

# Health Effects of Diesel Exhaust

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# Objectives

- Define exposure
- Discuss health effects
- Discuss potential mechanisms of effect
- Describe early controlled exposure results

# What is Diesel Exhaust?

- Complex mix of gas and particle phase constituents
- Very small carbonaceous particles with adsorbed organic compounds, and small amounts of sulfate, nitrate, metals, and other trace elements (EC/OC greater under engine load)
- Contains PAHs and nitro-PAHs, acid aerosols, VOCs, various hydrocarbons (including highly reactive quinones)
- Gases include CO<sub>2</sub>, CO, NO<sub>x</sub>, and SO<sub>2</sub>

# Diesel Particle Size Distribution: Effect of Engine Load

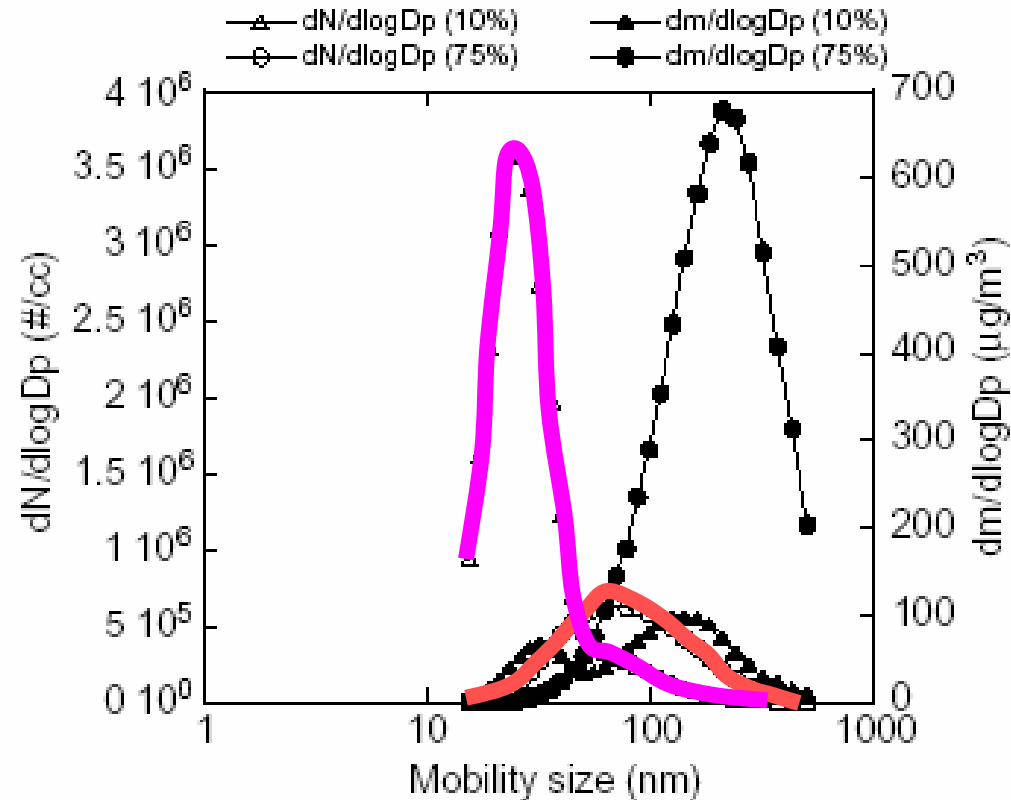
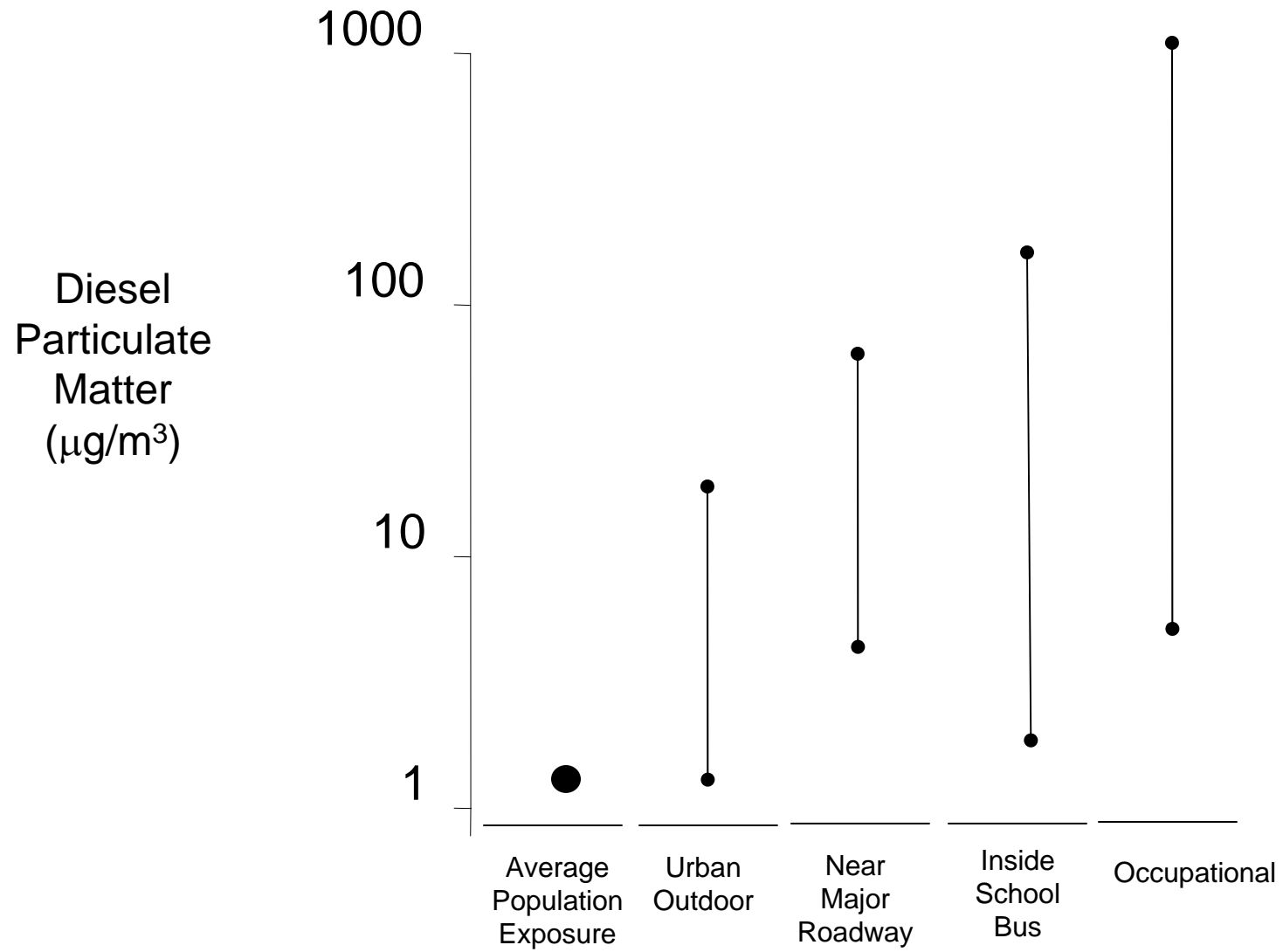


Fig. 5. Number and mass size distributions for diesel particles at 10% and 75% loads: John Deere engine, 1400 rpm, EPA fuel (360 ppm S).

# DEP Exposures



# Lung Cancer

## Health Assessment Document For Diesel Engine Exhaust

- Diesel exhaust is classified as “likely to be carcinogenic”
- Epidemiological studies suggest occupational exposure to diesel exhaust particulates causes increase in the risk of lung cancer
- No specific cancer unit risk estimate for diesel exhaust is adopted or recommended in the EPA assessment.
  - Animal (rat) cancer studies are not clear for human hazard prediction and unsuitable for environmental exposure risk estimate. Quantitative statements on human risk cancer should be based on human epidemiological studies. Currently available data, due to a number of uncertainties, is deemed unsuitable for quantitative risk assessment.

## Cell Toxicology (Lung)



- A. Nasal Epithelial Cells
  - A. Increased cytokine expression
  - B. Increased histamine release
- B. Bronchial Epithelial Cells
  - A. IL-8, adhesion molecules, GM-CSF
- C. Alveolar Macrophages
  - A. Decreased immune response
  - B. Increased oxidative stress response
  - C. Effect dictated by exposure level
- D. Eosinophils
  - A. Increased degranulation

# Cell Toxicology (Cardiovascular)

- Endothelium
  - Increased release of adhesion molecules
  - Increased Coagulation

# Controlled Human Studies to DE

## Healthy Participants

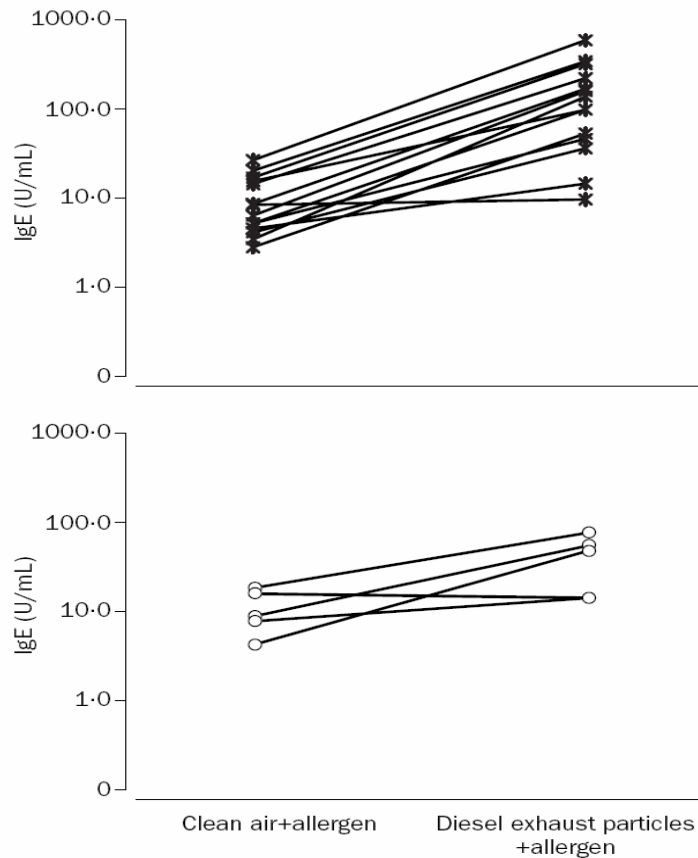
- A. Increased inflammatory cells in airways
- B. Increased chemokines/ cytokines
  - A. IL-8, Gro-alpha/ IL-1 beta, IL-6
- C. Decreased macrophage function
- D. Increased adhesion molecules
  - A. Bronchial biopsies



# Asthmatic Volunteers

- Increased hyper-responsiveness to methacholine
- Increased airway resistance
- Increased IL-6 in sputum
- No airway inflammation on biopsies

# Adjuvant Properties of DE



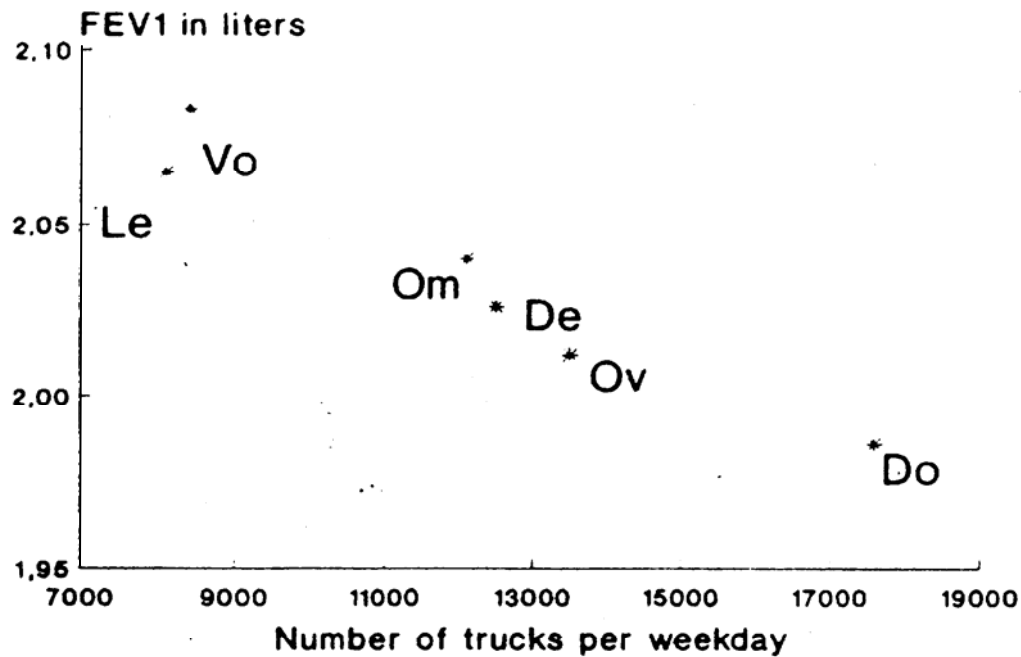
- Both groups show adjuvant effect
- Oxidant susceptible group shows larger effect

**Nasal allergen-specific IgE response to allergens plus clean air and allergen plus diesel exhaust particles for *GSTM1* absent (upper) and present (lower) genotypes**

Y axis is log scale of median IgE concentrations.

Gilliland, 2004

# Truck traffic vs. Lung Function



- SES gradient
- Truck vs. car
- Loop detectors

**FIGURE 1.** Association between truck traffic density and forced expiratory volume in 1 second ( $FEV_1$ ) in children living <300 m from a motorway, adjusted for age, gender, smoking in the home, presence of pets, damp or mold stains in the home, ethnicity, number of persons in the household, gas cooking, gas-fired, unvented water heaters, and parental education. *Le* = Leiderdorp; *Vo* = Voorburg; *Om* = Ommoord; *De* = Delft; *Ov* = Overschie; *Do* = Dordrecht.

Brunekreff et al, 1997

# Truck traffic vs. wheeze

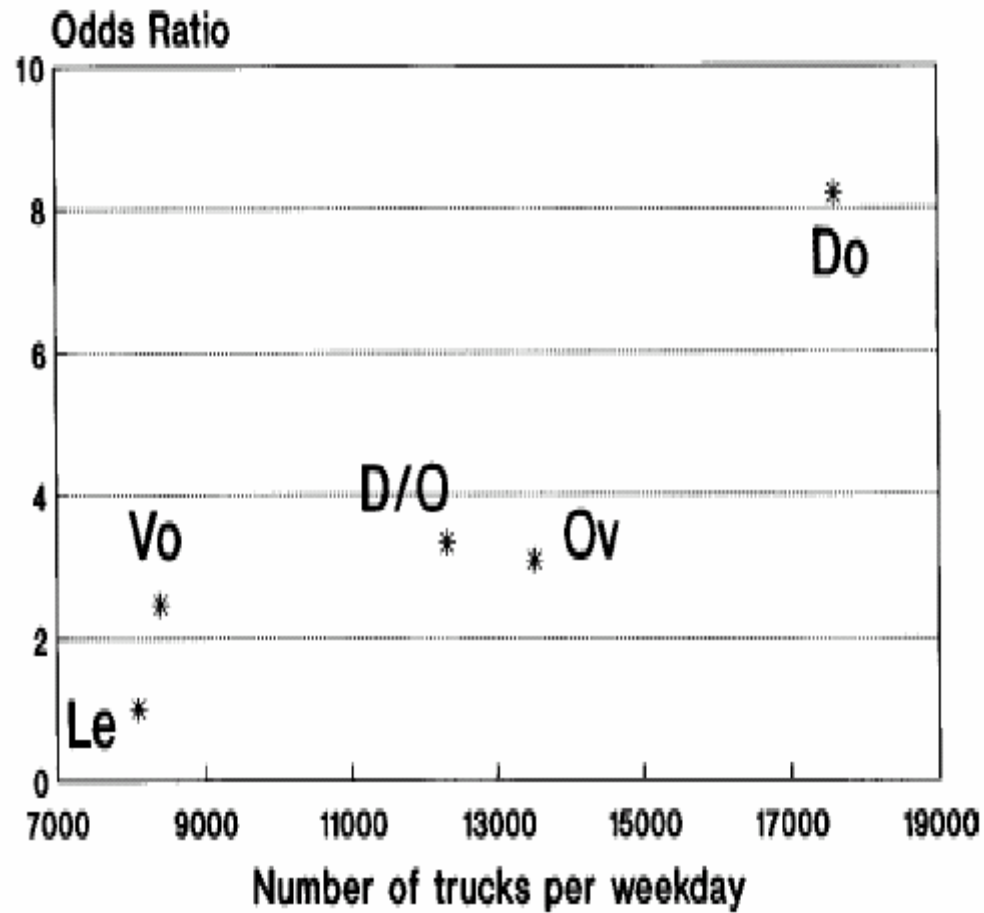


FIG. 1. Association between truck traffic density and wheeze in girls.

van Vliet et al, 1997

# Truck traffic vs respiratory symptoms

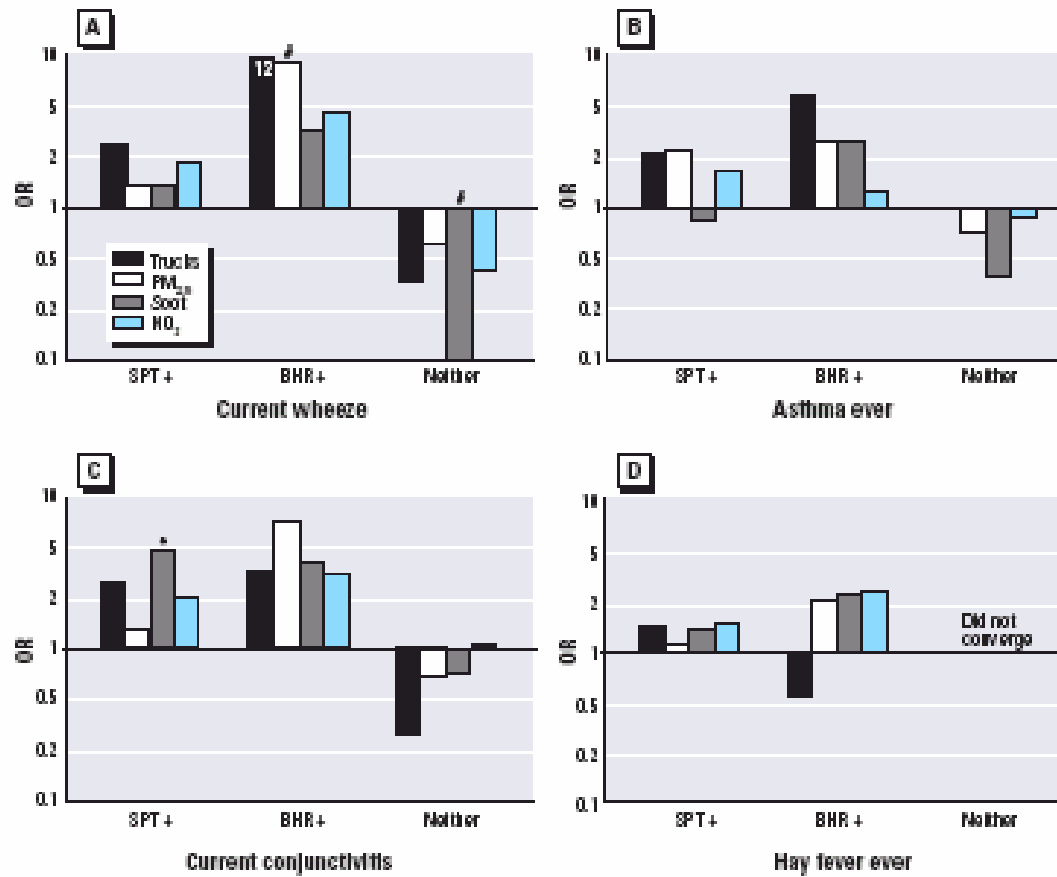
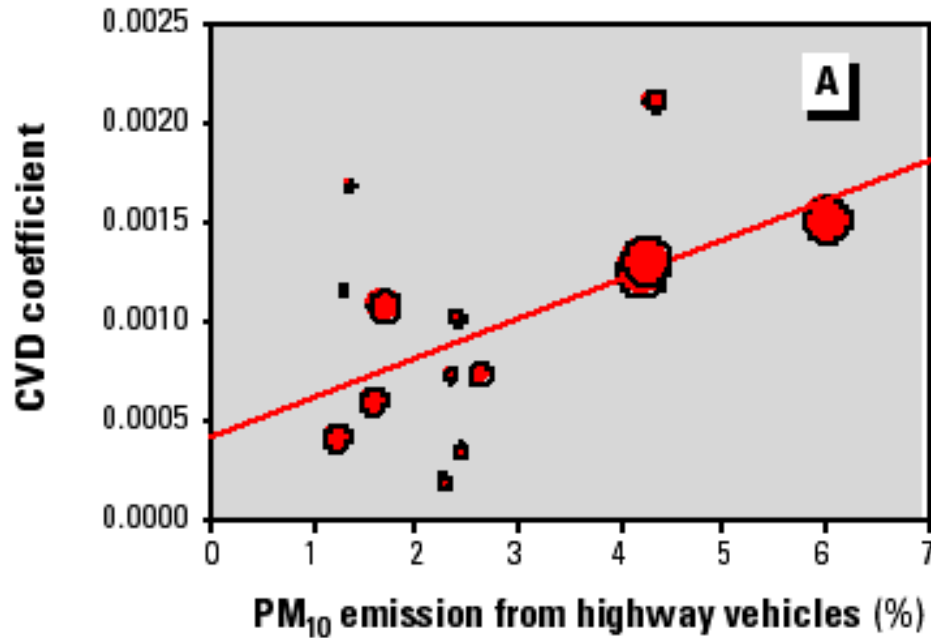


Figure 1. Adjusted ORs for the relationships between respiratory symptoms and truck traffic counts, PM<sub>2.5</sub>, soot, and NO<sub>2</sub> for children with and without a positive SPT (SPT+) and positive BHR (BHR+) test separately. Neither = negative on both tests. In (A) and (H), 12 and 16, respectively, are the exact values. #*p* < 0.10; \**p* < 0.05; \*\**p* < 0.01.

Janssen et al, 2003

# Cardiovascular Disease, and traffic-related PM?

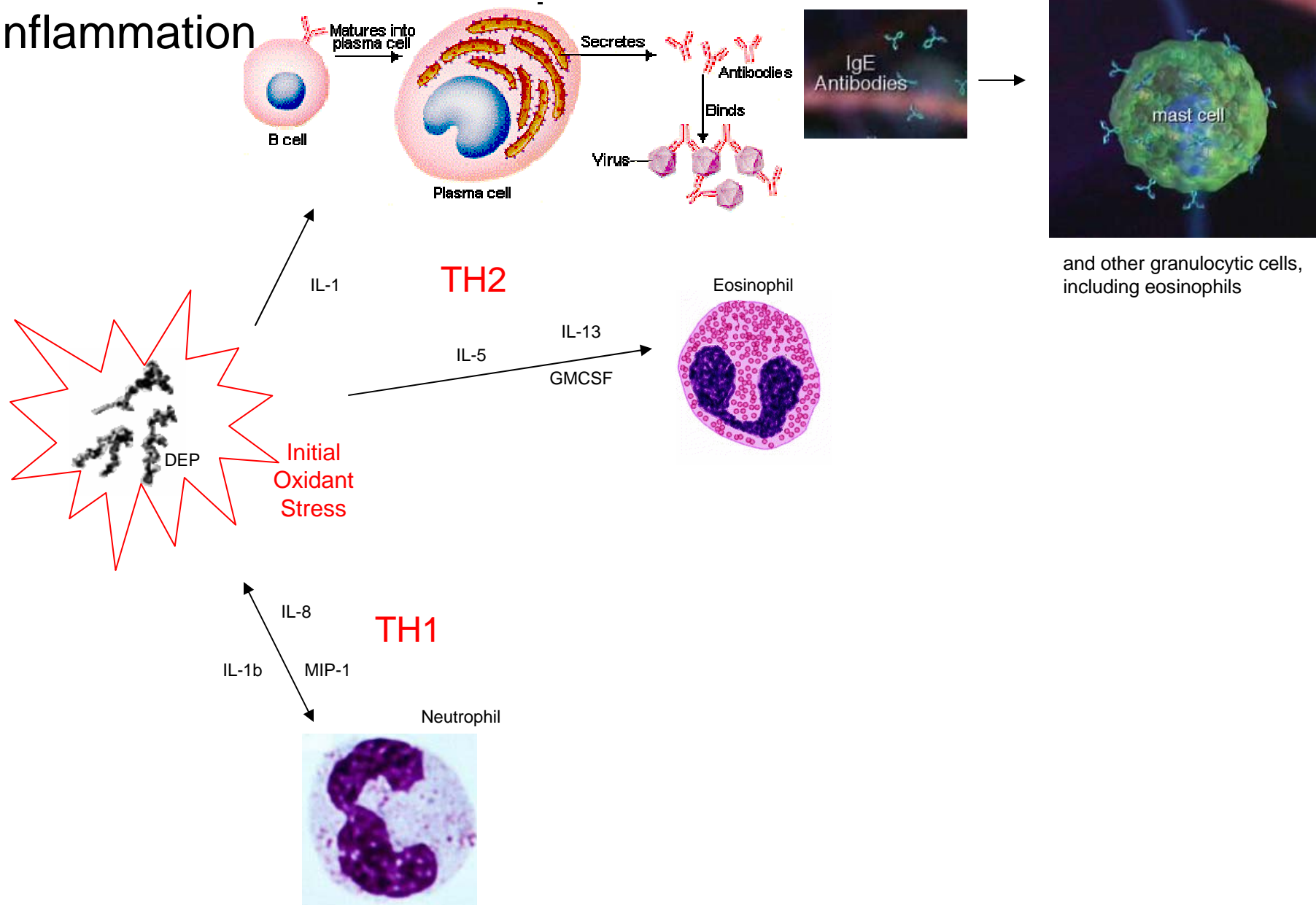


CVD Hospital Admissions in 14 US Cities

- Emission inventories
- PM10 emission factors

Janssen et al, 2002

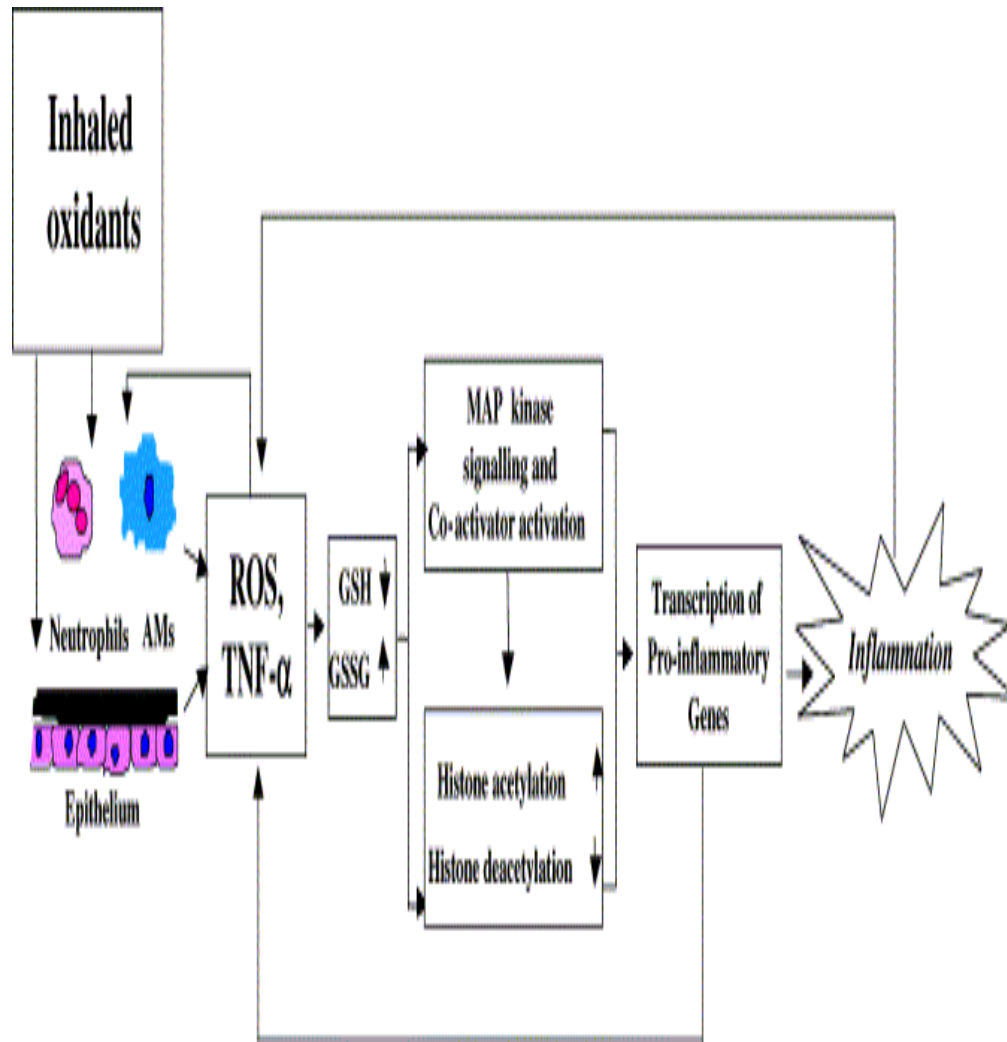
# DE and Inflammation



# Oxidative Stress

- Components of DE are known to contribute to oxidative stress
  - e.g., quinones, pyrenes, transition metals
- DE-induced oxidative stress may generate reactive oxygen species by macrophages and pulmonary epithelial cells
- Thiol-antioxidants blunt cellular response to DE

# Oxidative Response in Lung may Lead to Secondary Wave of Systemic Inflammation



- Increased release of pro-inflammatory mediators
- DE depletes lung defenses against oxidative stress

Rahman 2002

# UW Diesel Research Hypothesis

- Diesel Exhaust Particles exert oxidative stress resulting in inflammatory response
- Inflammatory response is propagated either through response in lung or in systemic circulation
- Oxidative Stress / Inflammatory response results in endothelial dysfunction, with resulting acute and chronic vascular effects

# UW Exposure Facility

Exposure Room



- Monitoring
  - Intensive initial and periodic characterization
  - continuous reading instruments during exposures
    - TEOM PM<sub>2.5</sub>
    - 2 CPCs (one with 100nm diffusion screen)
    - Particle Soot Absorption Photometer
    - FTIR

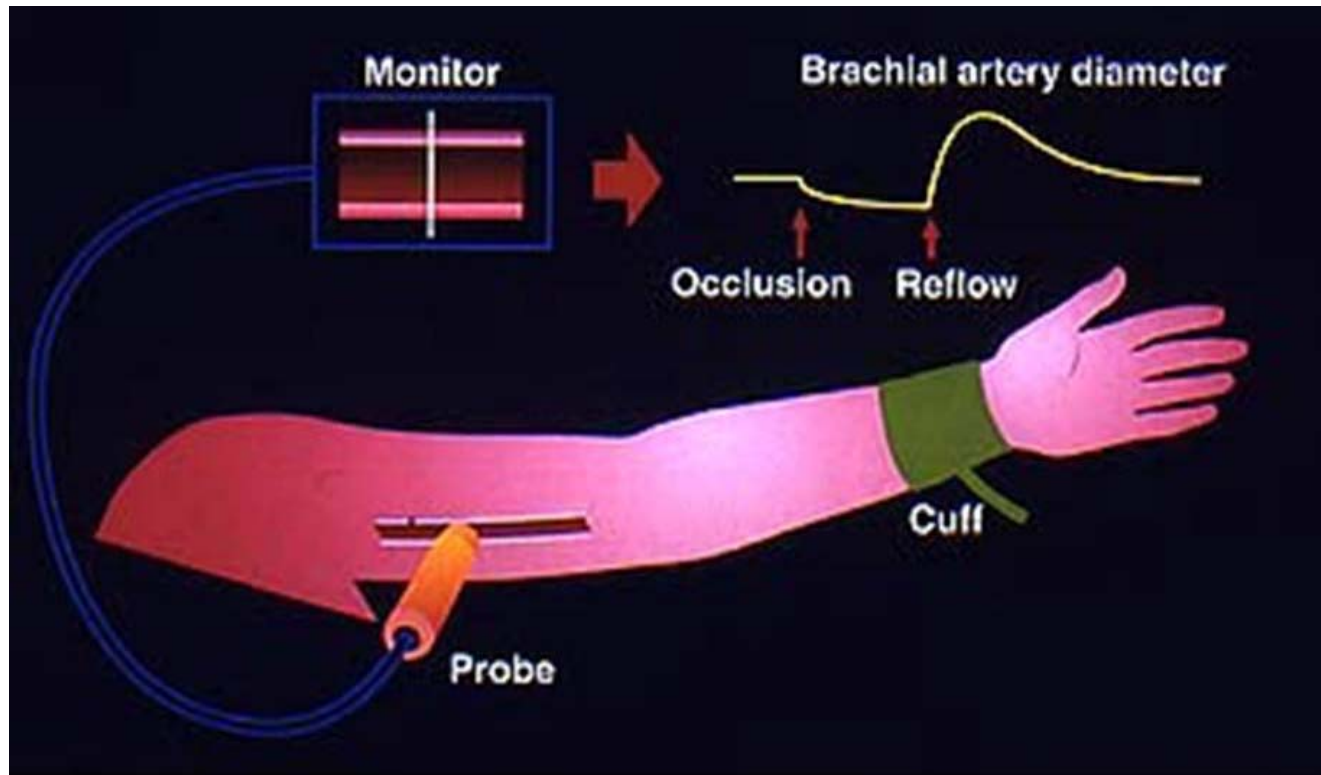
Diesel Source: Contemporary Cummins 5.9L direct injection, turbo-charged @ 75% load

courtesy of Joel Kaufman

# Health Outcomes

- Symptoms
- Pulmonary function measures
- Exhaled nitric oxide ( $FE_{NO}$ ).
- Plasma markers of inflammation
  - CRP, neutrophils, isoprostanes, cytokines
- Plasma markers of oxidative stress:
  - GSH:GSSG, nitrotyrosine, MPO, ascorbate
- Flow-mediated dilation (FMD) of the brachial artery.
- Plasma markers of endothelial function.
  - endothelin-1, ICAM-1, IL-6.
- Plasma markers of thrombosis: D-dimer, PAI-1, VWF
- Early gene responses

# Vascular Response to DE



# Brachial Artery Ultrasound

- Non-invasive measure of arterial response
  - Correlated to coronary artery response
- Within healthy and high risk sub-groups abnormalities in response are associated with increased risk of coronary artery disease.

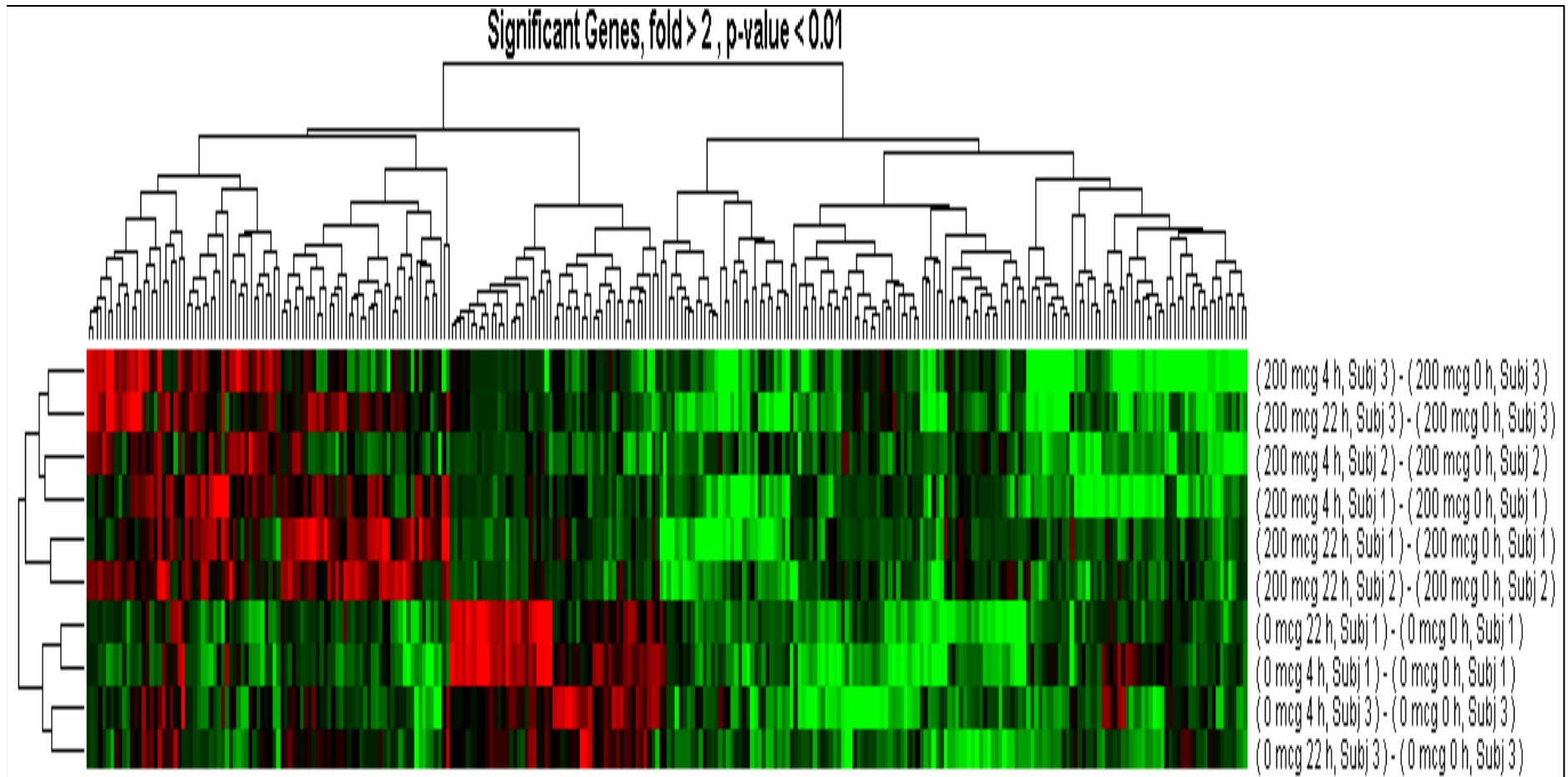
## Percent Change in Brachial Artery Diameter after DE Exposure.

Health Category	Filtered Air	200 mcg/m <sup>3</sup> DE
Healthy (n=6)	-0.3 <sub>±</sub> 1.3	-5.2 <sub>±</sub> 6.0
Metabolic Syndrome (n=7)	1.0 <sub>±</sub> 2.2	-1.8 <sub>±</sub> 2.3

# Microarray studies

- Purpose measure global gene expression
- Paired samples at pre, 4-h and 22-h after exposures
- Affymetrix platform

# Gene Responses to Diesel Exhaust



# Increased Gene Response

- 1335 out of 54675 probe sets were associated with DE exposure
- Oxidative Stress
  - ALOX5, SOD2
- Inflammatory Response
  - TLR4, CLC6, CCR5
- Vascular function
  - PDGF, VEGFR

# Summary

- Epidemiological studies
  - association between various respiratory effects and levels of truck traffic in persons living near major roadways
  - effects not confounded by SES or total traffic volume
  - effects greater in susceptible subpopulations

# Summary

- Toxicological studies/ Controlled Exposures
  - exert direct inflammatory effect via redox activity
  - influence key cytokines and chemokines
  - increase expression of genes known to regulate vascular response
  - increase baseline vascular tone

# Future Directions

- Assess maritime contribution of Diesel PM to Puget Sound ambient levels
- Voluntary Reductions
- Scientific evaluation of effect of reductions on health

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