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

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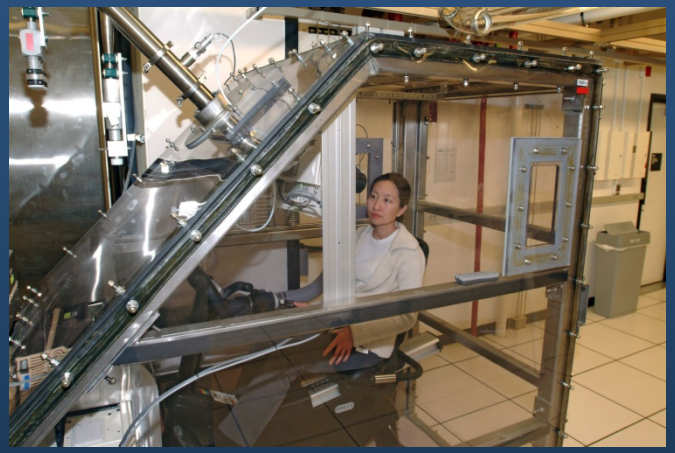
Three Approaches

- 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 in vitro toxicology studies
  - Understand mechanisms by which each size fraction causes adverse health effects
  - Compare the relative potency of particles collected from differetn geographical locations and across seasons

Exposure of Healthy Volunteers to Size Fractionated CAPS



V_E 20 L/min-m2,

Pre	2 Hr Exposure Clean Air and CAPS	0 Hr Post	24 hr Post
Lung function Blood Draw HRV DL_{CO}		Lung function Blood Draw HRV DL_{CO}	Lung function Blood Draw HRV DL_{CO} BAL

Particle Characterization

Mass
Filters, TEOM, Data RAM

Size
MOUDI
Particle Number (Ultrafine)

Biologicals
LPS
microbes

Chemical Composition
Elements - XRF, ICP-MS (water soluble metals)
Anions - IC (sulfate, nitrate), pH
Carbon - organic and elemental
SEM/EXD (coarse)

	Age (yrs)	PM Mass Concentration (ug/m^3)	PM Number Concentration (10e^3/cc)	PM Size (NMAD)
Fine	18-40	120.4 ± 14.1	-	0.65 ± 0.03
Coarse	18-35	89.0 ± 49.5	-	3.59 ± 0.58
Ultrafine	18-35	47.0 ± 20.2	151.8 ± 165.3	0.049 ± 0.009

Same concentration factor was used in all three studies

Chemical Profiles of PM Collected in Chapel Hill, NC

		October			April	
ng/ml	Coarse	Fine	Ultrafine	Coarse	Fine	Ultrafine
pH	4.72	3.70	3.87	4.68	3.74	4.24
Aluminum	1900	555	559	1950	310	408
Arsenic	2.42	19.7	37.0	3.43	14.9	25.3
Bromide	<DL	23.7	52.0	20.8	30.3	31.9
Chromium	5.54	3.62	4.27	5.34	3.37	4.75
Copper	64.9	48.8	64.0	76.7	25.9	31.4
Iron	3020	1132	278	2730	571	327
Lead	10.7	46.2	45.5	13.2	44.4	60.4
Nickel	5.9	7.76	10.9	7.57	8.88	10.3
Nitrate	37400	12200	8550	60300	11400	4130
Nitrite	<DL	94.8	56.2	<DL	115	104
Selenium	2.9	21.2	24.2	5.69	23.6	20.8
Silicon	1660	402	280	2150	243	308
Sulfur	4170	31400	37600	10200	48000	41000
Titanium	40.7	11.4	2.49	38.8	7.01	6.26
Vanadium	7.01	19.6	19.0	9.01	22.0	18.2
Zinc	116	311	577	174	221	238
OC, mass frac.	0.172	0.185	0.156	0.104	0.098	0.147
EC, mass frac.	0.008	0.041	0.064	0.008	0.032	0.038
CC, mass frac.	0.017	0.010	0.008	0.02	0.011	0
Non-CC C mass frac. (OC+EC)	0.180	0.226	0.220	0.112	0.13	0.186
Total C mass fraction	0.197	0.236	0.228	0.132	0.141	0.186

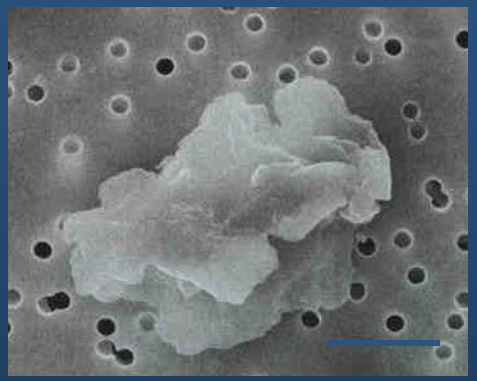
Approximate Concentration of Various Particle Types in Coarse PM

	Number %	Mass %
Non-Carbonaceous	75.0	87.2
MgAlSi	23.6	31.2
CaS + AlSi	8.2	5.7
AlSi	6.8	12.1
Ca-MgAlSi	6.7	9.9
Fe, TiAlSi	5.7	4.0
Quartz	5.1	5.8
Fe-rich	4.2	2.9
Other	6.6	8.6
Carbonaceous	25.0	12.8
Pollens	9.5	5.1
Spores, bacteria	6.9	3.6
Other Carbon	8.6	4.1

Analysis was done by scanning electron microscopy coupled with energy dispersive X-ray spectroscopy of several hundred particles

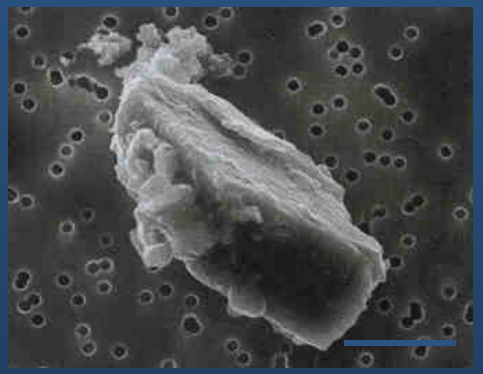
This type of analysis may under-represent carbonaceous components.

Various Particle Types in Coarse PM

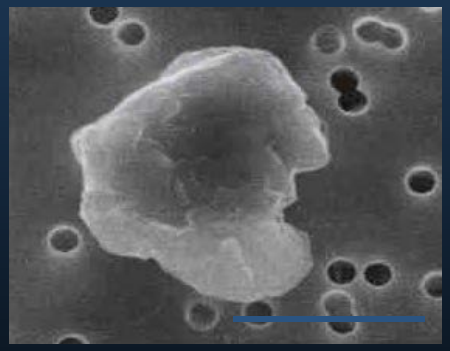


AlSi

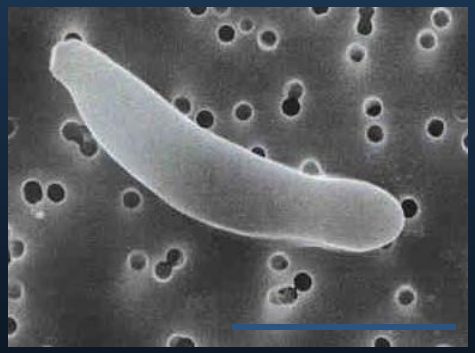
Spherical Fe rich



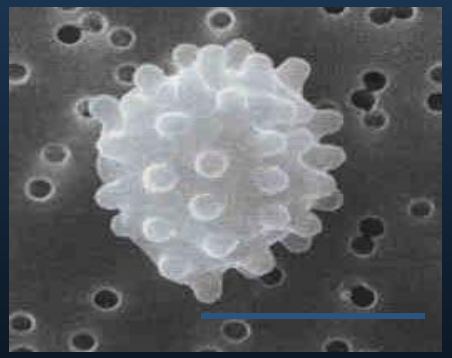
NaAlSi



Quartz



Pollen



Pollen

Exposure of Healthy Young Volunteers to Coarse, Fine, and Ultrafine CAPS

	Pulmonary Function	BAL Fluid Cells	BAL Fluid Markers	Cardiac Endpoints	Plasma Markers
Fine	No Effect	↑ PMNs ↑ Monocytes	↓ IL-8 ↓ Fibrinogen	No Effect	↑ Fibrinogen ↓ WBCs
Coarse	No Effect	↑ PMNs	↓ Protein	↓ SDNN	↓ tPA
Ultrafine	No Effect	No Effect	↑ IL-8	↑ HF ↑ QT variance	↑ D-Dimer ↓ VLDL ↓ Triglycerides

Ghio, Kim, and Devlin, 2000 Graff et al., 2009 Samet et al., 2009

Conclusions

- On the whole, the response of healthy young volunteers to any size class of particles was modest at best.
- Additionally, no one size class appeared to be significantly more potent than the others.
- There is a trend for mild pulmonary inflammation, increased potential for a more pro-thrombogenic environment, and decreased HRV.
- Its possible that these changes, though modest in healthy individuals, may be more substantial in susceptible populations.
- The concentrations used in these studies were not high; studies utilizing higher concentrations might yield more pronounced effects.

Effects of Fine CAPS on Healthy Young and Elderly Volunteers

	HRV	Blood Cells	Soluble Blood Markers
Young Population	No Effect	↓WBC	↑ Fibrinogen
Older Population	↓ SDNN ↓PNN50 ↓HF ↑VE	↑WBC ↑Lymphocytes ↑Monocytes	↓tPA ↑Prothrombin ↑Plasminogen ↑PAI-1

Average Age = 67

Devlin et al., 2003

Exposure of Healthy Middle-Aged Volunteers to Fine Plus Ultrafine CAPS

	Pulmonary Function	BAU and BP	Cardiac	Vascular
Fine	↓ DLco	↑DBP ↓ FMD	↓ SDNN (GSTM1-) ↓ PNN50 (GSTM1-) ↑ QTc ↑ QT	↓D-dimer (GSTM1-) ↑ Triglyceride ↑ VLDL ↓WBC
Ultrafine	↓ DLco (GSTM1-)	↓ FMD	↓ SDNN ↓ PNN50 ↑ QT	↓D-dimer (GSTM1-) ↓Plasminogen (GSTM1-) ↑ WBC (GSTM1-) ↑ PMNs (GSTM1-)

Average Age = 58

Average Mass = 293.2 $\mu g/m^3$
Average particle #/cc = 336,460

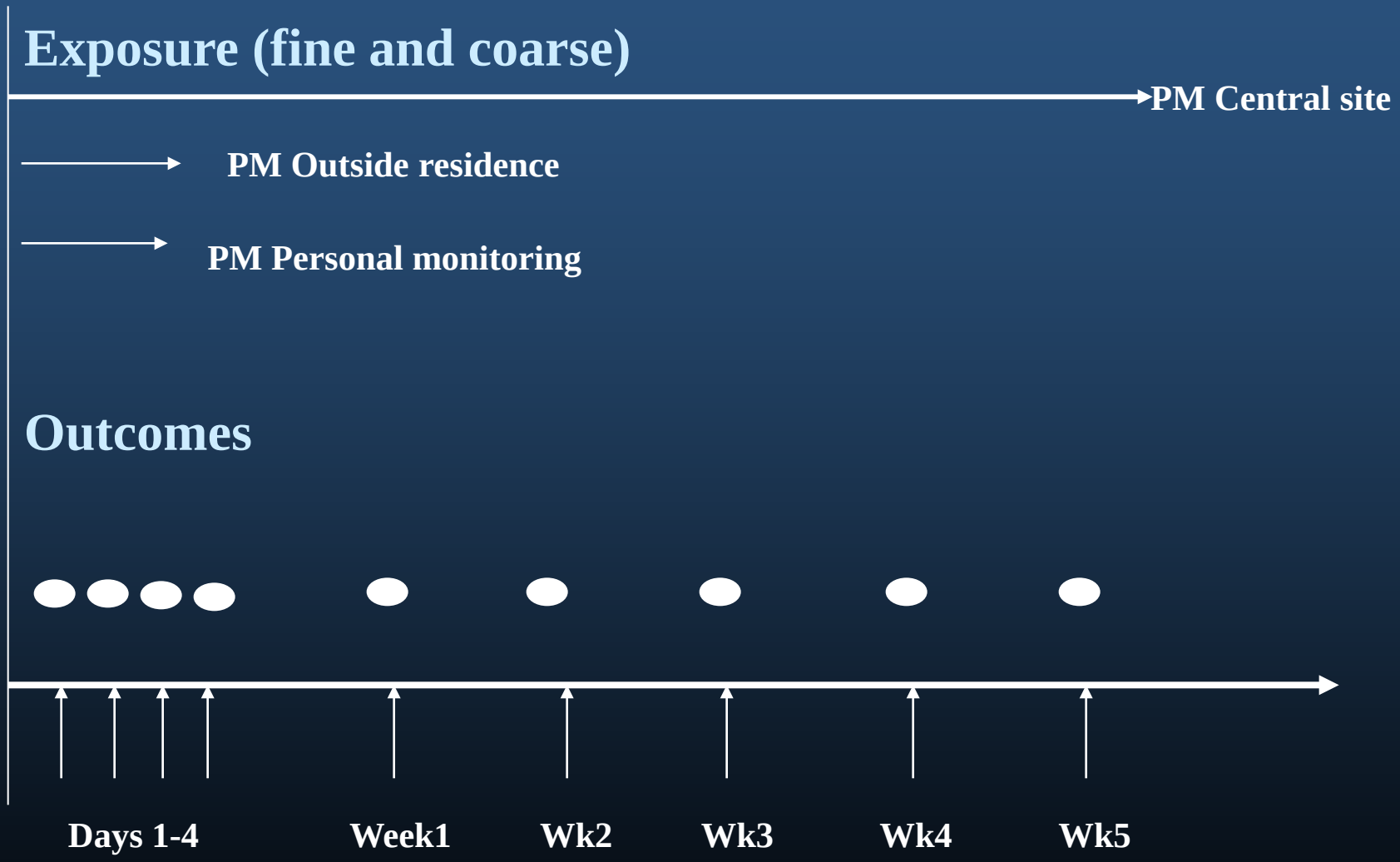
Tong et al., 2012

Association of Fine and Coarse PM with Biological Effects in Adult Asthmatics

RTP Asthmatic Panel Study

- Biological materials are found predominately in coarse PM
- Biological materials can exacerbate asthma
- Are asthmatics more responsive to coarse PM?

- Age (range 18-50)
- Asthma Severity: mild-moderate



Effects of Coarse and Fine Ambient PM on Asthmatics

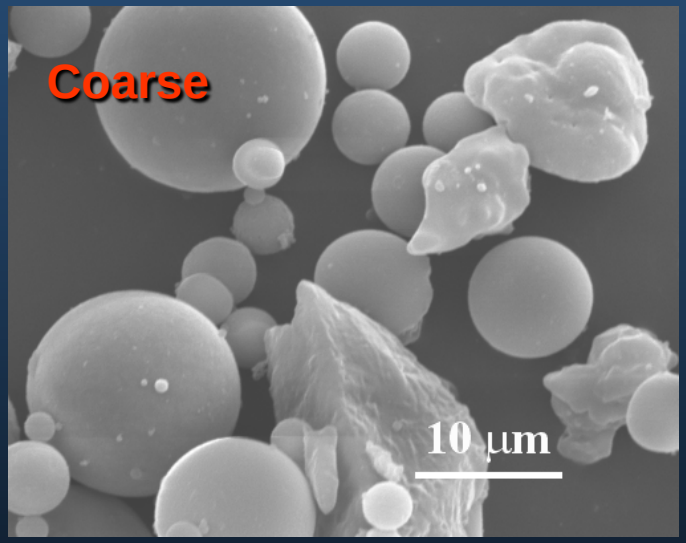
	Lung Function Medicine Use	HRV	Induced Sputum	Blood
Fine PM	No Effect	No Effect	No Effect	No Effect
Coarse PM	No effect	↓ SDNN ↓PNN50 ↓HF	No Effect	↑Eosinophils ↑Triglycerides ↑VLDL

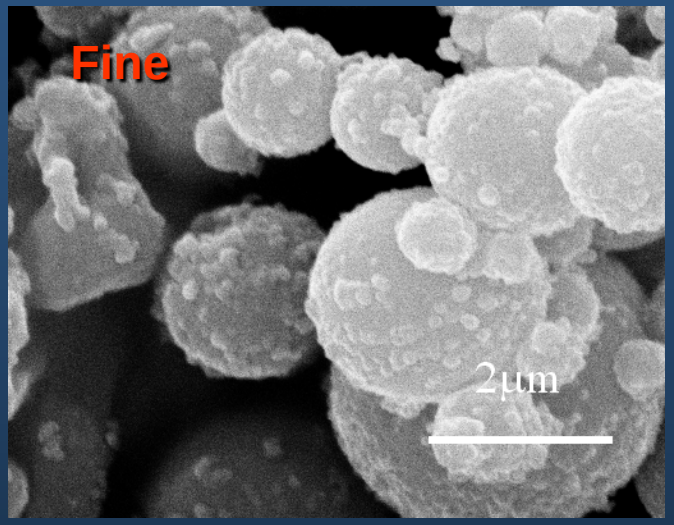
Yeatts et al., 2007

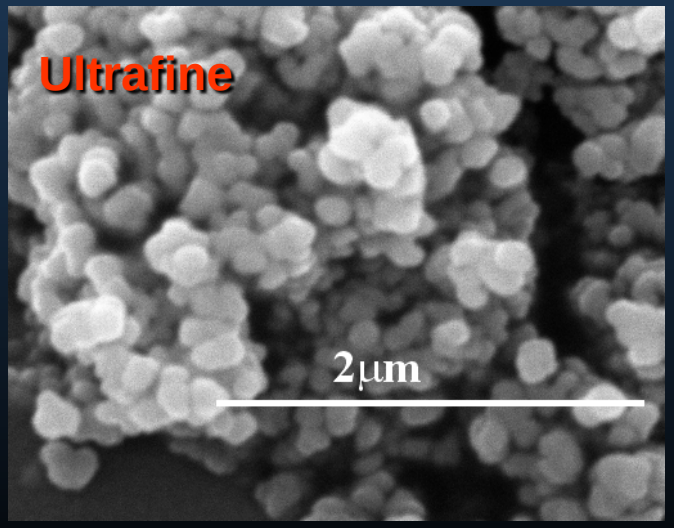
Ongoing Studies

- Response of mild asthmatics and healthy subjects to both fine and coarse CAPS
- Panel study comparing the response of mild, moderate and severe asthmatics to fine and coarse PM
  - In vitro challenge of cultured cells with fine and coarse PM
- Panel study comparing the response of black children who are refractory to asthma medication with black children who are not to fine and coarse PM

Toxicological Changes Associated with Different Size PM From Chapel Hill

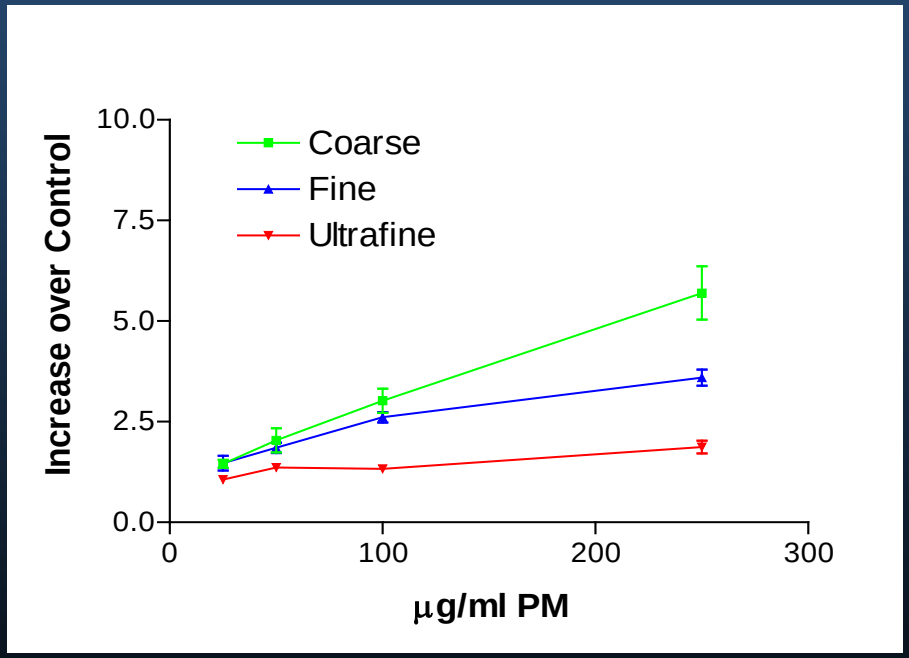




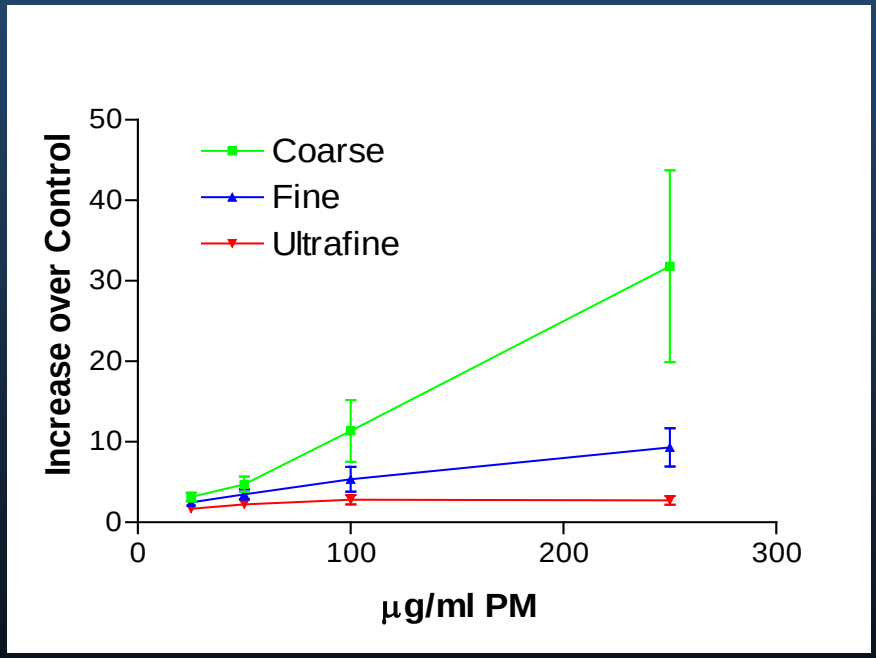


Coarse PM Elicits Larger IL-8 Production Than Fine or Ultrafine PM at 24 Hrs

Protein



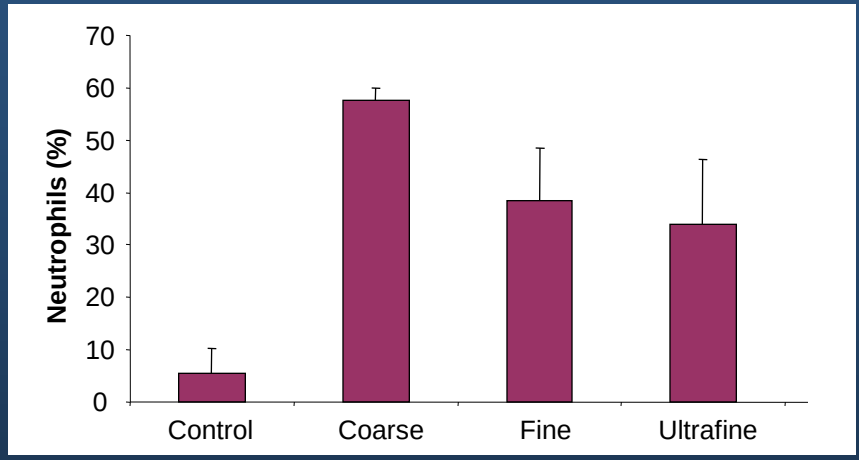
mRNA

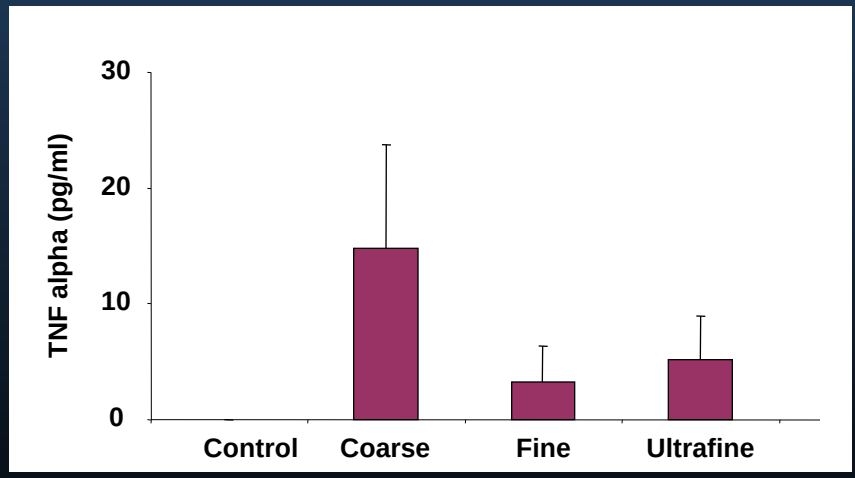


Coarse PM Causes More Inflammation in Mice

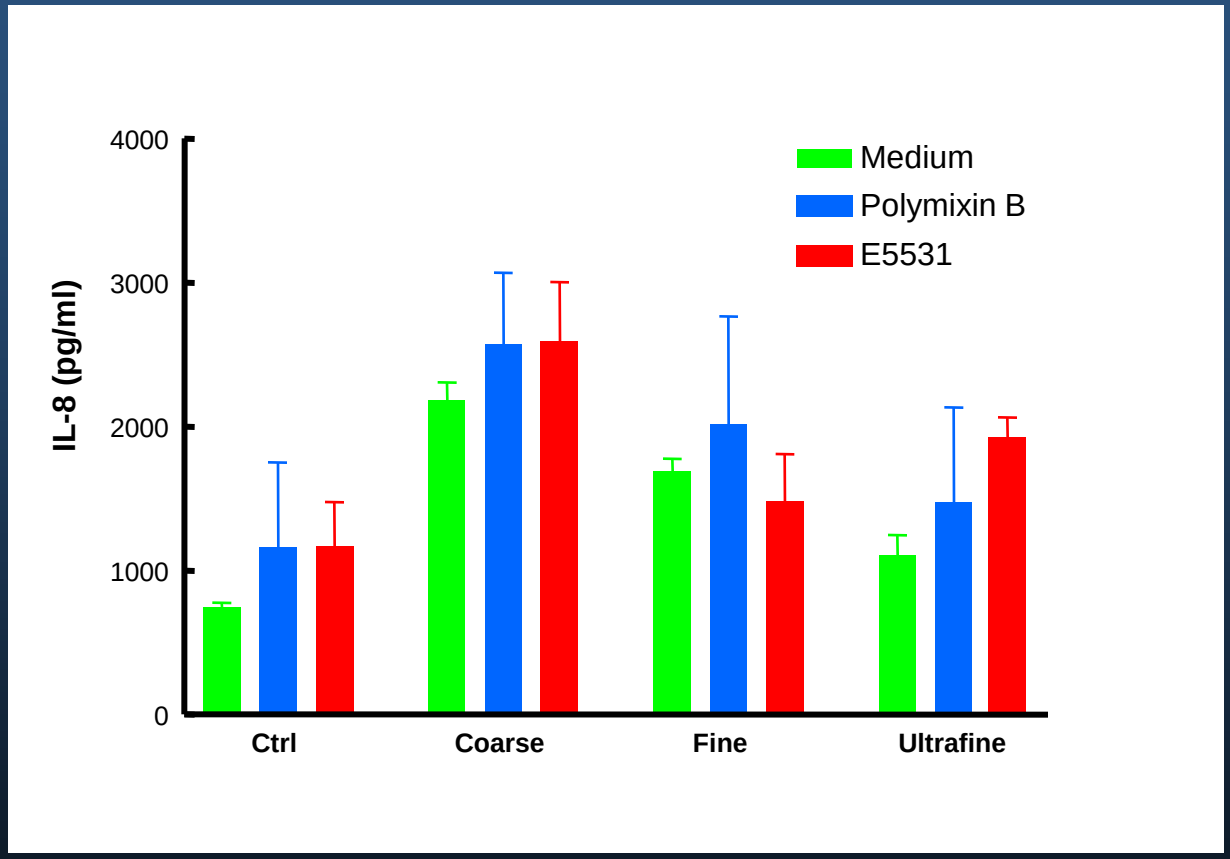
Saline and 100 μg coarse, fine, or ultrafine PM were instilled into C3H/HeJ mice.

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



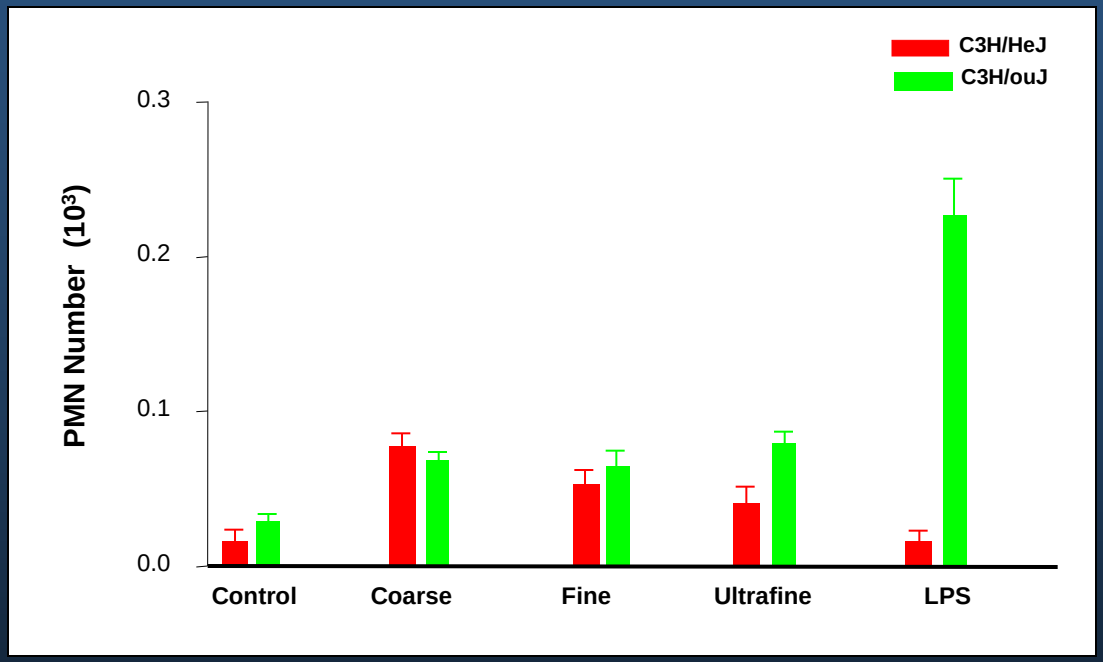


Is LPS Responsible for Coarse Effects?



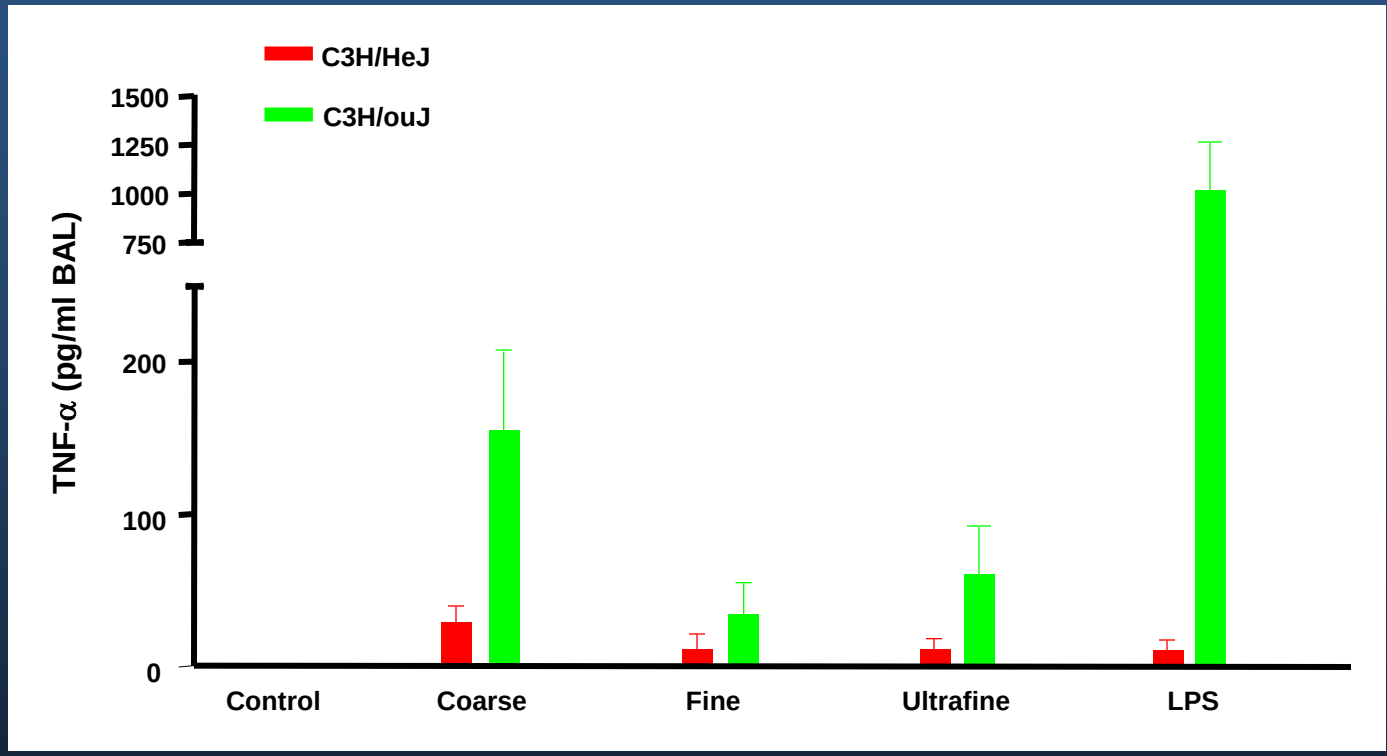
Neither Polymixin B nor E5531 Inhibit IL-8 Production by PM in NHBE cells

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 the this effect.

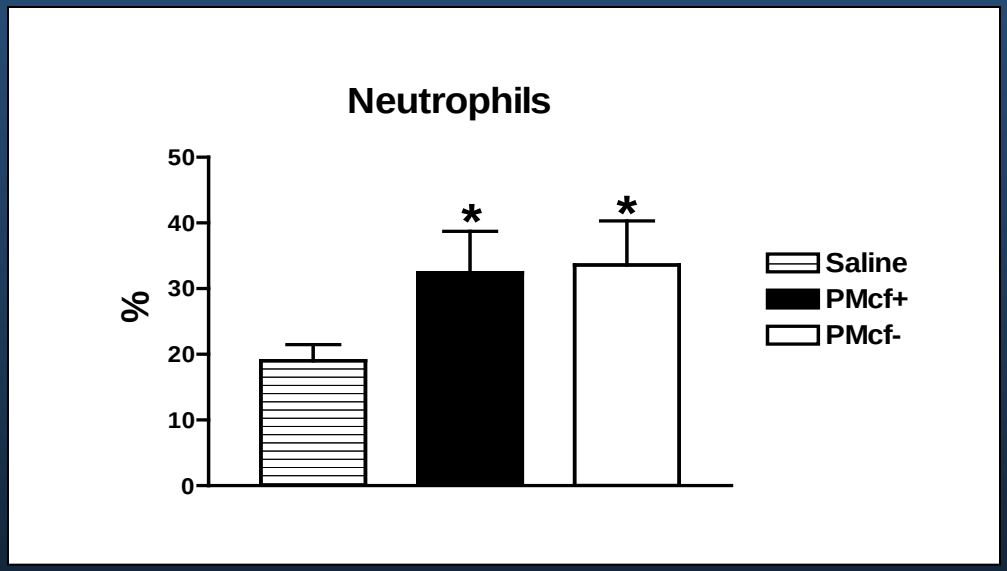
TNF Response to Coarse PM in LPS Sensitive and Insensitive Mice



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).

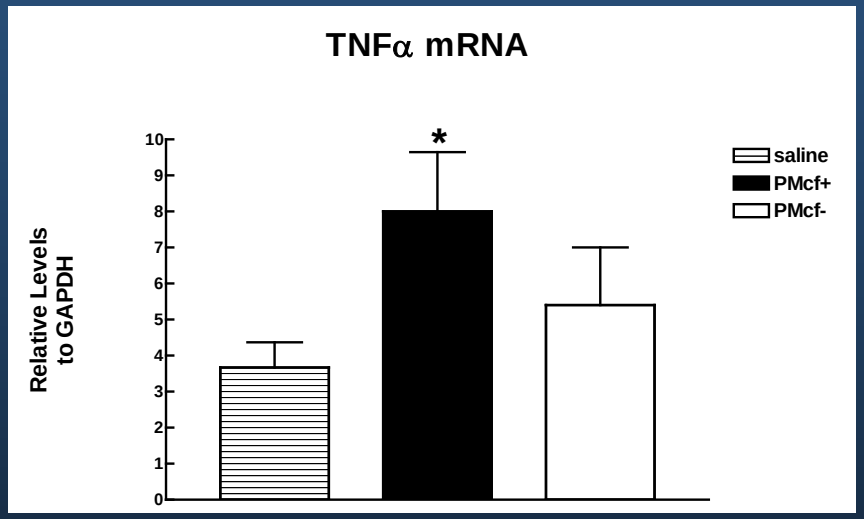
Heat Inactivation of Coarse PM Does Not Diminish PMN Response in Human Volunteers

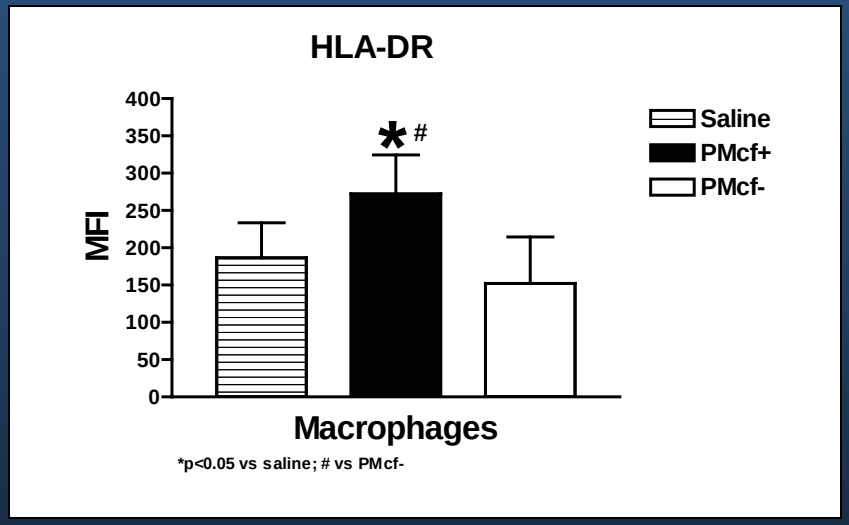
- A portion of coarse PM was heat treated to inactivate LPS..
- PM was administered to volunteers via nebulization (MMAD = 5 μm).
- Approximately .65 mg of PM was deposited in the respiratory tract (equivalent to breathing 70μg/m^3 for 24 hrs).
- Each subject was exposed 3 times: once to unbaked PM, once to baked PM, and once to saline.
- Induced sputum was collected 3hrs after exposure.



Alexis et al., 2006

Heat Inactivation Does Diminish TNF and HLA-DR Response

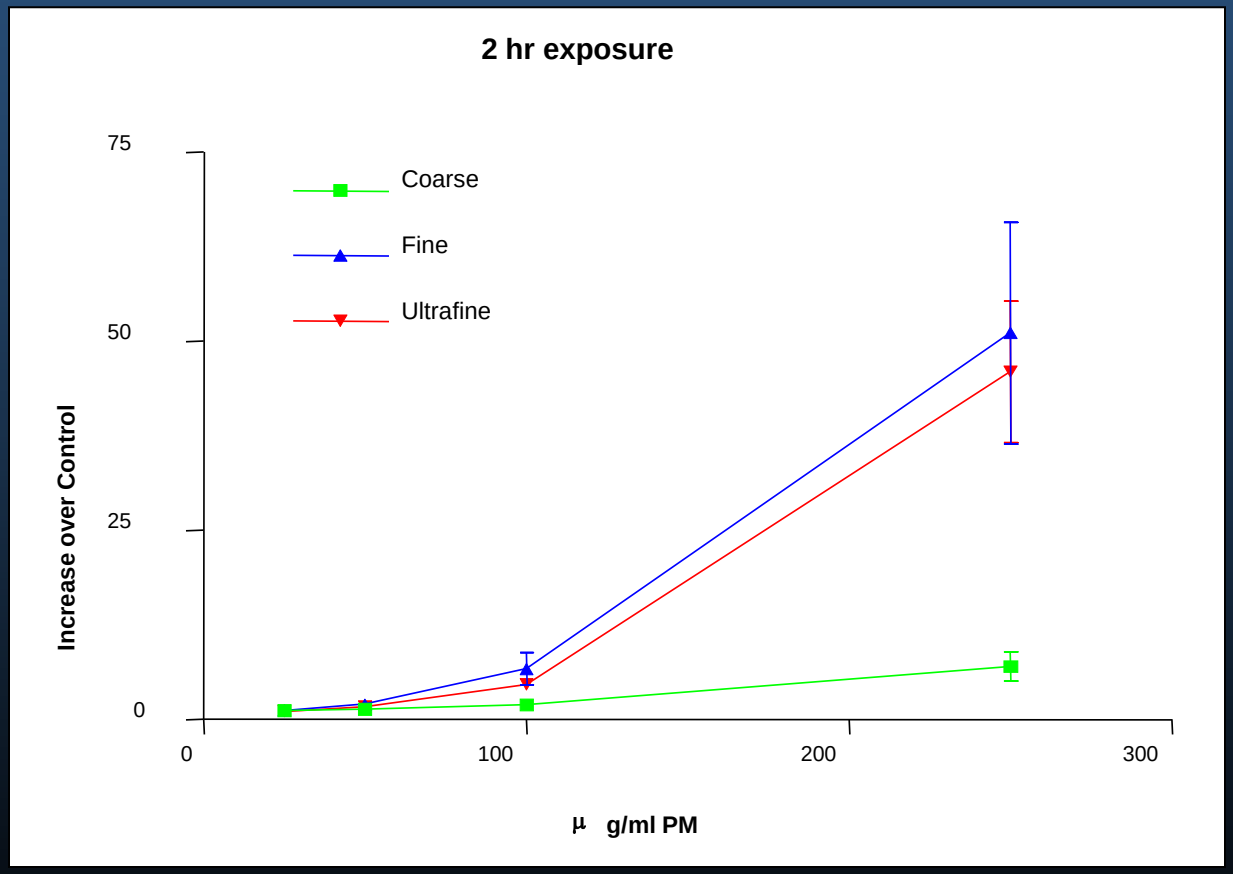




However, biological material present on particles that interacts with cells via the TLR2 receptor (e.g. gram positive bacteria) stimulates the production of inflammatory mediators (Becker et al., 2005)

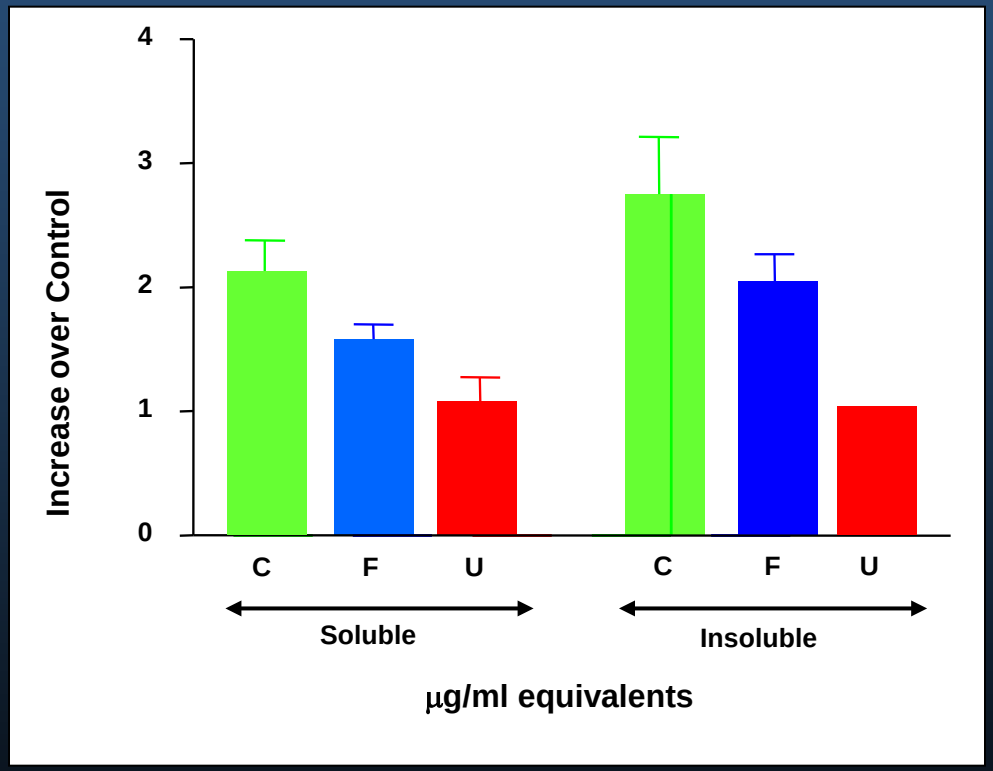
Is Coarse PM Always More Potent than Fine or Ultrafine PM?

Heme Oxygenase mRNA

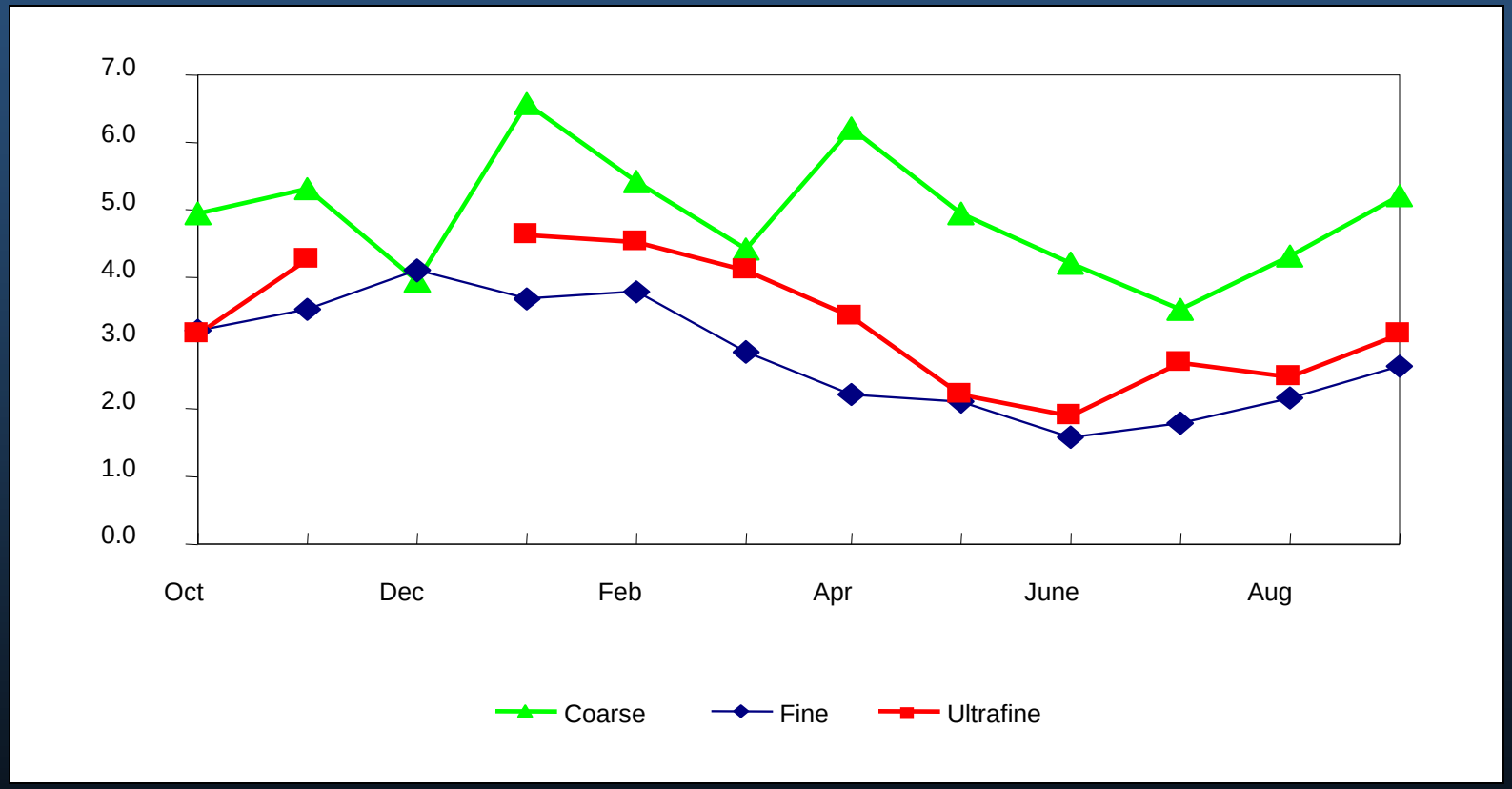


Exposure of Cells to Soluble or Insoluble PM Fraction

IL-8



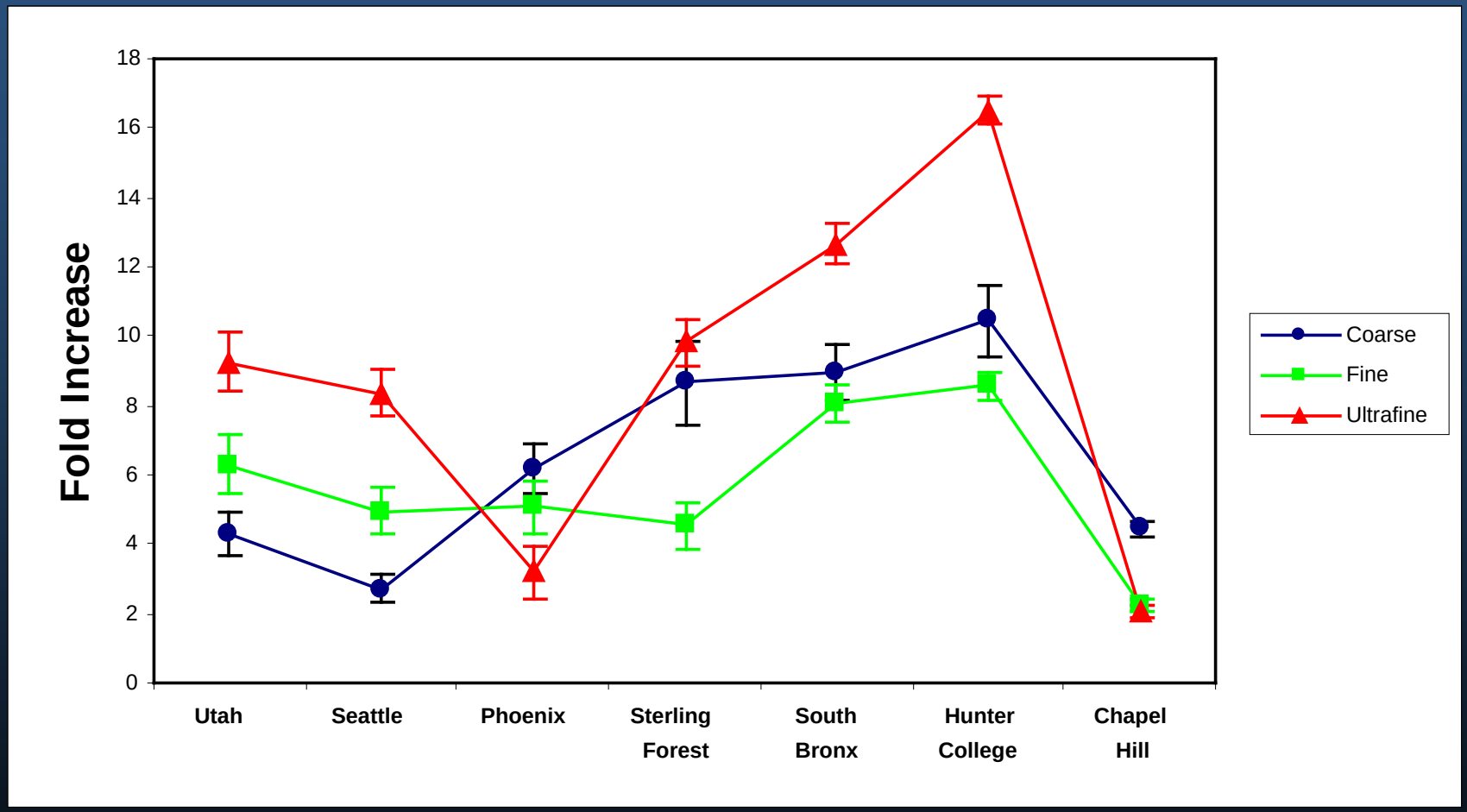
Seasonal Variation in IL-8 Response



Multi-city Air Pollution Study (MAPS)

- Particles were collected in 7 US (and 2 German) cities
- Cities were chosen because they have different source profiles

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



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