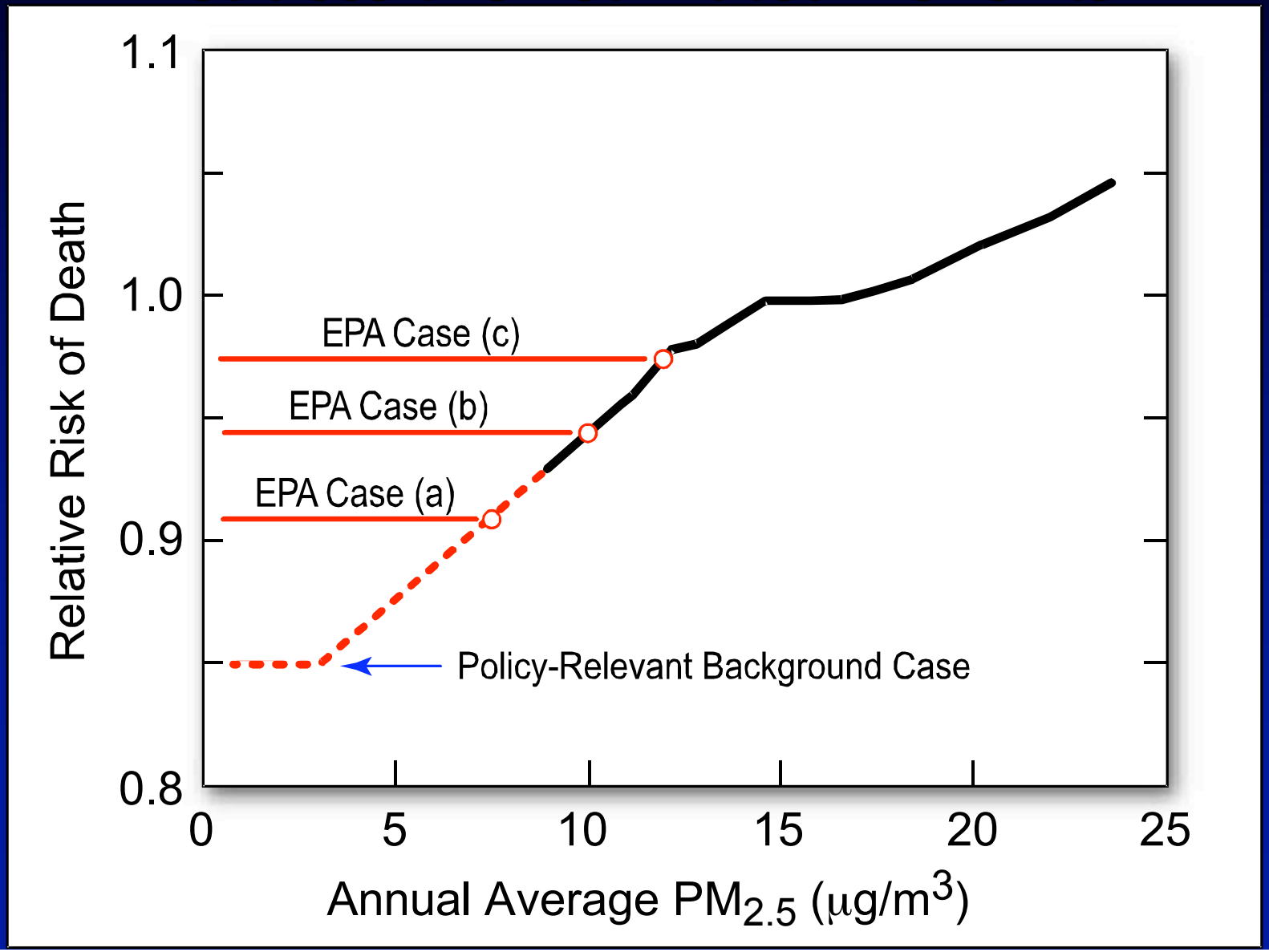

**Figure 5A-1(a)** **Estimated percent reduction in $PM_{2.5}$-related long-term mortality risk for alternative standards *($99^{th}$ percentile form)* relative to risk associated with meeting current standards (based on assumed cutpoint of 7.5 $\mu g/m^3$).** Risk associated with meeting current $PM_{2.5}$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

# Most Mortality Benefits are Associated With Lowering the Annual Average $PM_{2.5}$

## (Source: U.S. EPA PM Staff Paper, 2005)

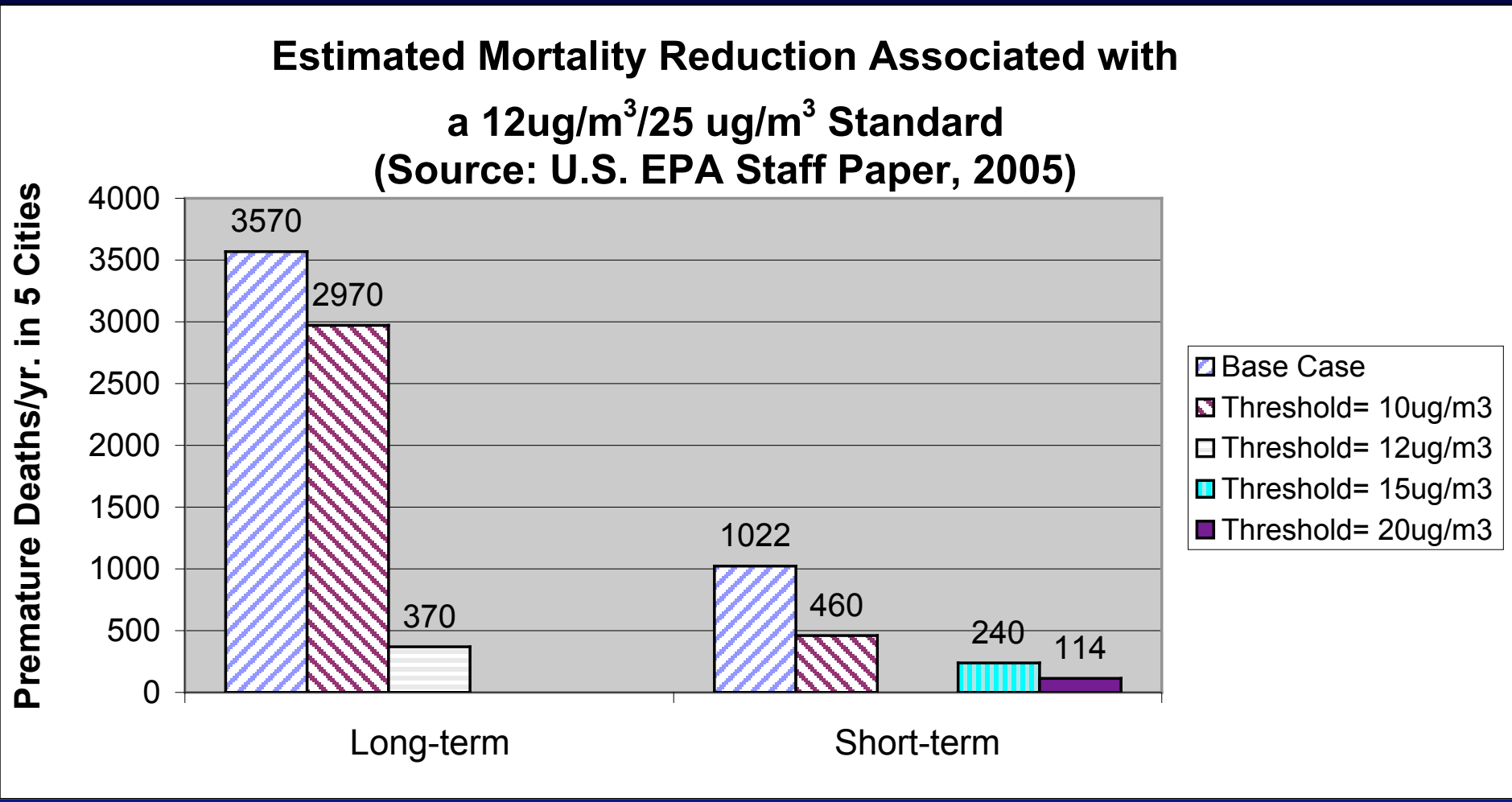


# But Mathematically Imposing a Threshold (Cutoff) of Effects on the PM Mortality Curve Reduces the Estimated Benefits



# 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