

US EPA ARCHIVE DOCUMENT

Comparison of Health Effects of Coarse Particles with Effects of Fine and Ultrafine Particles: Que es Mas Macho?

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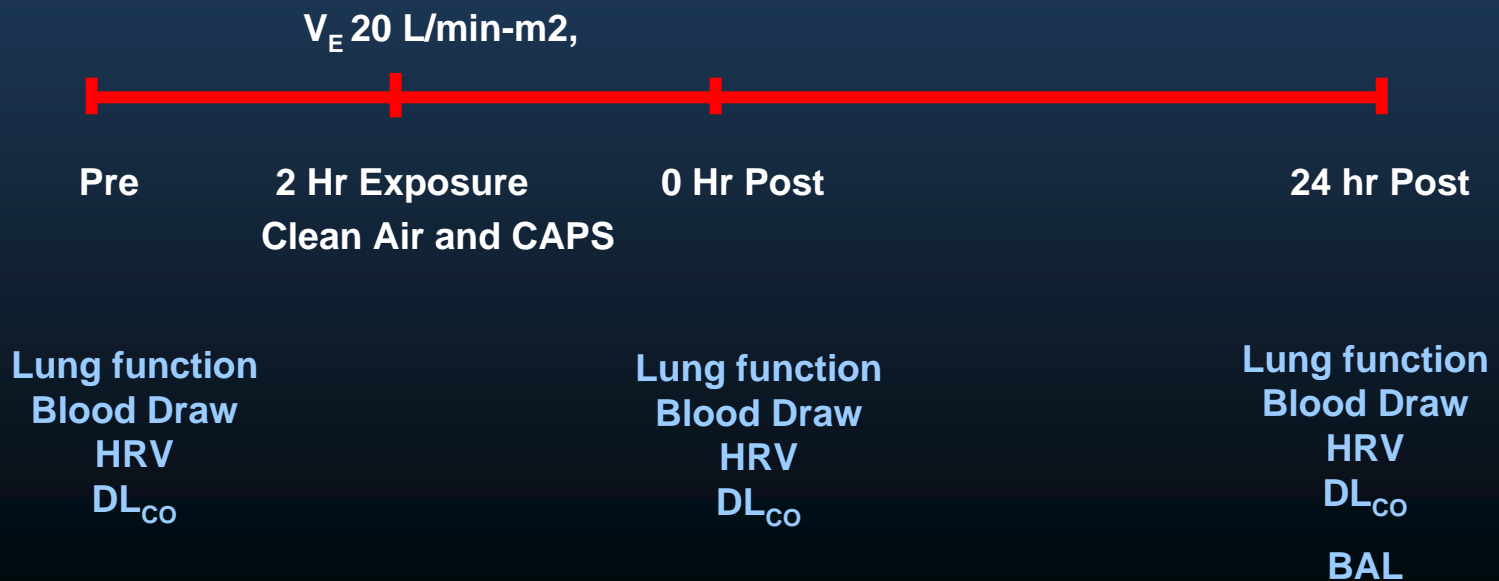
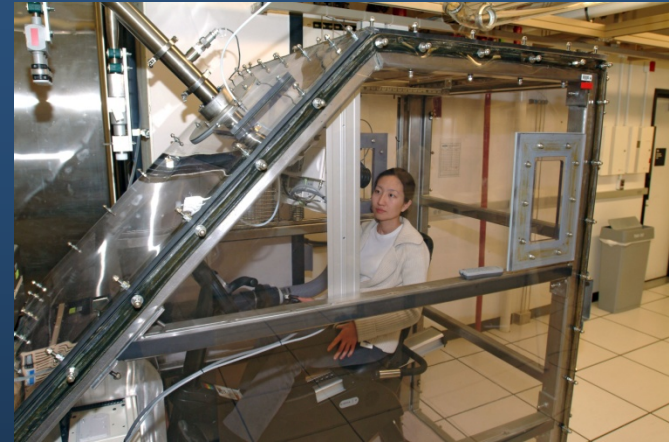
Three Approaches

- **Expose humans to size fractionated ambient PM (CAPS)**
- **Use Panel studies to associate health effects with exposure to PM of different sizes**
 - Populations which cannot be intentionally exposed
 - Exposure scenarios that cannot be easily replicated in chambers
- **Collect size fractionated particles for toxicology studies**
 - Understand mechanisms by which each size fraction causes adverse health effects
 - Compare the relative potency of particles collected from different geographical locations and across seasons

Exposure of Healthy Volunteers to Concentrated Coarse Ambient Air Particles

Coarse CAPS Study Design

Subject #	15
Age	18-35
PM _{2.5-10} ($\mu\text{g}/\text{m}^3$)	89.0 \pm 13.2
PM ₁₀	105.1 \pm 15.6
PM Size (MMAD)	2.59 \pm 0.58



Particle Characterization

Mass

Filters, TEOM, Data RAM

Size

MOUDI

APS

Chemical Composition

Elements - XRF, ICP-MS (water soluble metals)

Anions - IC (sulfate, nitrate), pH

Carbon - organic and elemental

SEM/EXD (coarse)

Biologicals

LPS

Gases

Ozone, NO₂

Exposure of Healthy Volunteers to Coarse, Fine, and Ultrafine CAPS: Summary of Effects

	Pulmonary Function	BAL Fluid Cells	BAL Fluid Markers	Cardiac Endpoints	Plasma Markers
Fine	No Effect	PMNs Monocytes	IL-8 Fibrinogen	No Effect	Fibrinogen WBCs LDH
Coarse	No Effect	PMNs Monocytes	Protein	SDNN	tPA D-dimer
Ultrafine	No Effect	No Effect	IL-8	HF LF Mean QT Norm. QT var	D-Dimer tPA Tryglycerides cholesterol

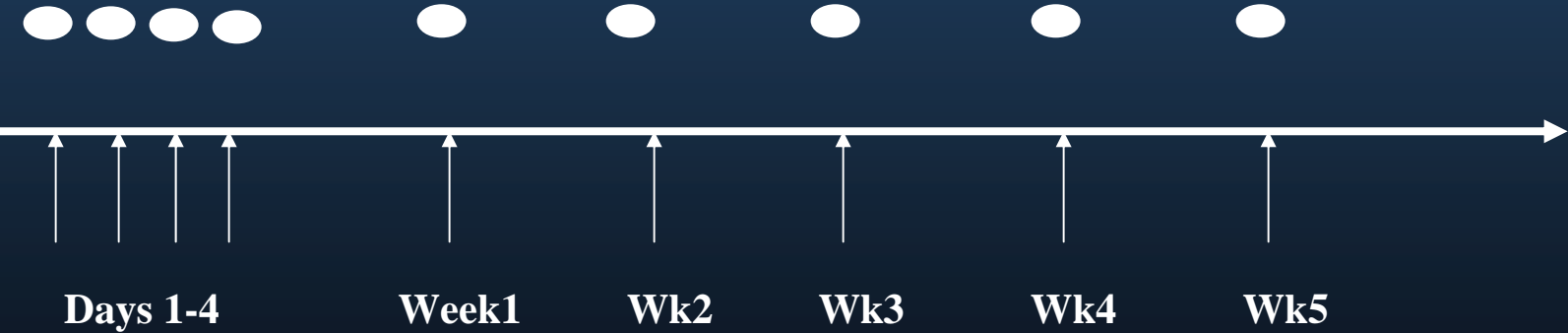
RTP Asthmatic Panel Study

- **Biological materials are found predominately in coarse PM**
- **Biological materials can exacerbate asthma**
- **Therefore, we hypothesized that asthmatics should be more responsive to coarse, rather than fine, PM.**

Exposure



Outcomes



Respiratory and Cardiopulmonary Outcomes

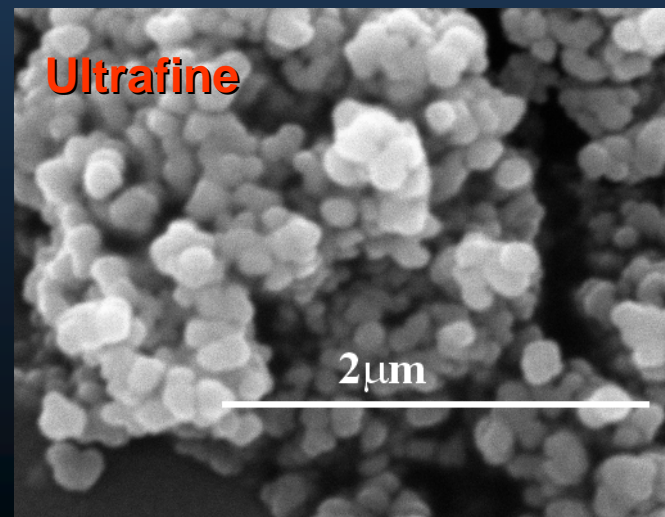
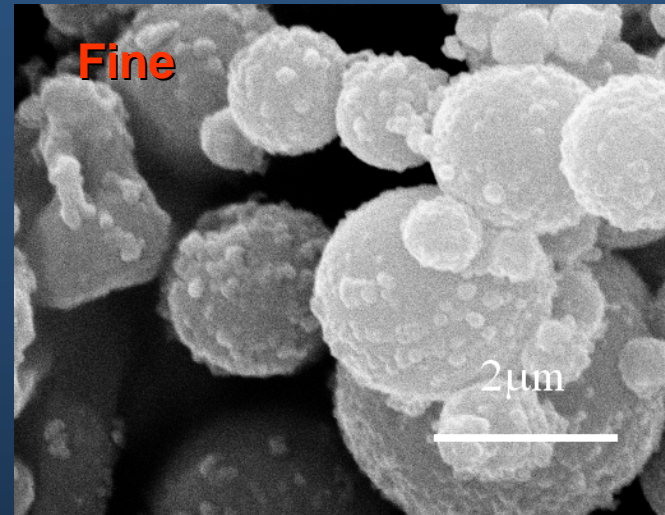
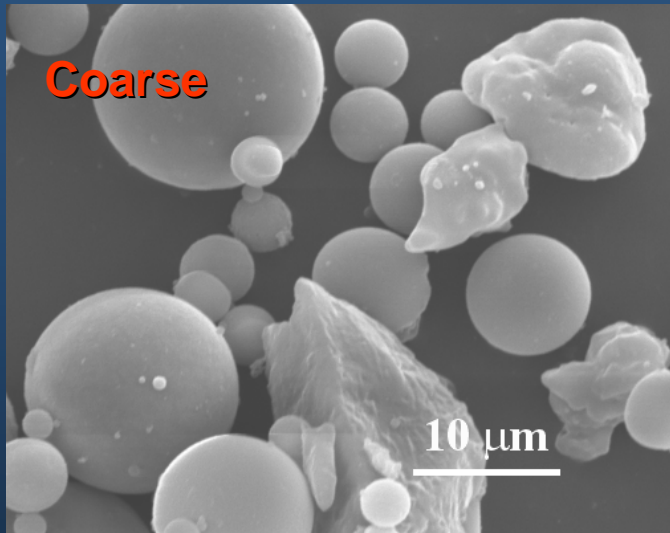
- Respiratory symptoms and asthma medication use
- Pulmonary function
- Markers of airway inflammation
Induced sputum, exhaled nitric oxide
- Vascular markers
Clotting/coagulation factors
Lipids (triglycerides, VLDL)
Cells (circulating eosinophils)
- Heart rate variability (SDNN, PNN50, HF)

Associations were only observed with coarse, not fine, PM.

Ongoing Studies

- **Response of mild asthmatics to fine and coarse CAPS**
- **Panel study comparing the response of healthy individual, and those with mild or severe asthma to fine and coarse PM**
 - In vitro challenge of cultured cells from these individuals with PM**

Health Effects Associated with Different Size PM From Chapel Hill



- Particles collected in weekly batches for a year, using a ChemVol sampler (pooled to obtain 12 monthly samples)
- UF, F, C fractions extracted and used for in vitro and animal instillation studies

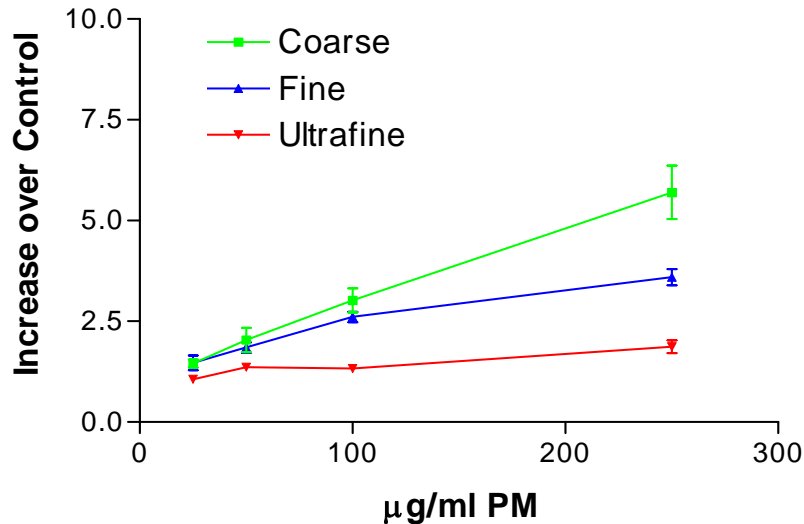
Coarse PM Elicits Larger IL-8 Production Than Fine or Ultrafine PM at 24 Hrs

Human primary airway epithelial cells exposed to UF, F, C particles

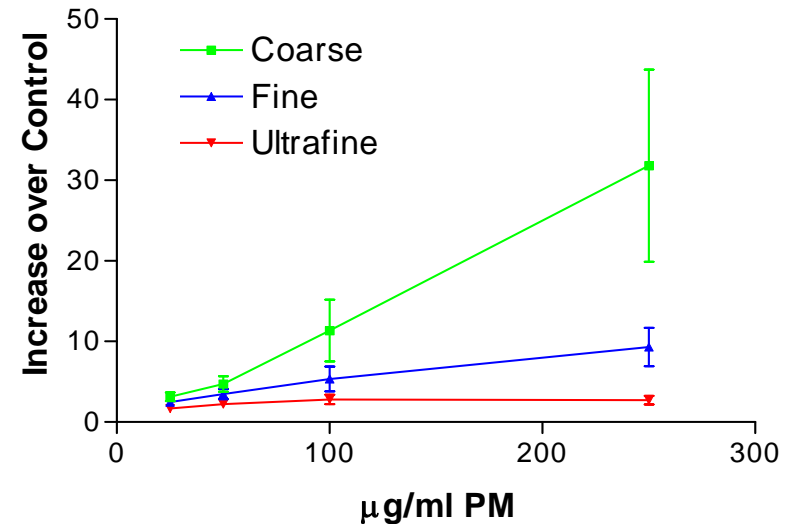
PROTEIN

mRNA

October PM

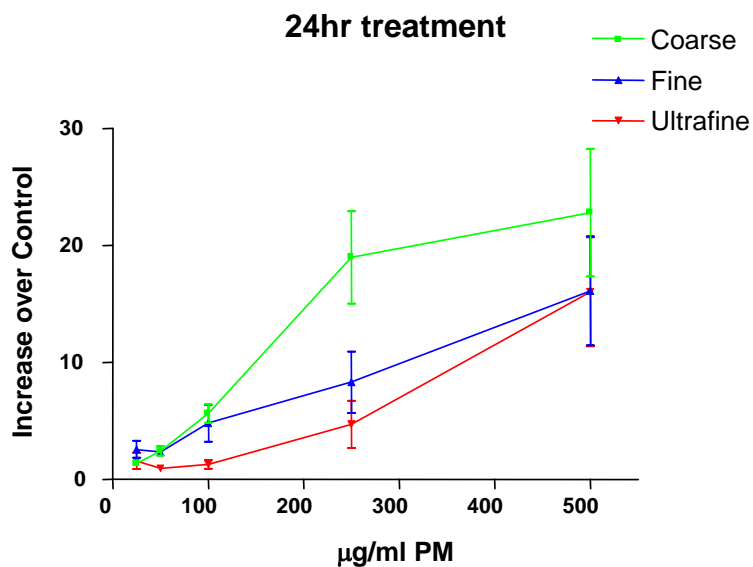


October PM

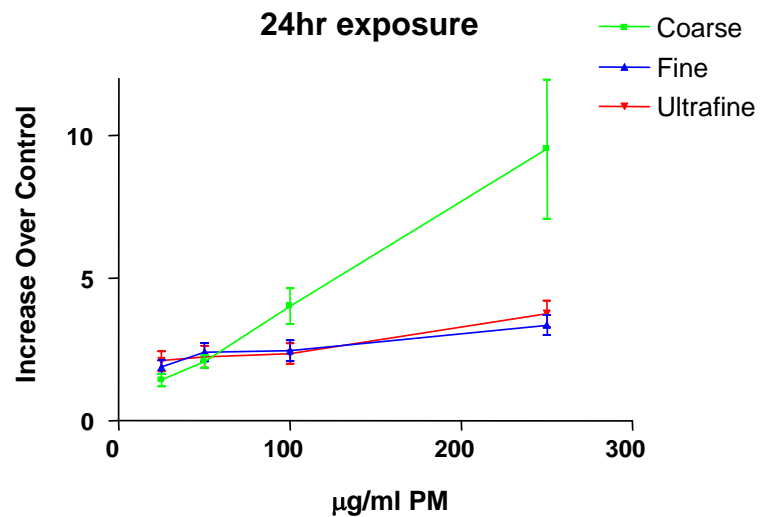


Coarse PM Elicits Larger GM-CSF and Cox2 mRNA Production at 24 Hrs

GM-CSF



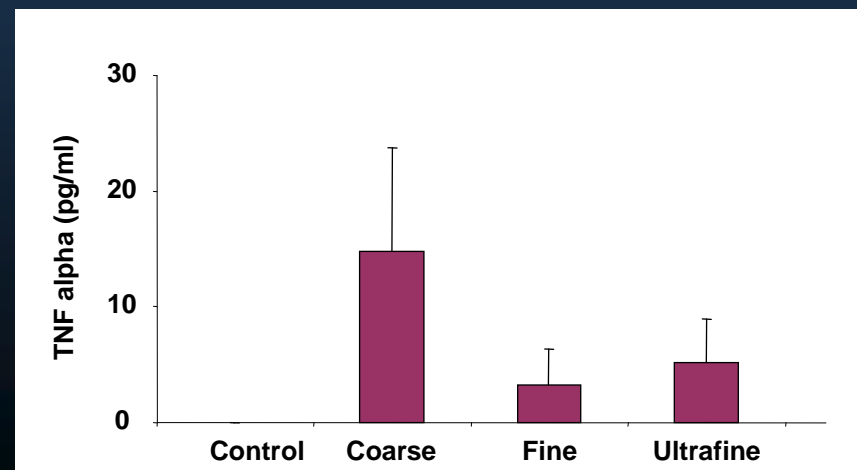
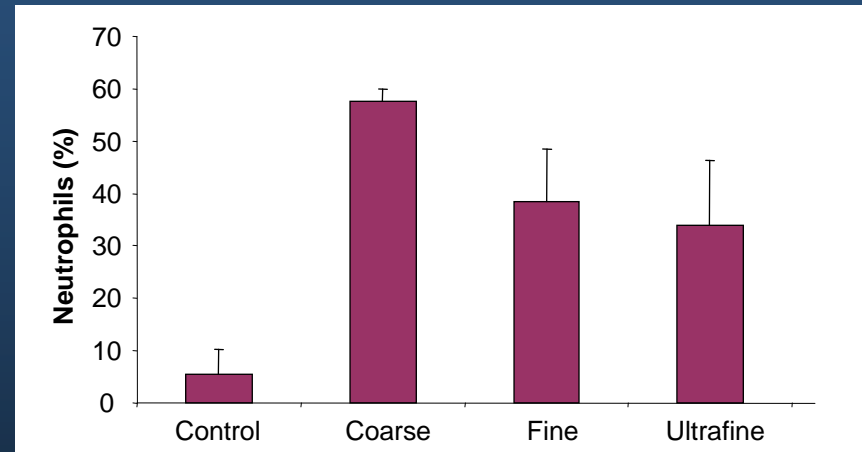
Cox2 mRNA



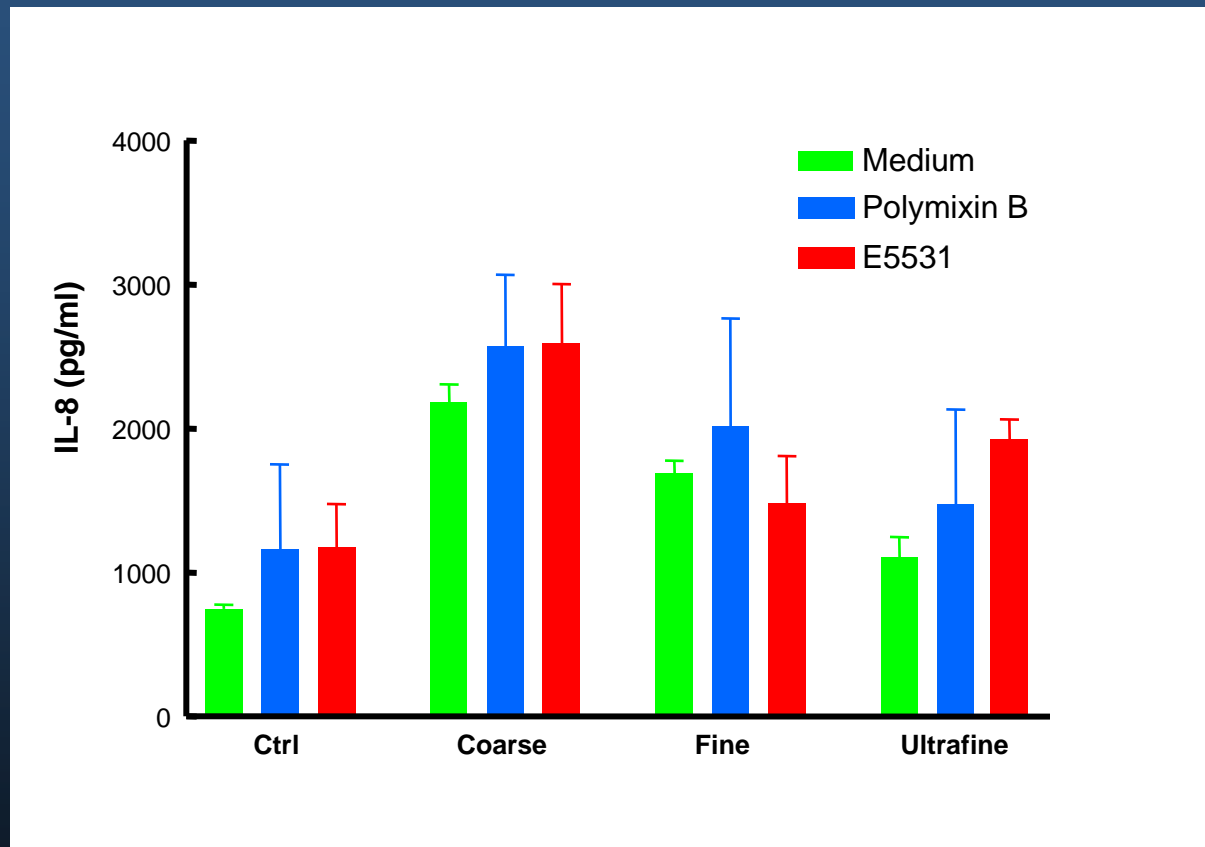
Coarse PM Causes More Inflammation in Mice

Saline and 100 μg coarse, fine, or ultrafine PM were instilled into C3H/HeJ mice.

Lavage was performed 24 hrs later and % neutrophils assessed, as well as BAL TNF levels.

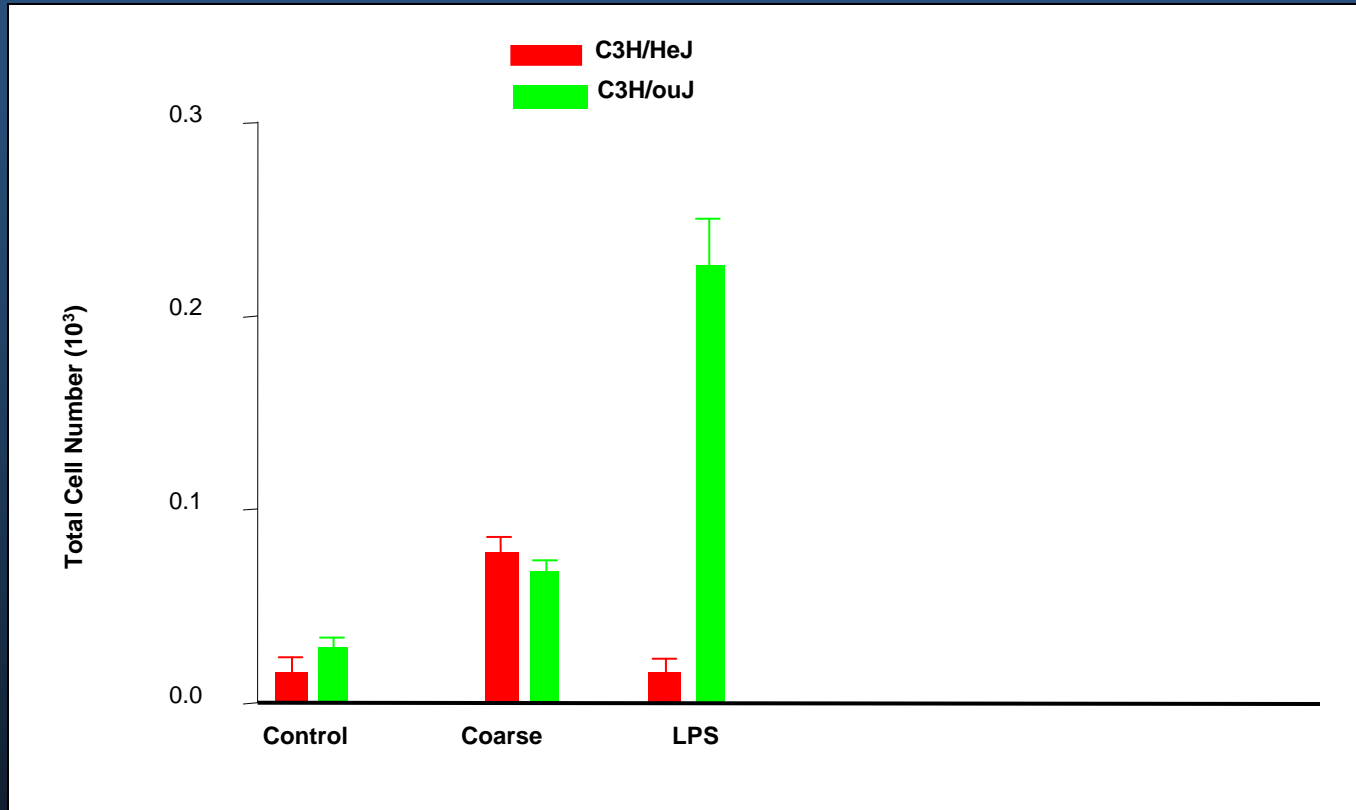


Is LPS Responsible for Coarse Effects?



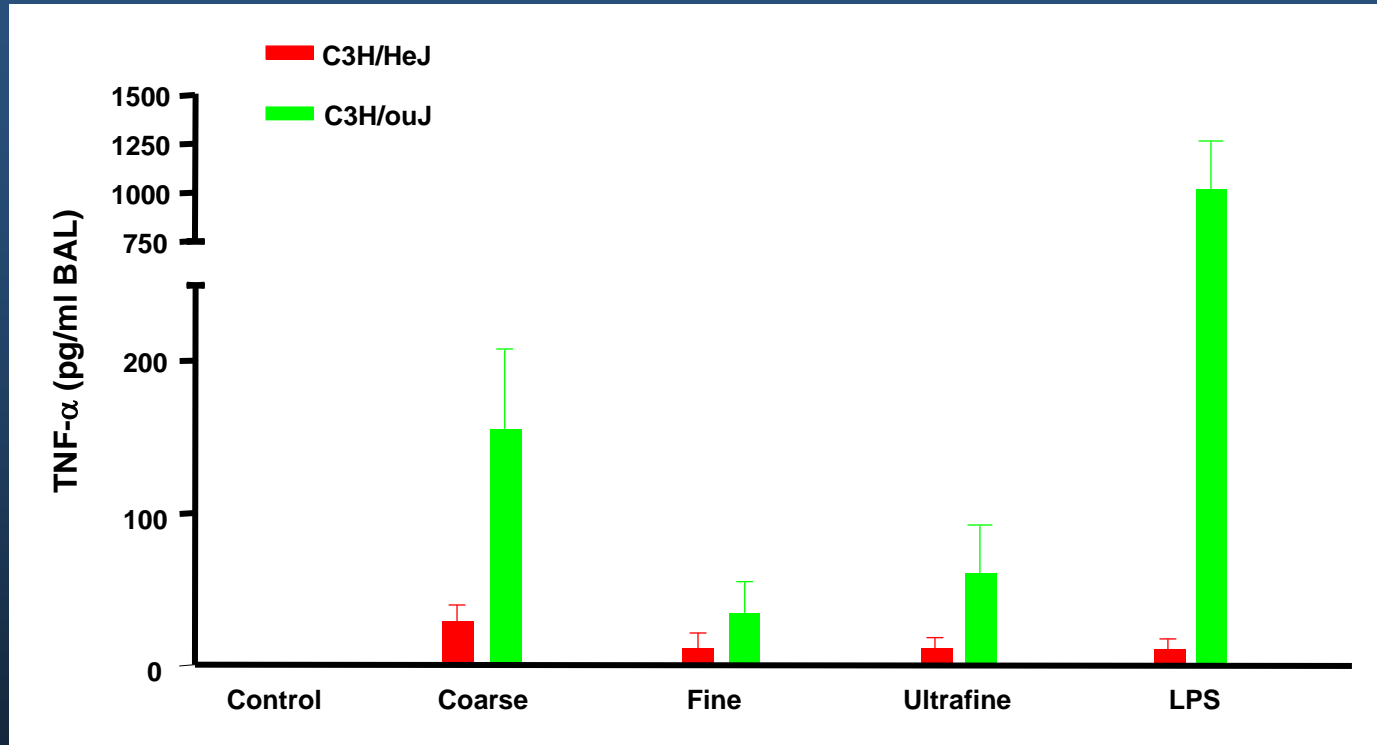
Neither Polymixin B nor E5531 Inhibit IL-8 Production by PM in NHBE cells

PMN Response to Coarse PM in LPS Sensitive and Insensitive Mice



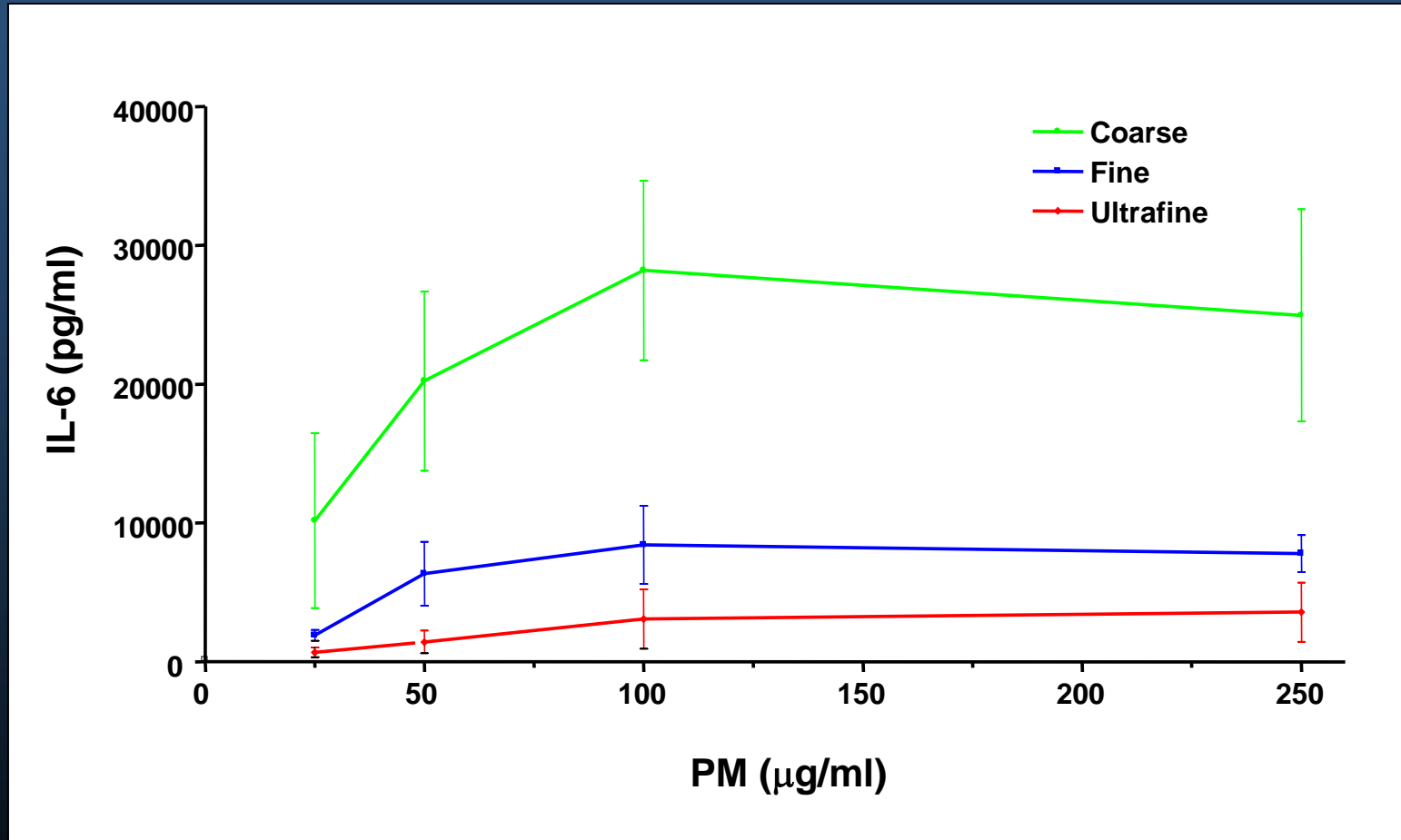
No strain-specific differences in pulmonary neutrophils were evident across the various size fractions suggesting that LPS was not required for this effect.

TNF Response to Coarse PM in LPS Sensitive and Insensitive Mice

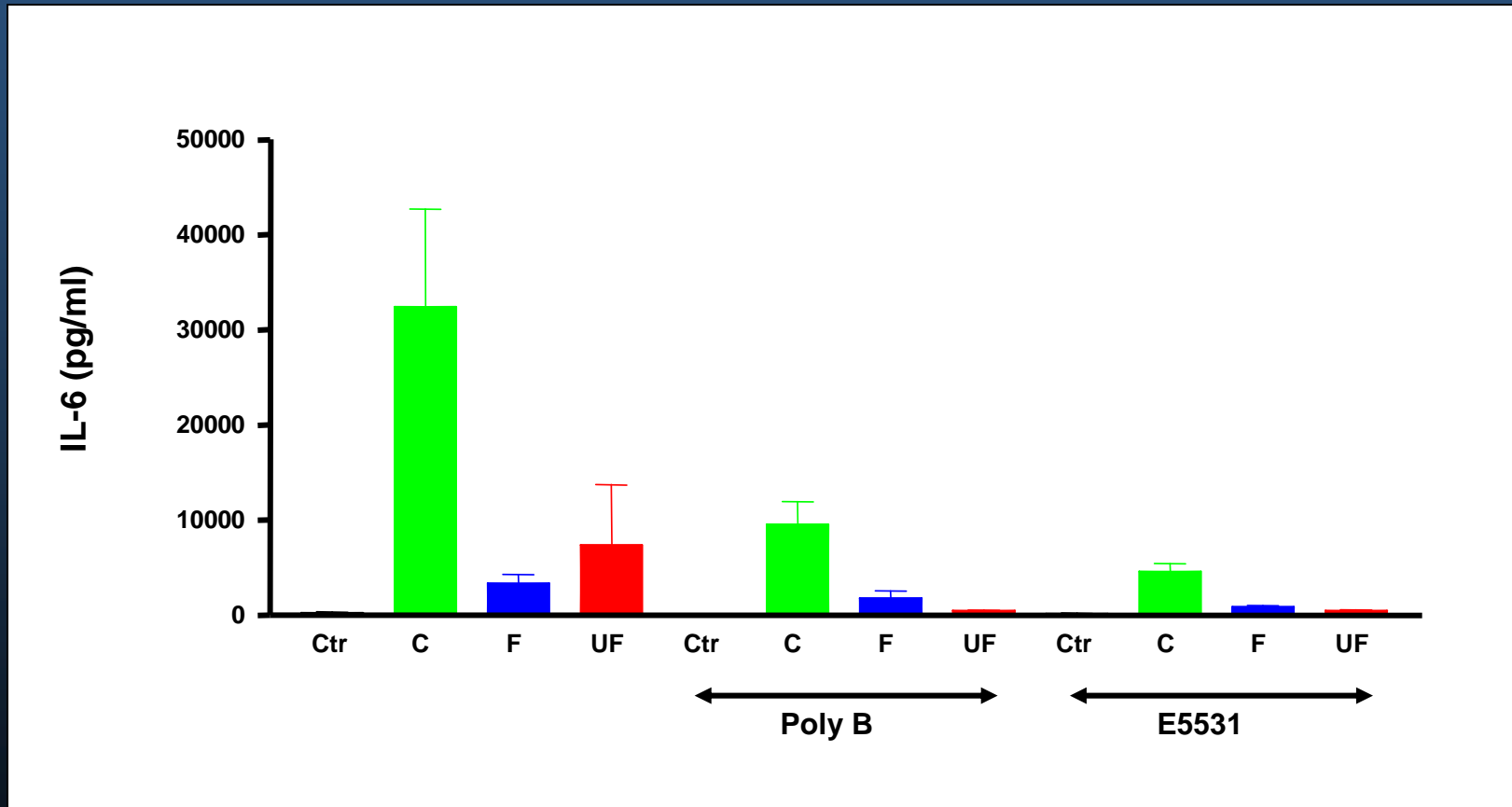


- TNF is likely produced by alveolar macrophages (known to respond to LPS) whereas the PMN response is likely mediated by IL-8 produced by epithelial cells (which do not respond to LPS).

Coarse PM Stimulates More Cytokine Production in Alveolar Macrophages

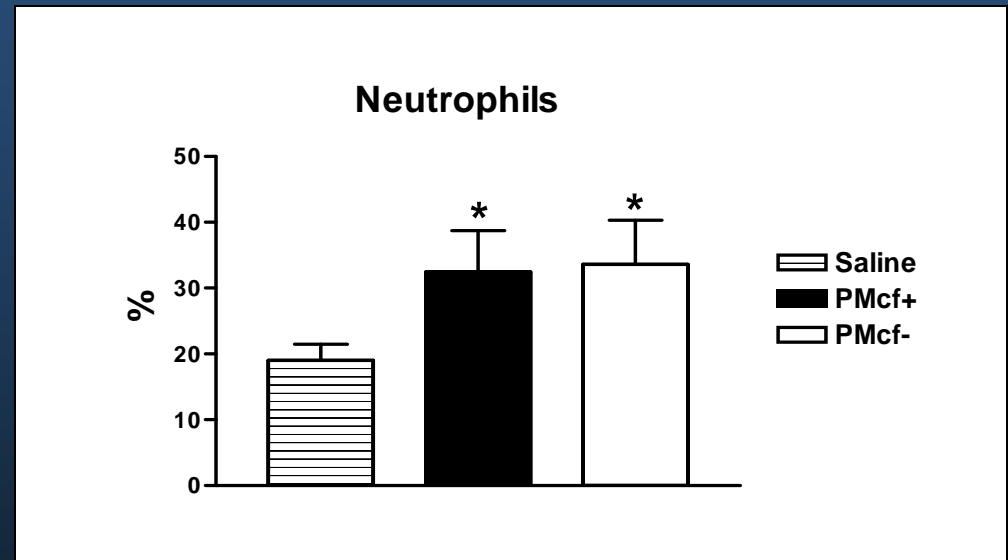


LPS Inhibitors Block Production of IL-6 by AM

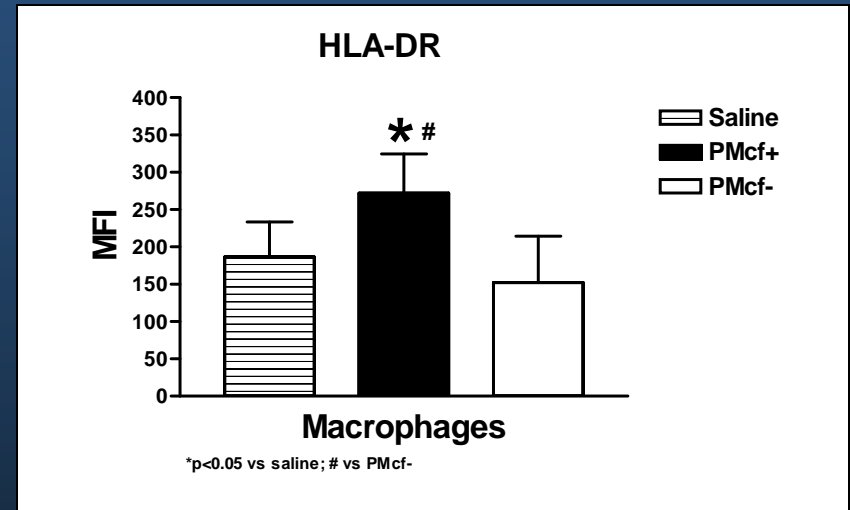
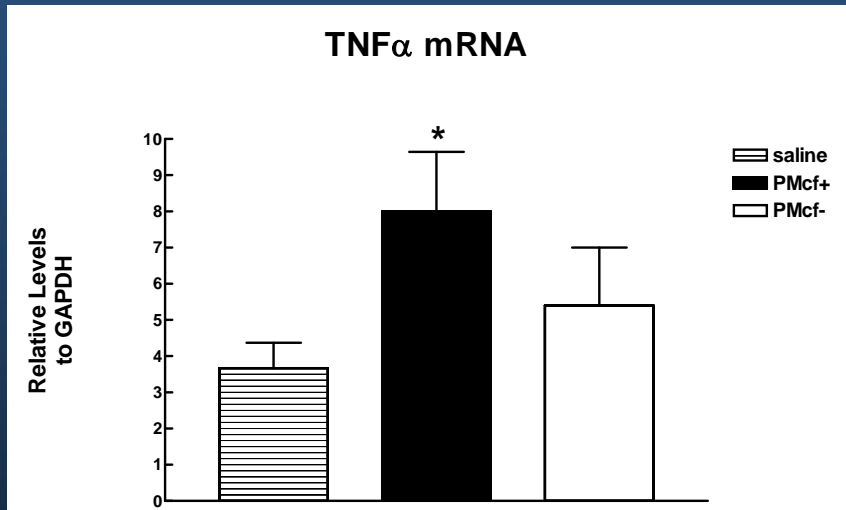


Heat Inactivation of Coarse PM Does Not Diminish PMN Response in Human Volunteers

- Coarse PM was collected in Chapel Hill and UV treated to inactivate viable bacteria.
- A portion was baked at 120°C for 20hrs to inactivate LPS.
- PM was administered to volunteers via nebulization
- Each subject was exposed 3 times: once to unbaked PM, once to baked PM, and once to saline.
- Induced sputum was collected 3hrs after exposure.



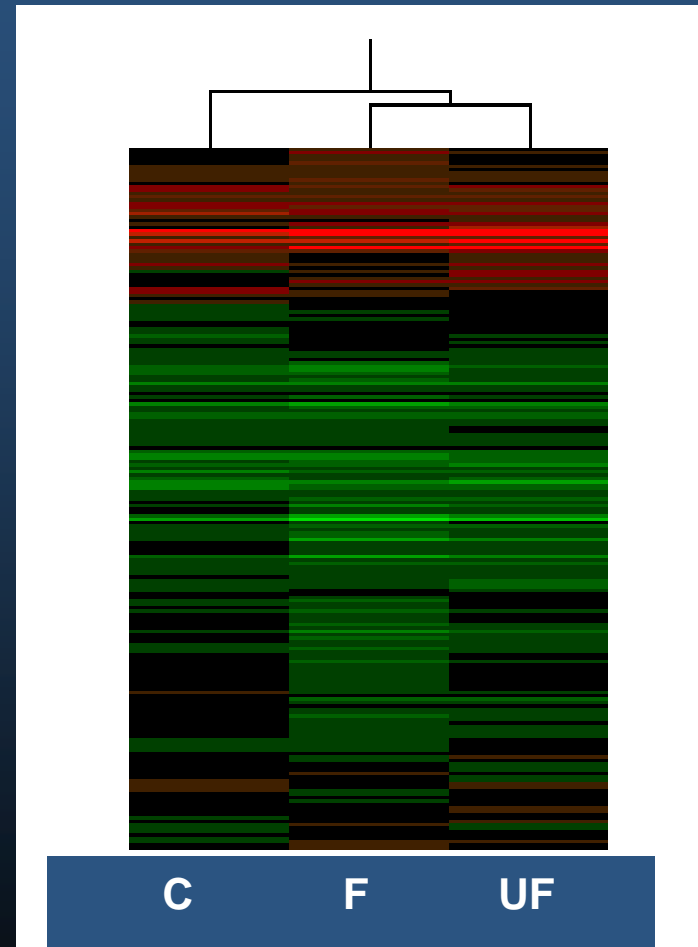
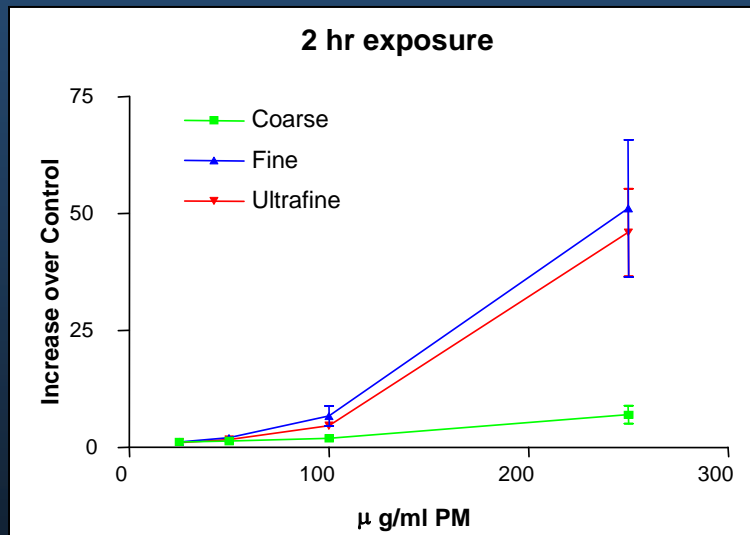
Heat Inactivation Does Diminish TNF and HLA-DR Response



- LPS present on coarse PM does not appear to affect processes driven by epithelial cells
- It does, however, stimulate macrophages.

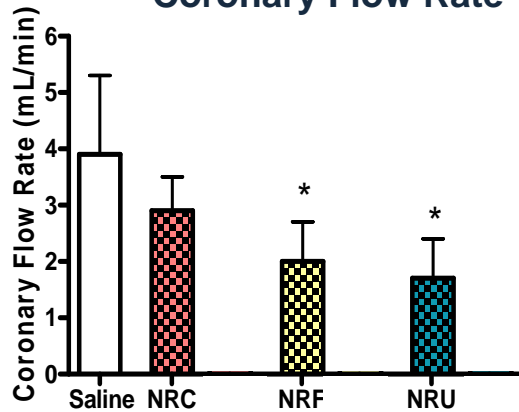
Is Coarse PM Always More Potent than Fine or Ultrafine PM?

Heme Oxygenase mRNA

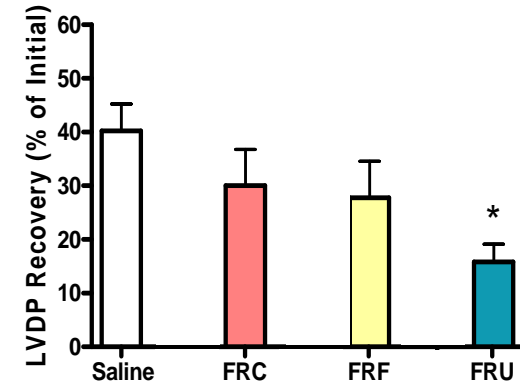


Langendorff Perfusion System

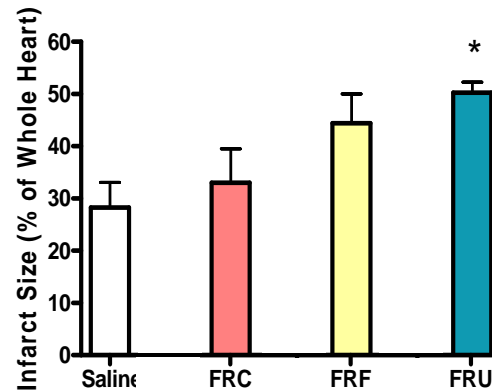
Ultrafine PM Reduced Baseline Coronary Flow Rate



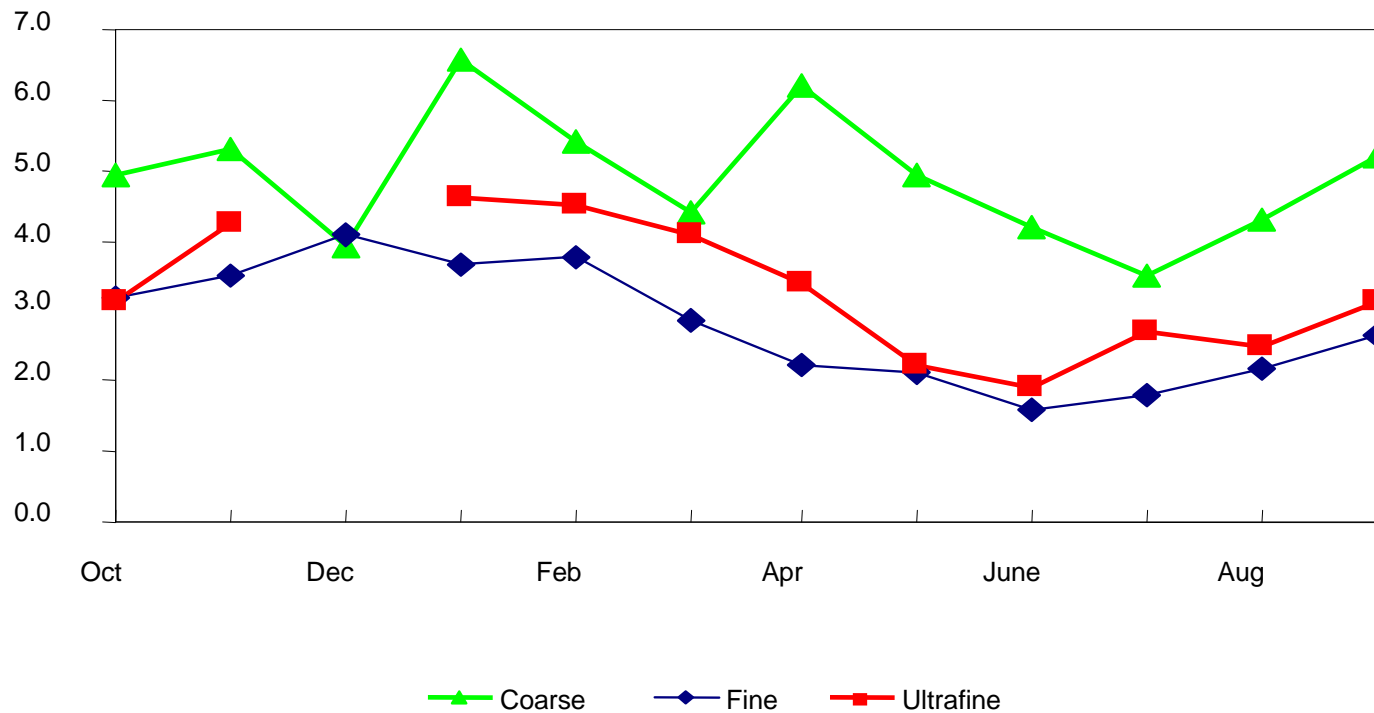
Ultrafine PM Decreased Recovery of Post-Ischemic Cardiac Function



Ultrafine PM Increased Cardiac Necrosis



Seasonal Variation in IL-8 Response



Summary

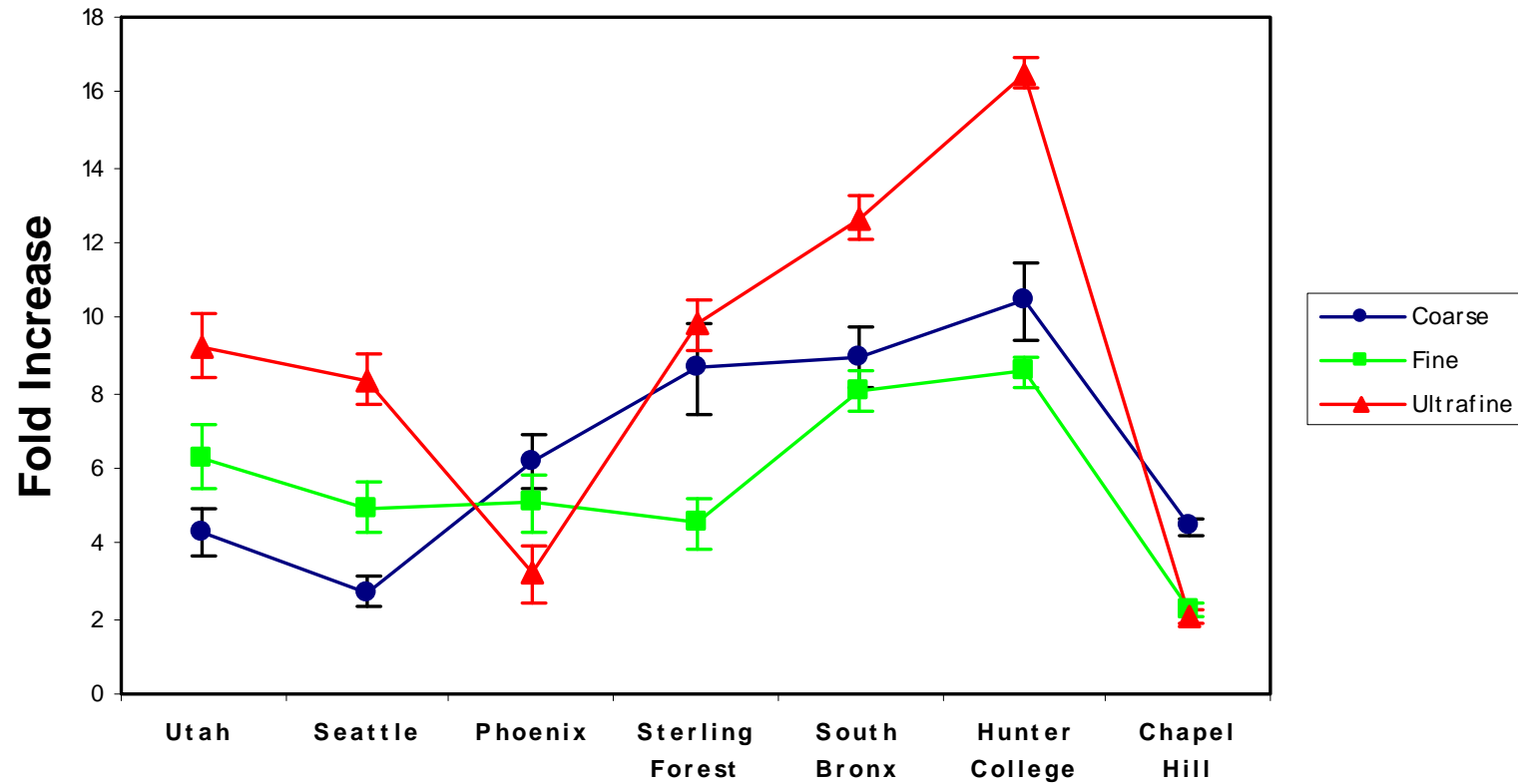
- **Size fractionated particles collected in Chapel Hill, NC cause different effects, depending on the cell type.**
- **Coarse particles seem to cause more inflammation, which does not seem to be driven by LPS.**
- **Fine and ultrafine particles cause more oxidative stress**
- **Ultrafine particles cause cardiac effects.**

Beyond PM Mass

- Particles were collected in 7 US cities
- Cities were chosen because they have different source profiles

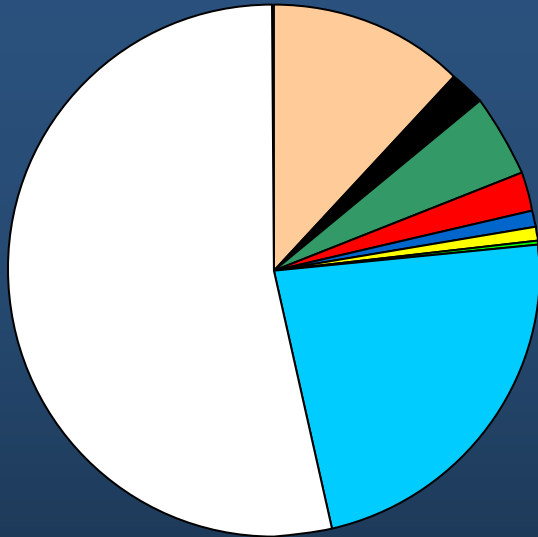


IL-8 Levels in C, F, UF PM Collected from MAPS Cities

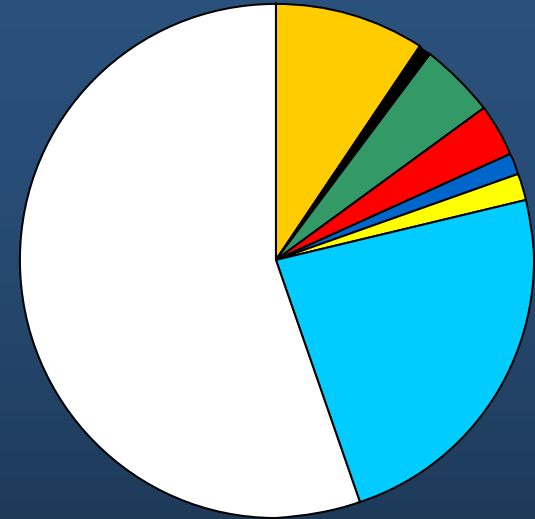


Coarse

Seattle



Utah



South Bronx

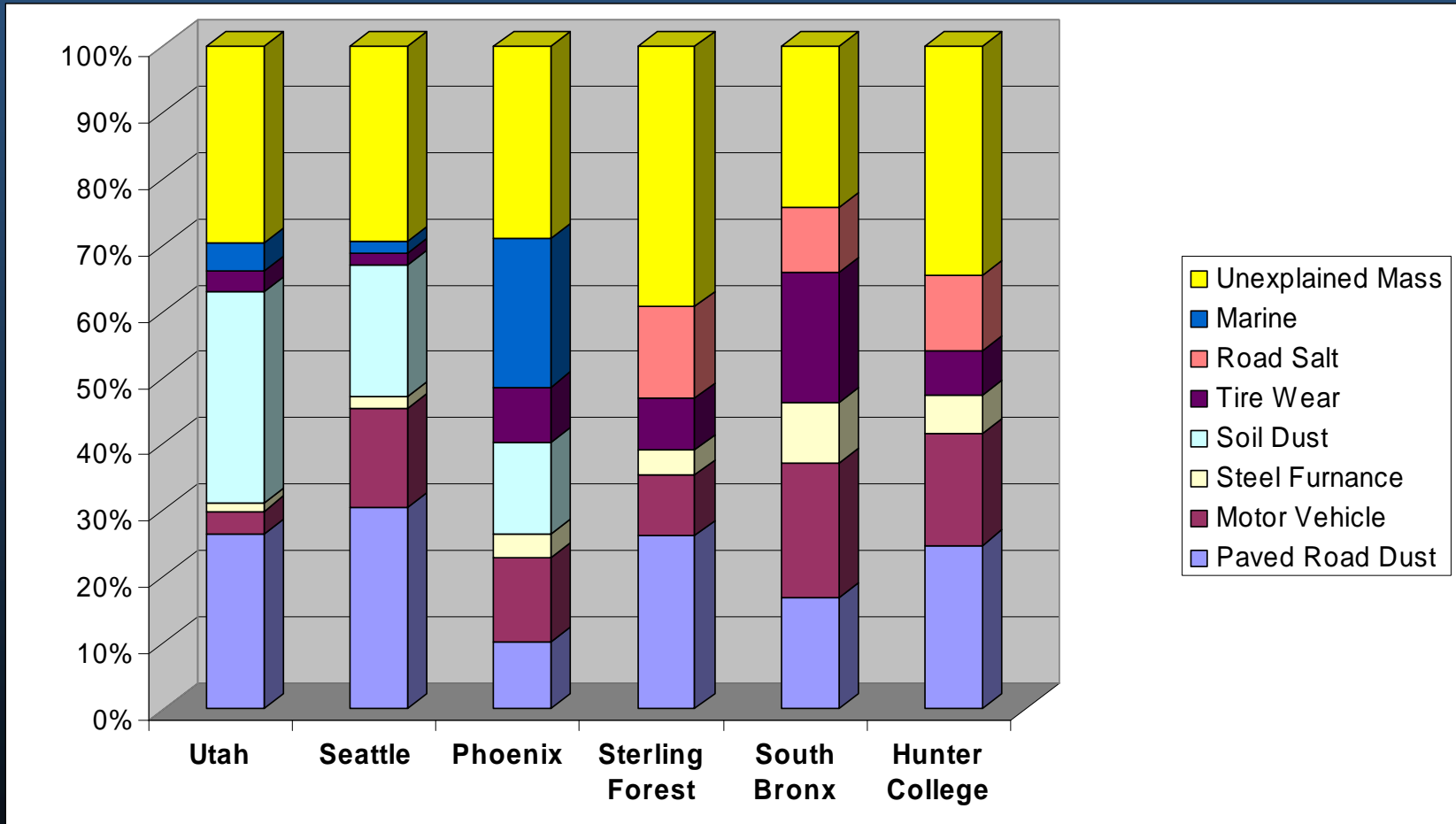


Sterling Forest

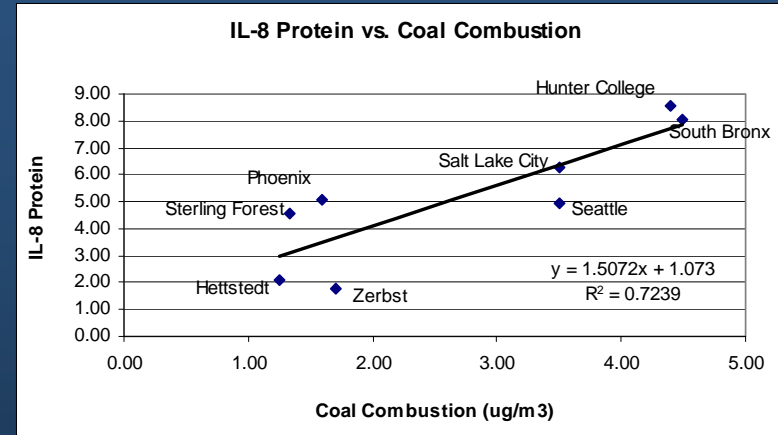
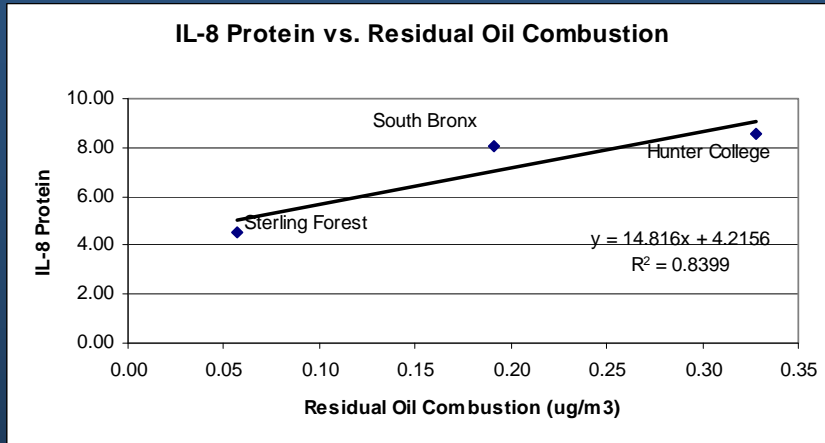


- Unknown
- Organic Carbon
- Elemental Carbon
- Ammonium Ion
- Nitrate
- Sulfate
- Sodium
- Chloride
- Sum Method 200.7 Elements, no Na

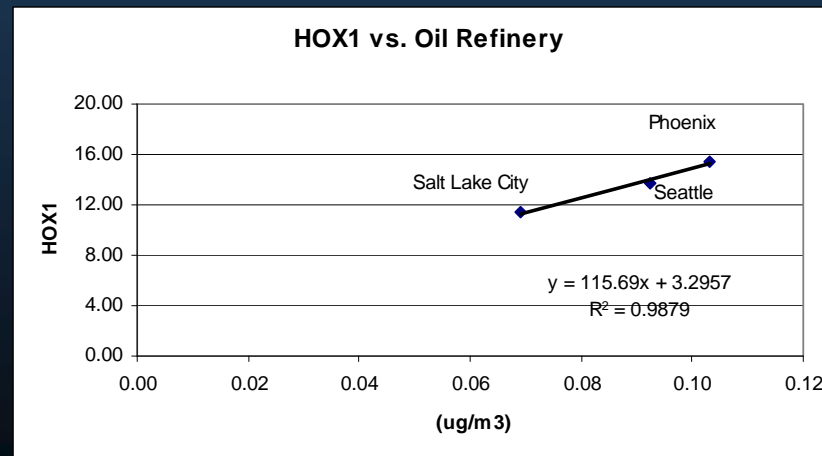
Source Profile of PM in MAPS Cities



Association of Biological Changes to Sources in MAPS Cities



IL-8 protein is correlated with coal combustion ($r^2=0.72$) and residual oil combustion ($r^2=0.84$)



HOX1 is correlated with Oil Refinery ($r^2=0.98$)

Acknowledgements

CAPs Studies

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