Assessment of Health Hazards of Repeated Inhalation of Diesel Emissions, with Comparisons to Other Source Emissions

Joe Mauderly
(et <u>many</u> al.)

NATIONAL ENVIRONMENTAL RESPIRATORY CENTER

Because you <u>never</u> breathe only one pollutant

Lovelace Respiratory Research Institute, Albuquerque, NM

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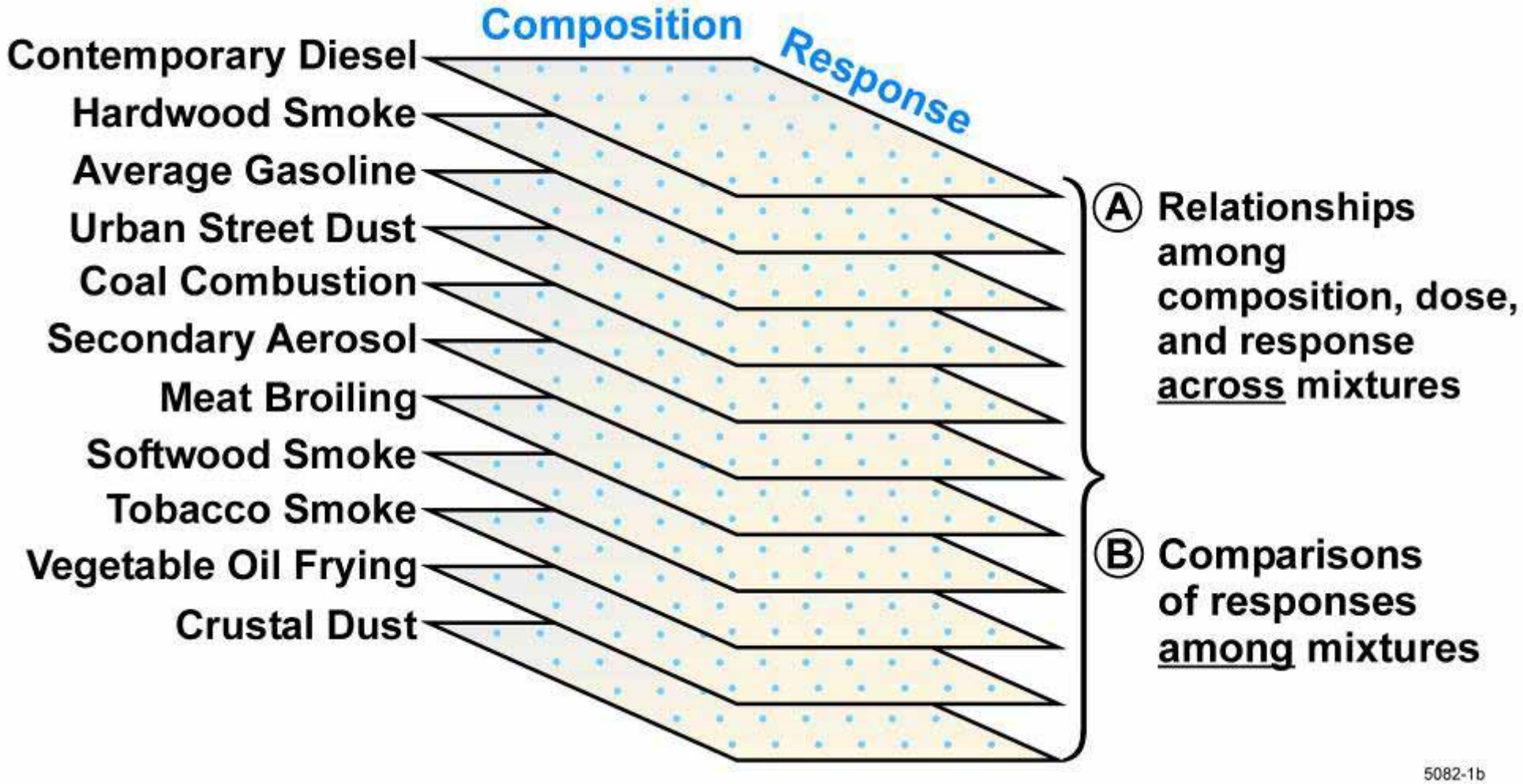
Strategy: Build and analyze a composition-concentration-response data matrix



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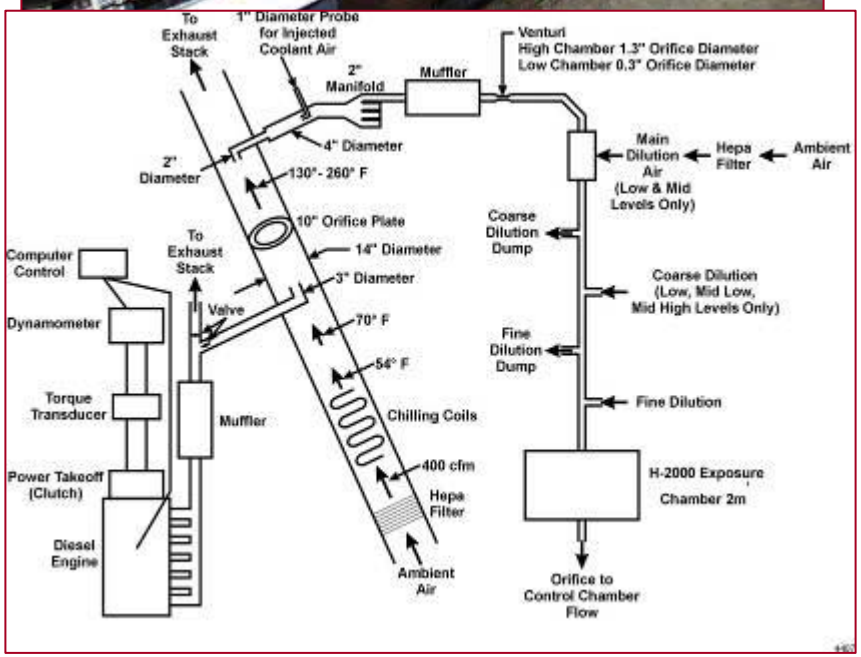
STATUS OF THE NERC PROGRAM

- Exposure to diesel emissions is completed, nearly all results analyzed, and several papers published
- Exposure to hardwood smoke is completed, many data analyzed, and papers are in process
- Exposure to gasoline emissions being initiated at this time
- Exposure to urban street dust scheduled next. We are collecting dust
- Exposure to simulated "downwind" coal emissions is planned, and key components of the atmosphere are defined
- Exposure to simulated secondary aerosol (e.g., organic, sulfate, nitrate) is under discussion

DIESEL EMISSIONS



2000 Cummins 5.9L ISB 6 cyl. Turbo

D-2 Cert. Fuel (370 ppm S, 29% aromatics)

Shell Rotella® 15W-40 crankcase oil

Stock exhaust system with muffler

Repeated heavy-duty certification cycle

Cold start excluded

Emissions diluted with carbon- and HEPA-filtered air

Expose at 1000, 300, 100, 30, 0 µg PM/m^3 (dilutions ≈ 1:10 to 1:300)

(Now a baseline for "Clean Diesel"

[Reed et al., *Inhal. Toxicol*. 16:177, 2004]

[McDonald et al., *Env. Sci. Technol*. 38: 2513, 2004]

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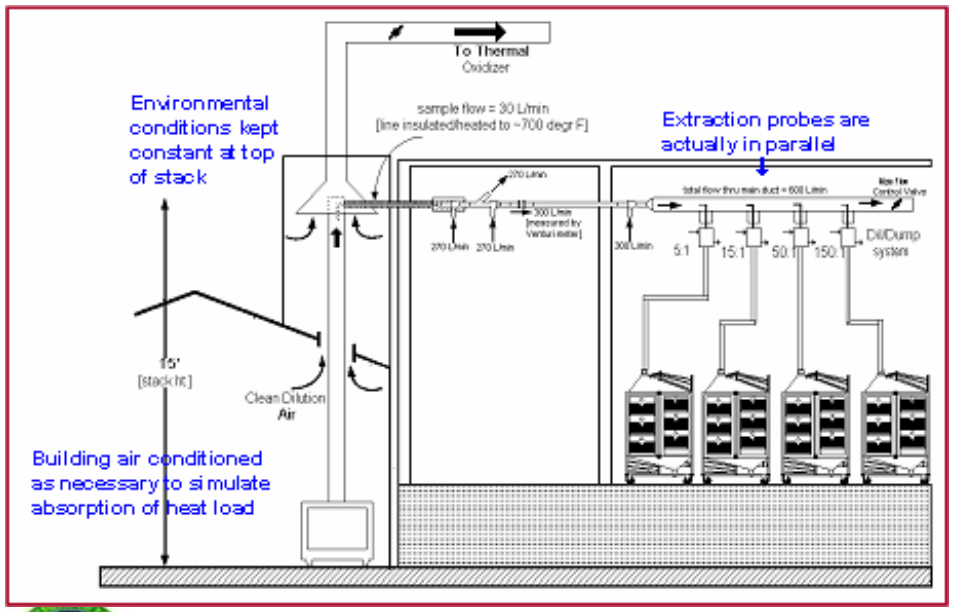
HARDWOOD (OAK) SMOKE



Uncertified heating stove (Pineridge, 2 ft^2)

Scaled room, air conditioned to absorb heat load

Oak from Missouri at 20% moisture

15 ft (4.6 m) stack from floor of stove

Constant draft conditions at top of stack

3-phase burn cycle

Extracted smoke 0.3 m from top of stack

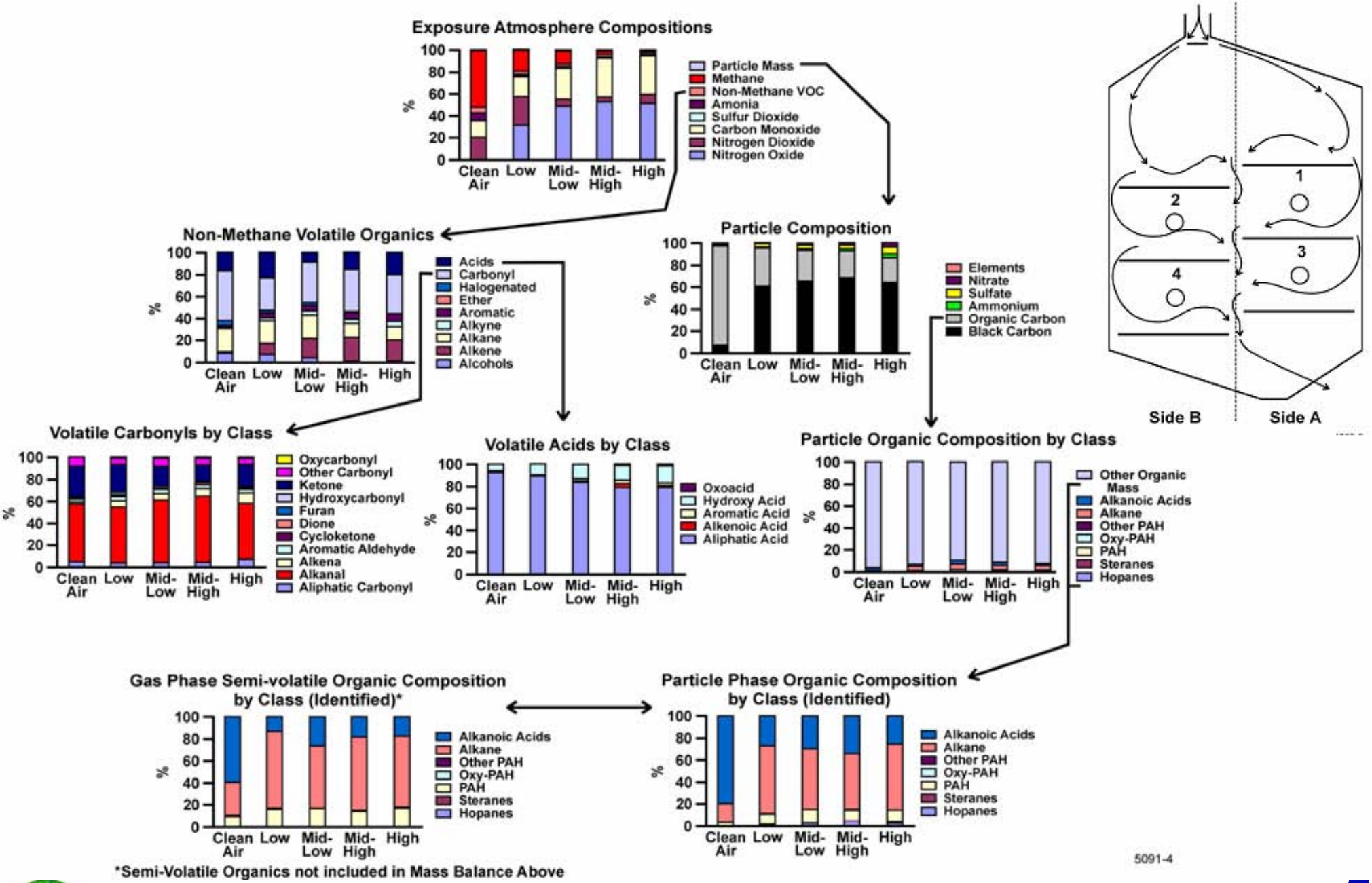
Exposed at same PM mass concentration as diesel - 1000, 300, 100, 30, 0 µg/m^3

(Dilutions ≈ 1:300 to 1:9000)

[Reed et a., *Am. J. Respir. Crit. Care Med.* 169:561, 2004]

EXPOSURES ARE CHARACTERIZED IN DETAIL

(in the animal exposure chambers)



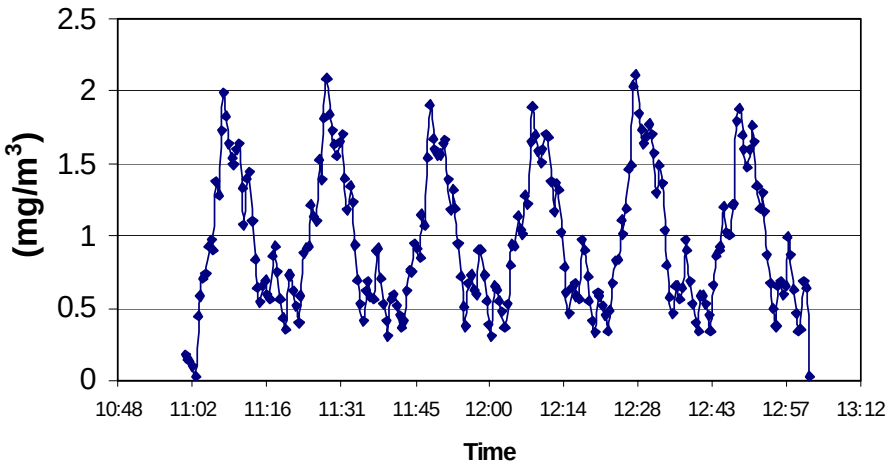
*Semi-Volatile Organics not included in Mass Balance Above

[McDonald et al., *Env. Sci. Technol.* 38: 2513, 2004]

PARTICLE MASS AND NUMBER

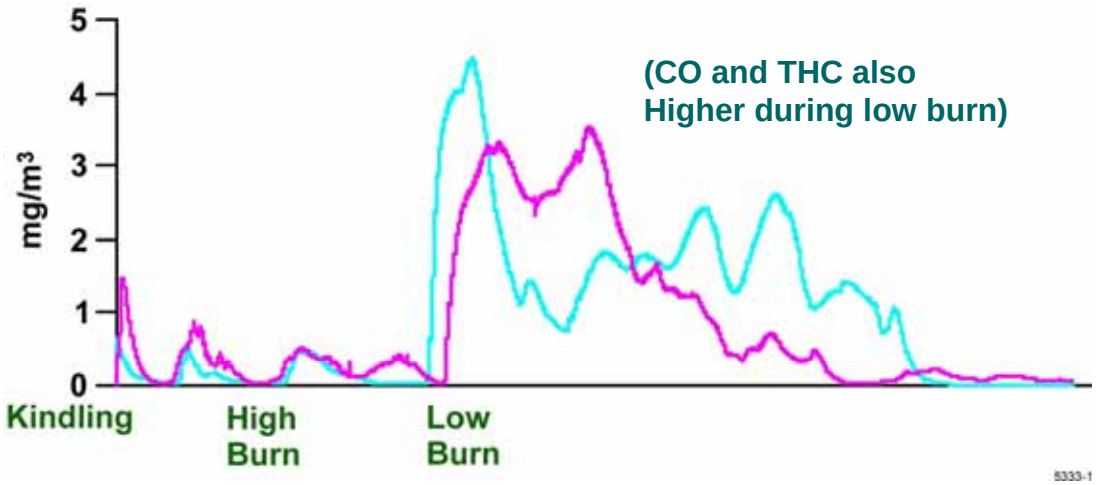
Diesel

PM Concentration in High Level Chamber During Multiple Cycles



Hardwood Smoke

PM Concentration in High Level Chamber During a 6-hr Day



[McDonald et al., *Env. Sci. Technol*. 38: 2513, 2004]

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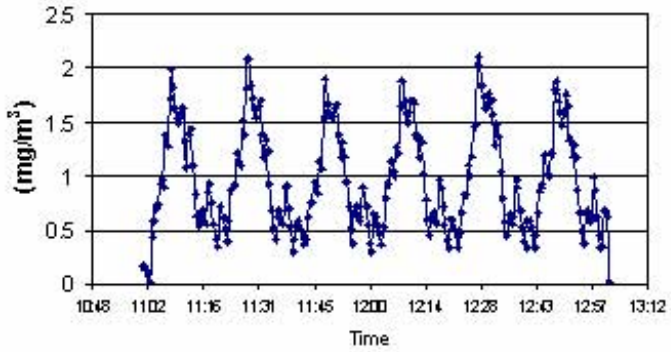

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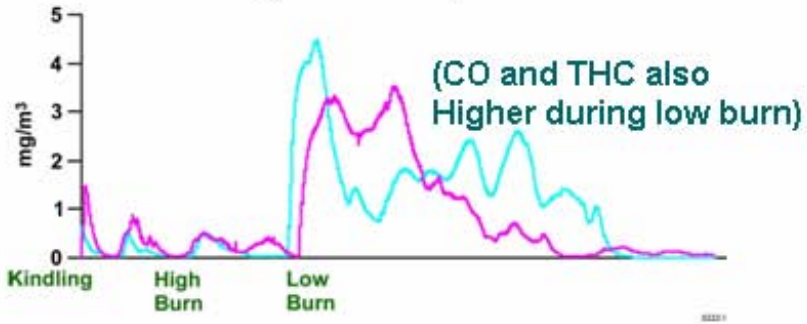
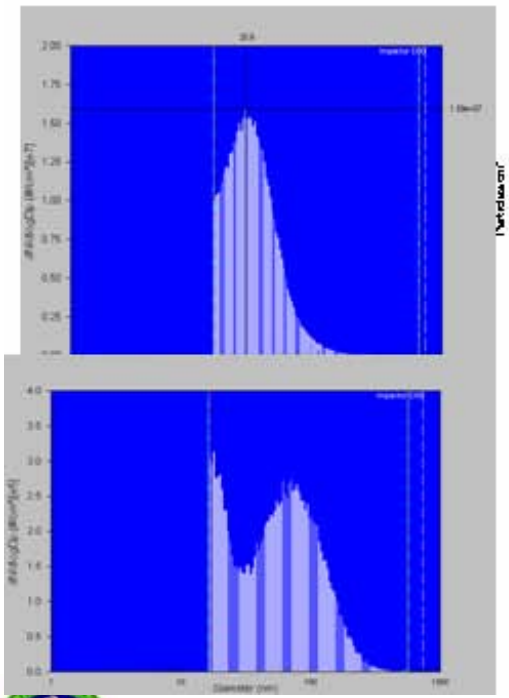
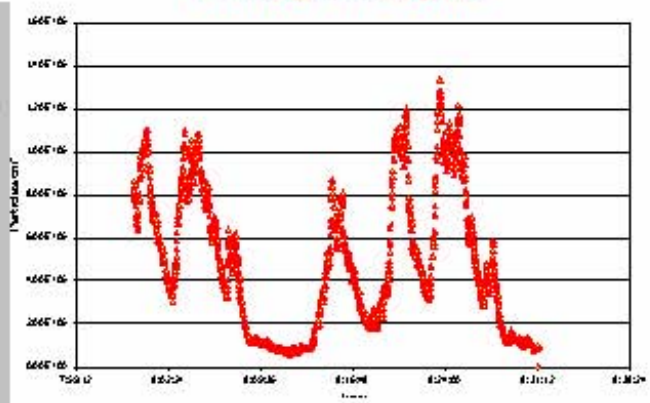
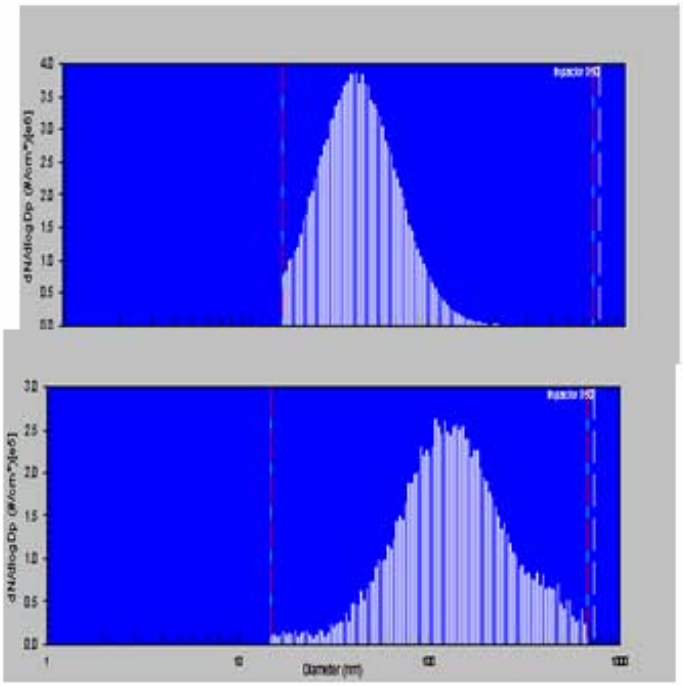


2 Points in Cycle



Number of 20 nm Particles/cc
During One Cycle





High
Burn

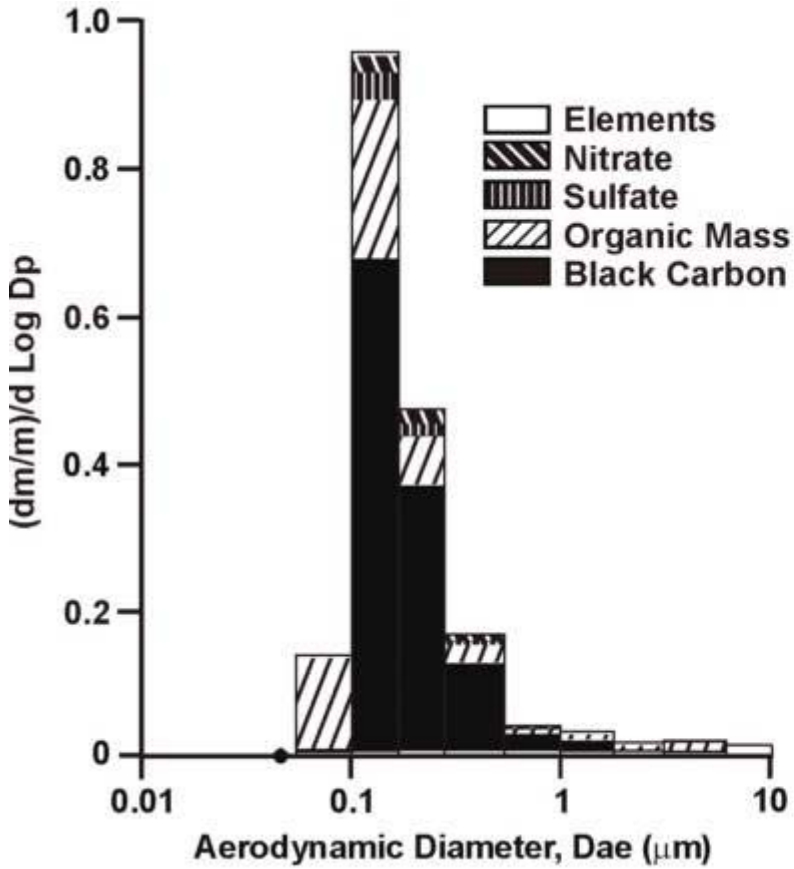
Low
Burn

[McDonald et al., *Env. Sci. Technol*. 38: 2513, 2004]

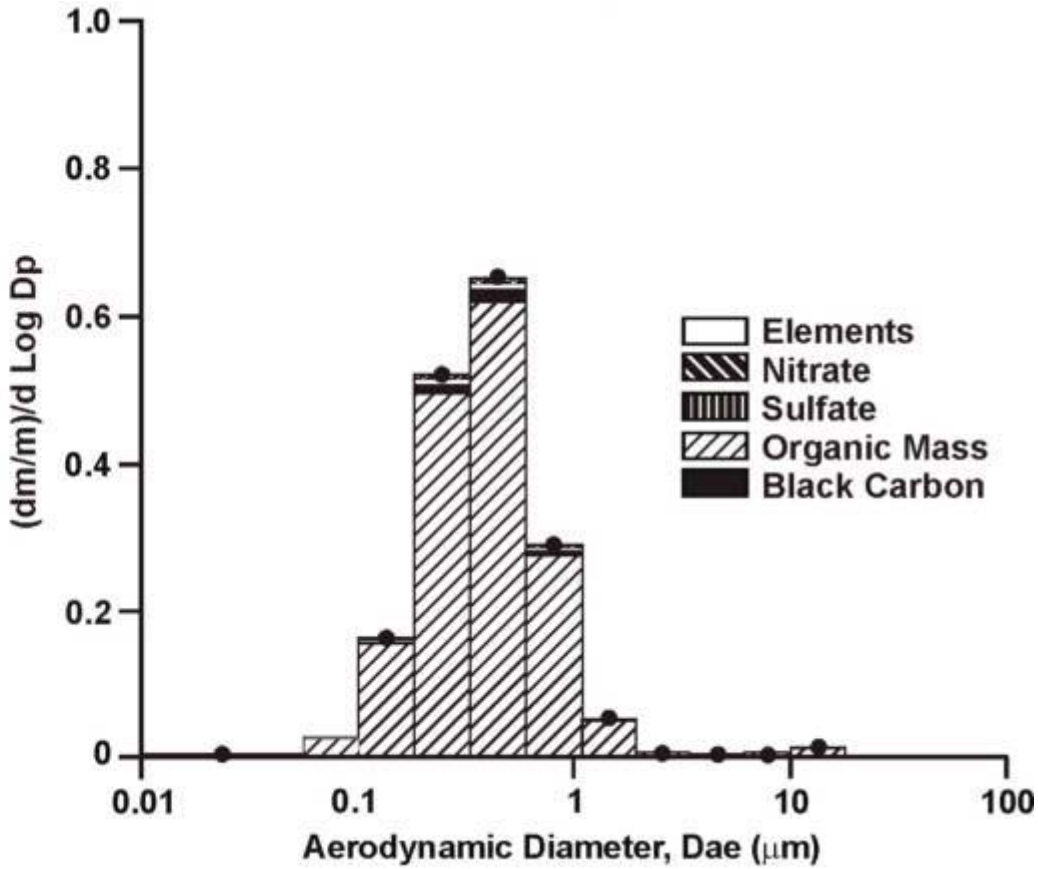
PARTICLE MASS-SPECIFIC COMPOSITION

At High Exposure Concentration (1,000 µg PM/m^3)

Diesel



Hardwood Smoke



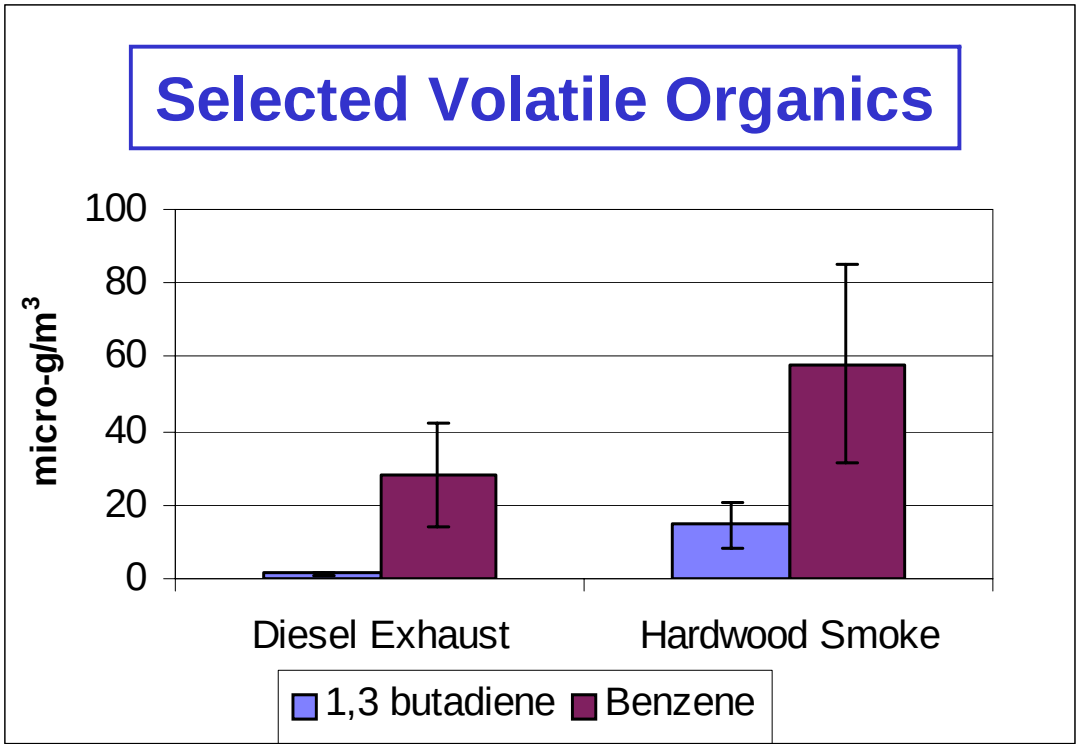
[McDonald et al., *Env. Sci. Technol*. 38: 2513, 2004]

GASES AND VAPORS

Selected Gases (ppm)

	DE	HWS
CO	30	13
NOx	49	"0"
THC	2.2	3.1

Selected Volatile Organics



Therefore – comparative toxicity would depend on the exposure parameter used for comparison

E.g., If toxicity were identical per unit of PM mass:

DE would be more toxic per unit of PM organic carbon

HWS would be more toxic: per unit ofPM black carbon

[McDonald et al., *Env. Sci. Technol*. 38: 2513, 2004]

HEALTH OUTCOMES

General toxicity in F344/CrlBR rats and A/J mice

- Body & organ weights
- Hematology, serum chemistry
- Bronchoalveolar lavage
- Histopathology
- Lung gene expression

Cardiovascular effects in SHR/Crl rats

- Heart rate and variability
- ECG segments
- Heart and vessel histopathology

Susceptibility to respiratory infection in C57/BL6 mice

- *Pseudomonas aeruginosa*
- Respiratory Syncytial Virus

Pulmonary immune responses in BALB/C mice

- Development of allergic responses
- Exacerbation of allergic responses

Carcinogenic potential in F344/CrlBR rats and A/J mice:

- DNA Methylation
- Oxidative DNA damage
- Micronuclei
- Lung adenomas in A/J mice

[Reed et al., *Inhal Toxicol*. 16:177, 2004]

MANY HEALTH ENDPOINTS WERE NOT SIGNIFICANTLY AFFECTED BY EITHER EXPOSURE (Even at the Highest Exposure Level !!)

Screening criteria for "significant exposure-related effect":

1. Significant trend across all groups
2. One or both highest level groups significantly different from control by multiple comparison

No Significant exposure-related effect on:

Morbidity, mortality, body weight, most organ weights

Clinical observations

Histopathology (other than ↑ alveolar macrophages with PM)

Most bronchoalveolar lavage parameters

Development of allergic responses

Micronuclei & lung adenomas

DNA methylation and oxidative injury, and lung gene microarray not yet completed

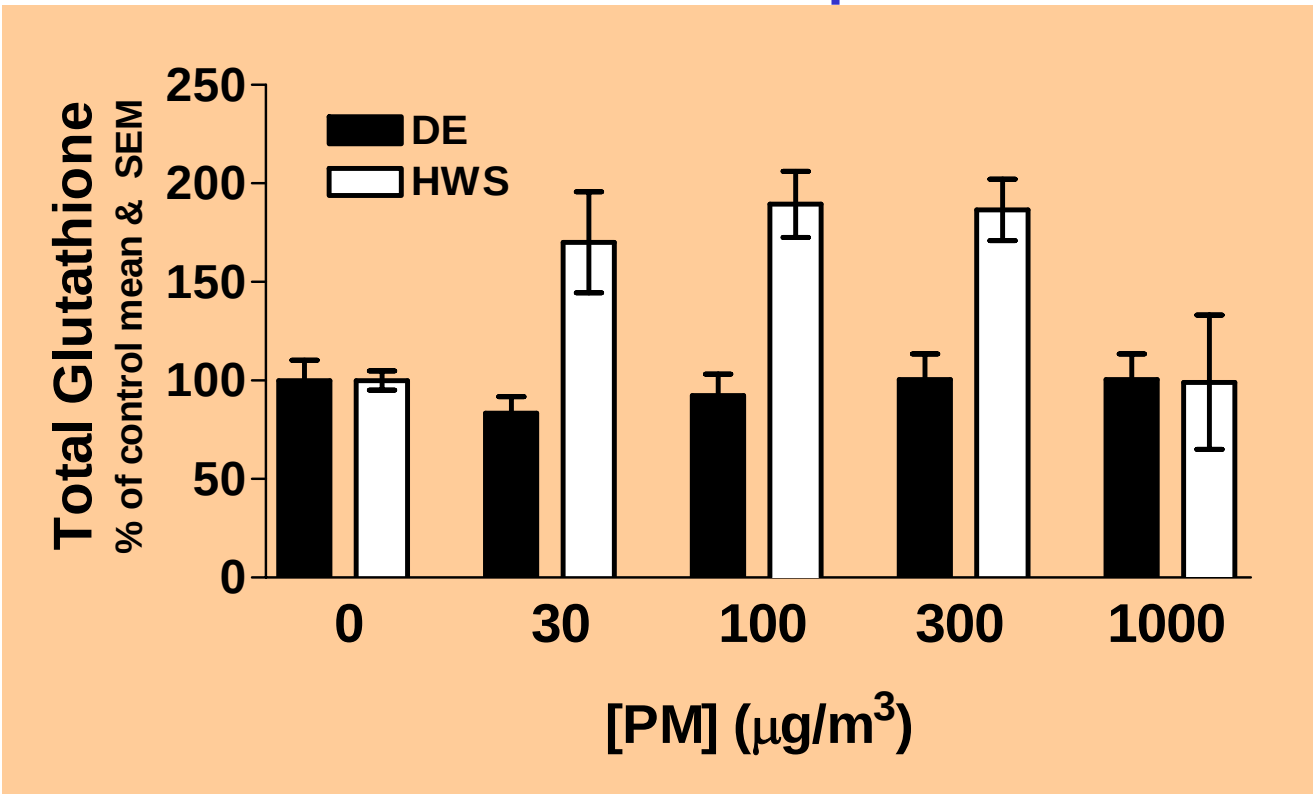
[Reed et al., *Inhal Toxicol*. 16:177, 2004]

[Reed et al., *Am. J. Respir. Crit. Care Med.* 169:561, 2004]

[Seagrave et al., *Toxicologist* 78: 1380, 2004]

ONLY HWS CAUSED LUNG ANTI-OXIDANT RESPONSE

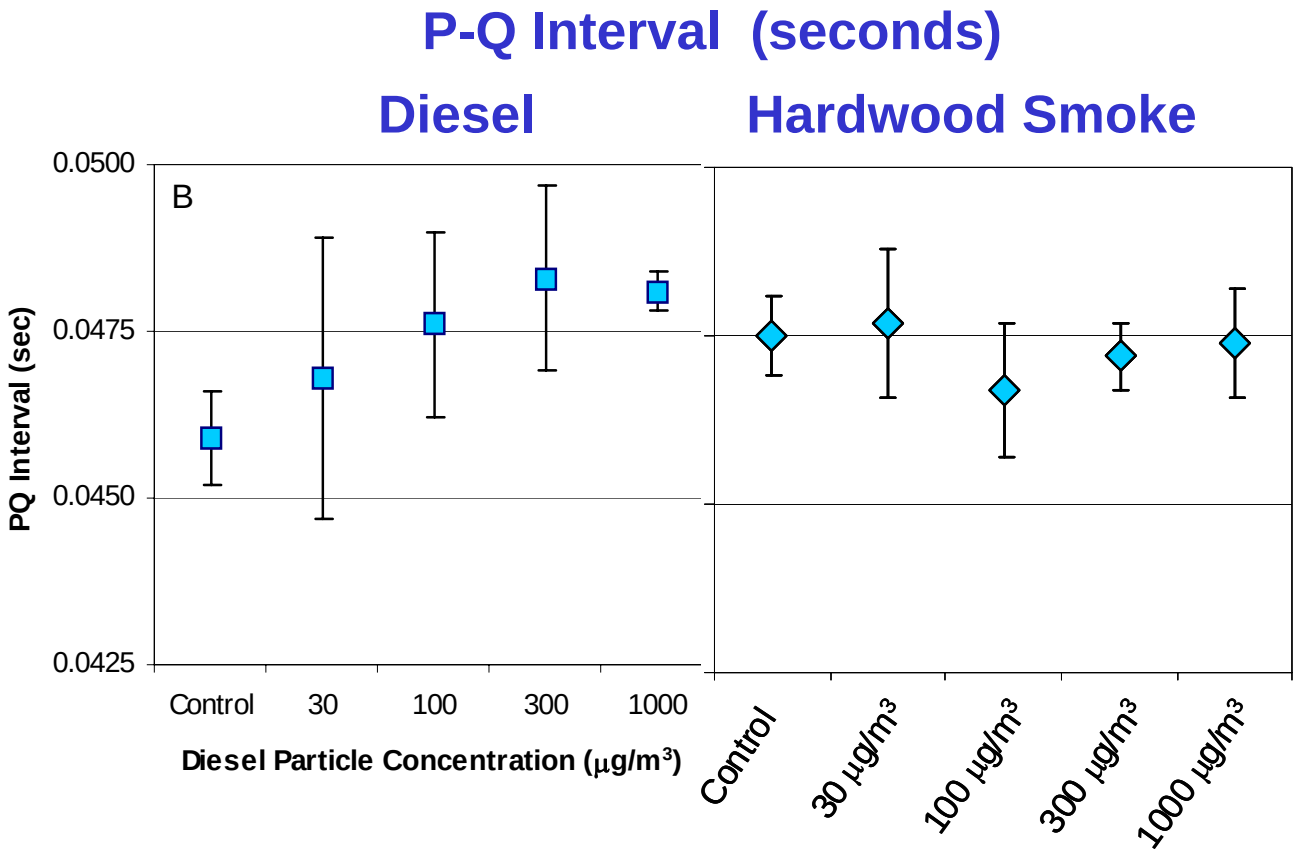
Total Glutathione (reduced + oxidized) in Bronchoalveolar Lavage (airway) Fluid of Rats after 6 Months of Exposure



- HWS caused an anti-oxidant response in the lung
- DE did not

[Seagrave et al., *Toxicologist* 78: 1380, 2004]

P-Q INTERVAL OF ELECTROCARDIOGRAM WAS INCREASED BY DE BUT NOT HWS

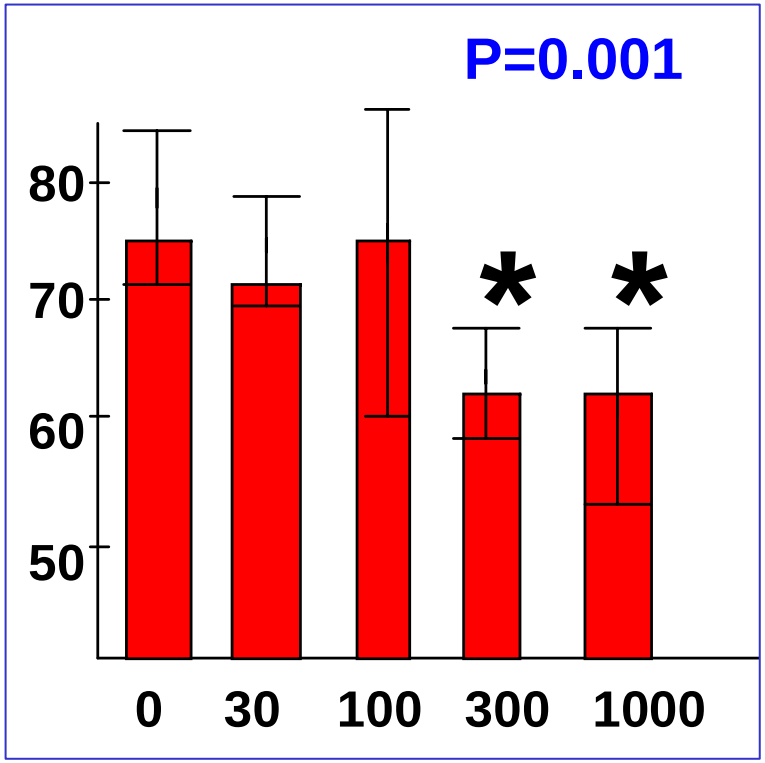


- Suggests slowing of conductivity between the atria and ventricles
- Significant only at the highest two exposure levels
- Hardwood smoke had no significant effect

[Campen et al., *Cardiovascular Toxicology*, 03: 353-361, 2003]

DE AND HWS HAD DIFFERENT EFFECTS ON BLOOD CLOTTING FACTORS

DE reduced Factor VII at 7 days of exposure



Factor VII also ↓ in humans associated with ambient PM and experimental CAPs exposure

[Reed et a., *Am. J. Respir. Crit. Care Med.* 169:561, 2004]

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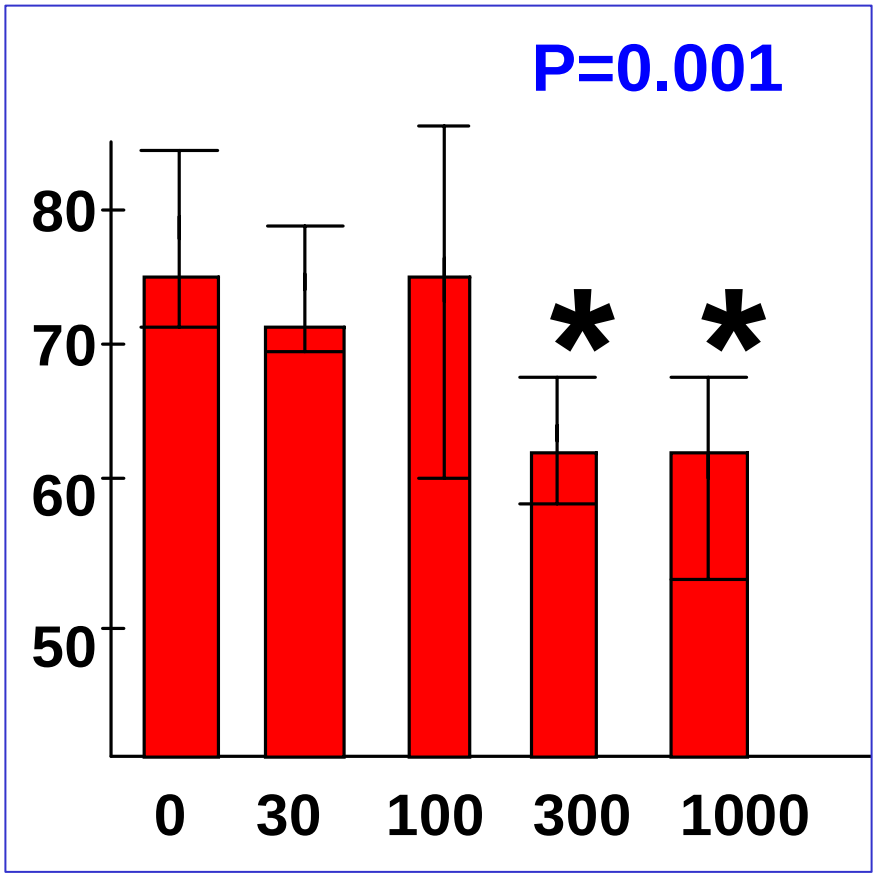
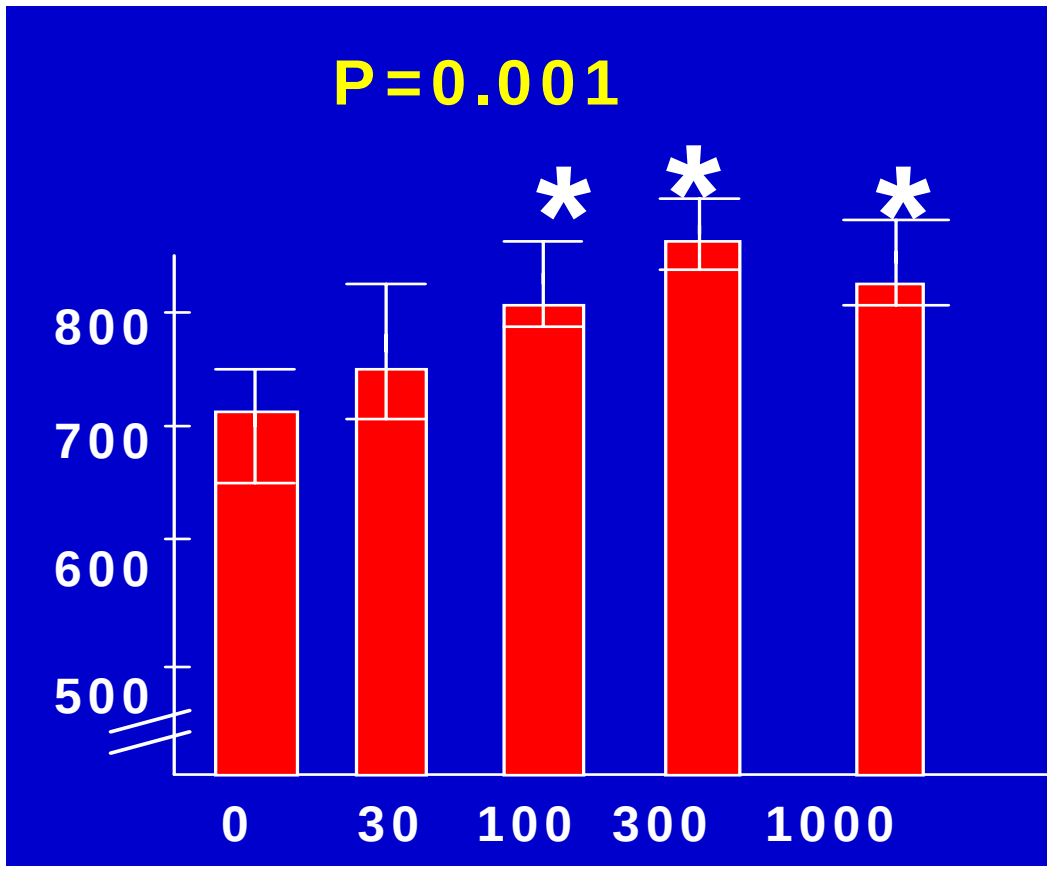


HWS increased platelets at 6 months of exposure



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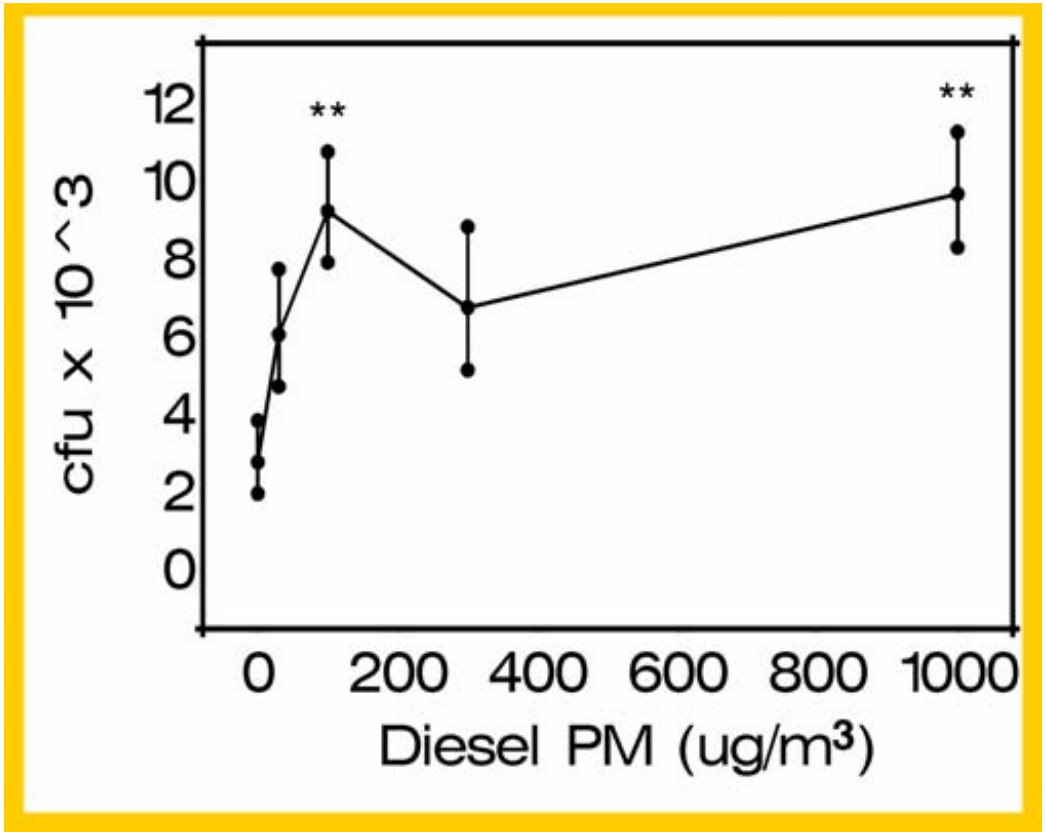
CLEARANCE OF BACTERIA WAS SLOWED BY DE, BUT NOT HWS

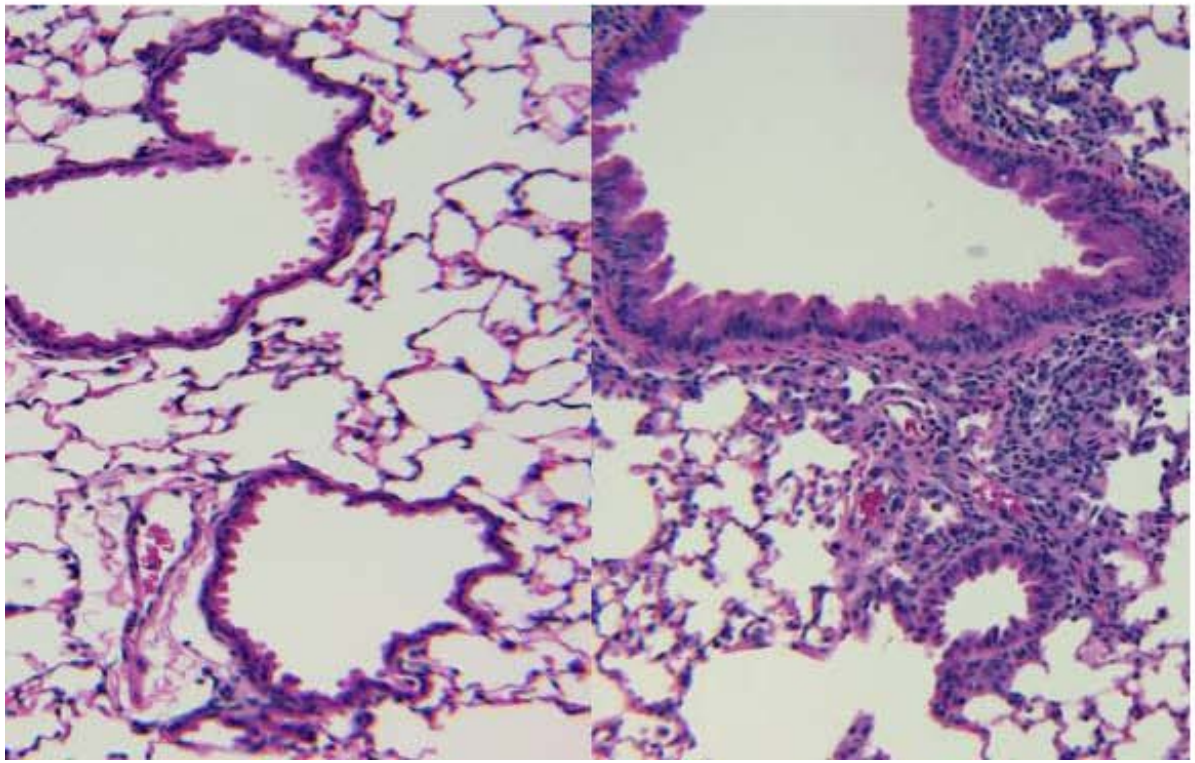


- The number of live *Pseudomonas aeruginosa* in the lung at 18 hours after infection was increased by DE
- Clearance of bacteria was not slowed by HWS

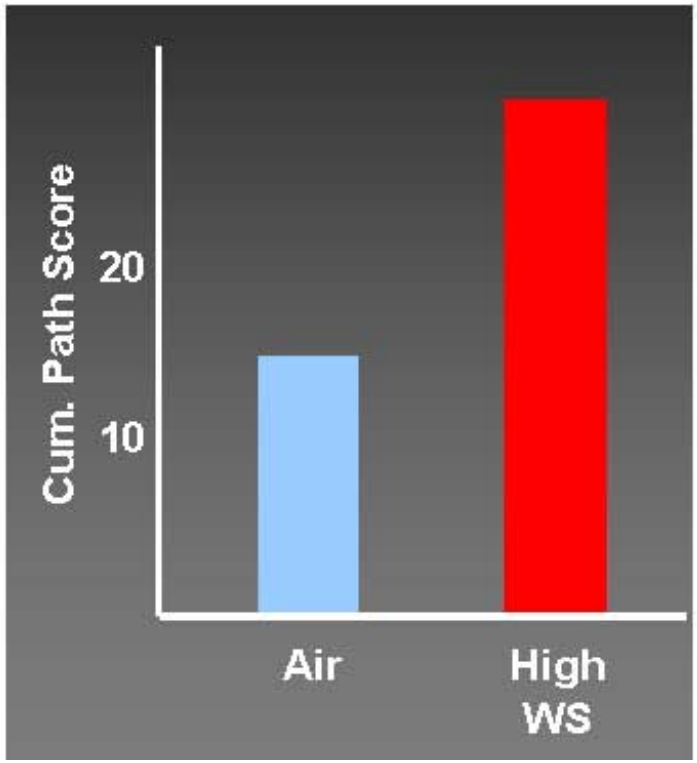
[Harrod et al., Toxicol. Sci, in press]

BOTH DE AND HWS INCREASED RSV PATHOLOGY, DE ALSO SLOWED CLEARANCE OF RSV

Pathology of Small Airways e.g., DE



Total Histopathology Score e.g., HWS



[Harrod et al., *Am. J. Respir. Cell. Mol. Biol.* 28:451, 2003]

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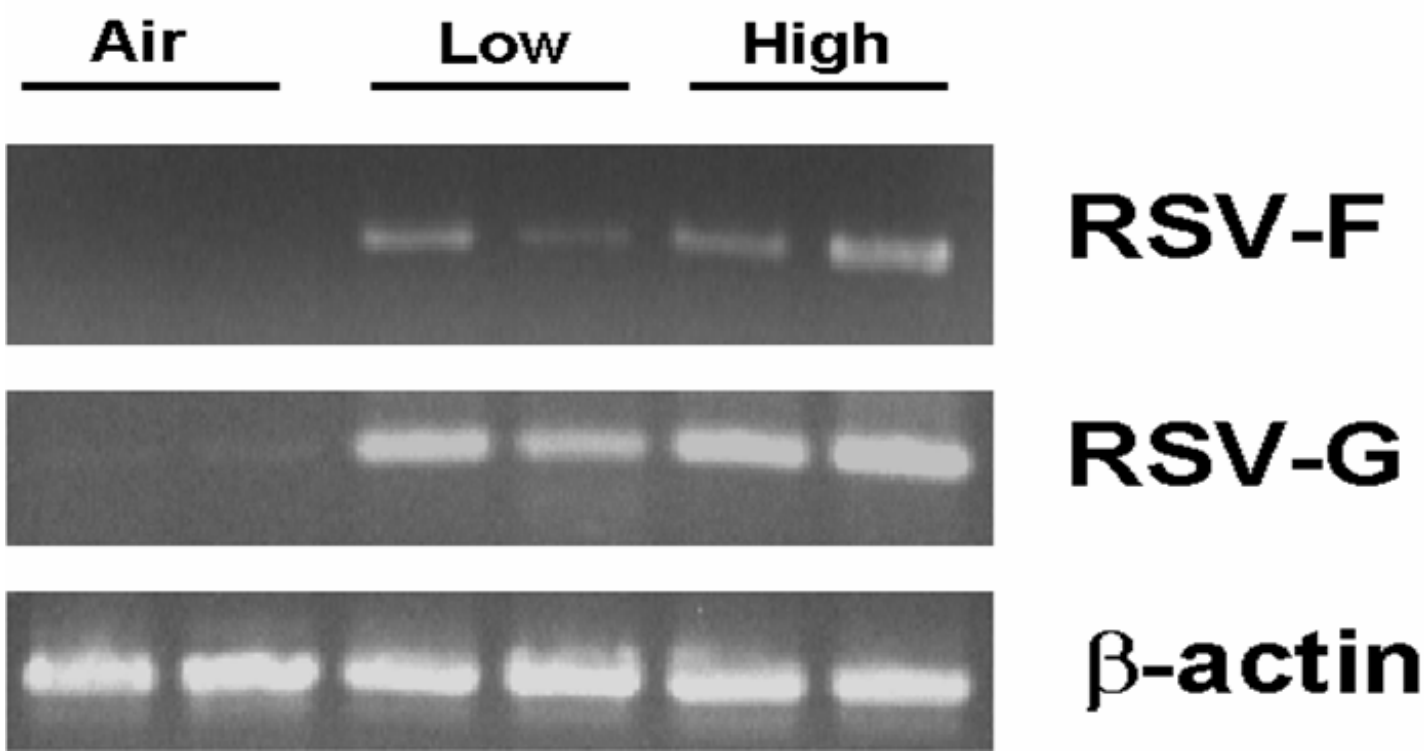
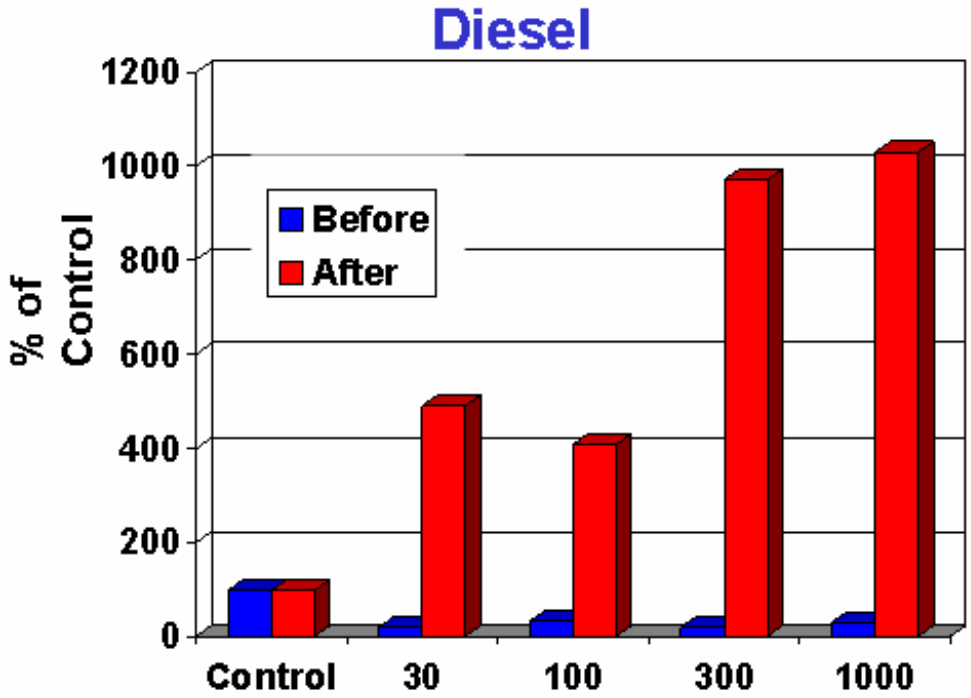


- More respiratory syncytial virus RNA was present at 4 days after infection in DE-exposed mice
- HWS did not slow clearance of RSV

[Harrod et al., *Am. J. Respir. Cell. Mol. Biol.* 28:451, 2003]

EFFECT OF EXPOSURE ON LUNG ALLERGIC RESPONSES VARIED BY BOTH EXPOSURE MATERIAL AND EXPOSURE ORDER

Effect of Exposure Before or After Allergen Challenge on Numbers of Allergic Inflammatory Cells in the Lung



- DE before challenge suppressed allergic response
- DE after challenge increased allergic response

[Barrett et al., Am J Respir. Crit. Care Med. 169: 652, 2004]

[Barrett et al., Am. J. Physiol. Lung Cell Mol. Physiol, in press]

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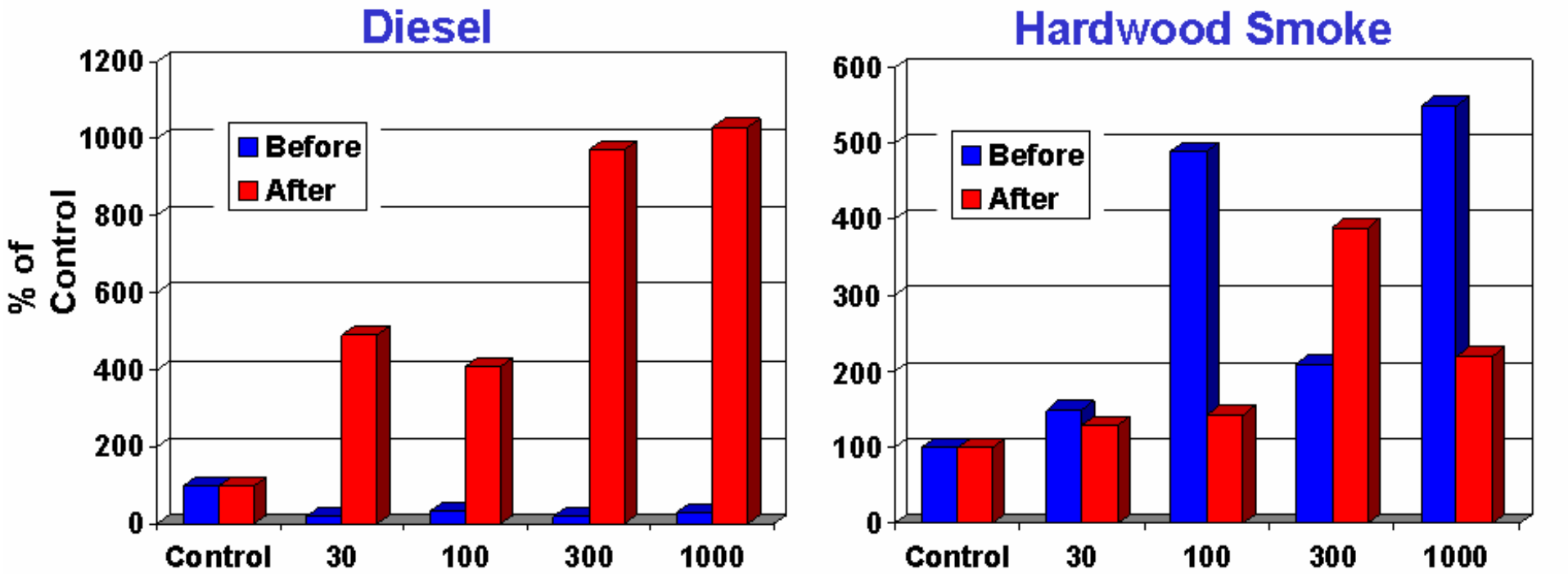

- DE before challenge suppressed allergic response
- DE after challenge increased allergic response
- HWS tended to increase allergic response in either sequence

[Barrett et al., Am J Respir. Crit. Care Med. 169: 652, 2004]

[Barrett et al., Am. J. Physiol. Lung Cell Mol. Physiol, in press]

BOTTOM LINES

You can't understand risk unless you understand the doses necessary to cause effects

Everything is toxic at some exposure level

You can't understand relative risk unless you make direct comparisons

You can't compare data collected using different methods

Effects of diesel emissions and wood smoke differ… *(duh)* … but relative risk depends on the exposure metric

There is no single "correct" metric

(except perhaps risk per unit of work)

Our goal is to identify physical-chemical species that cause important effects - so they can be reduced or avoided

We are taking multiple approaches to the problem

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