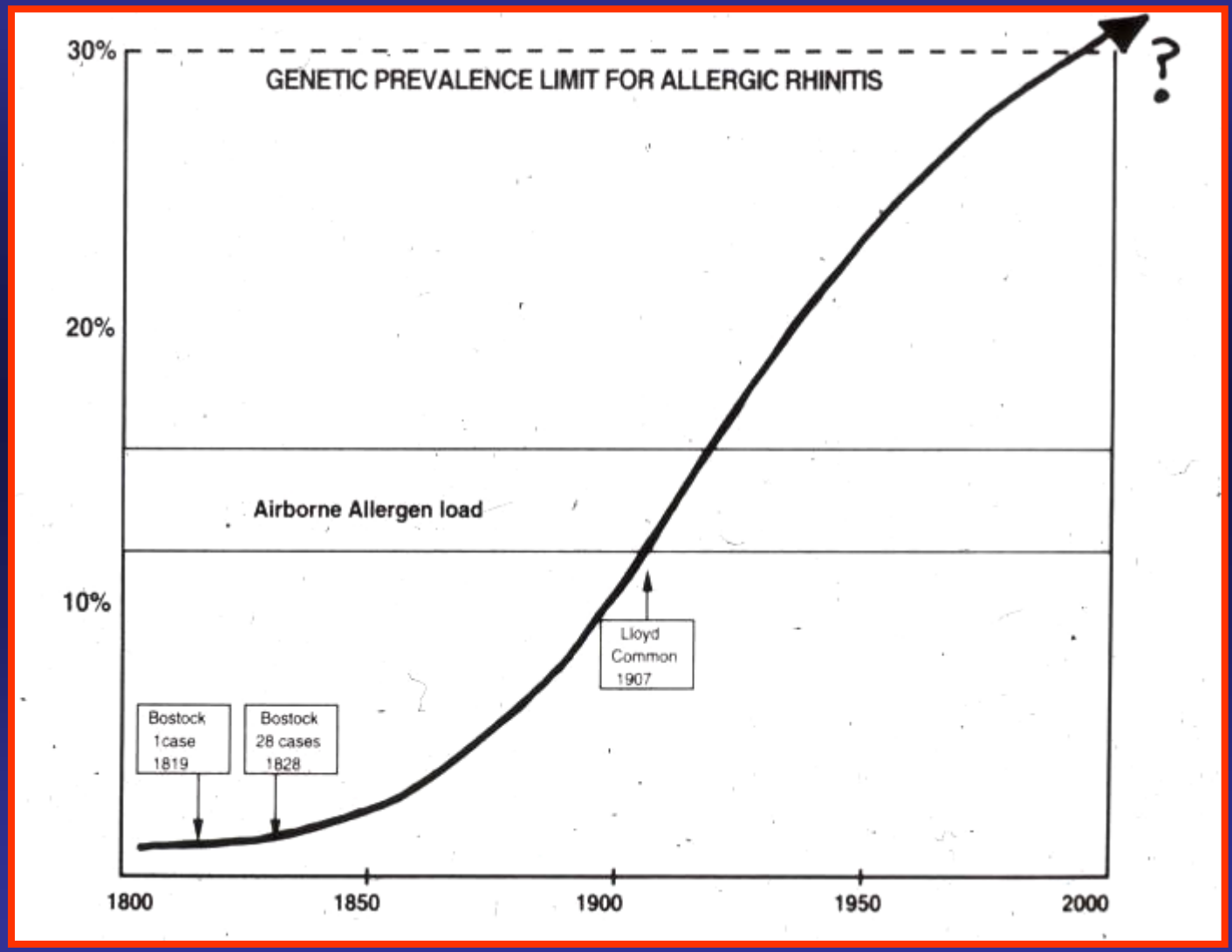
Pulmonary Health Effects I: Inside the lungs

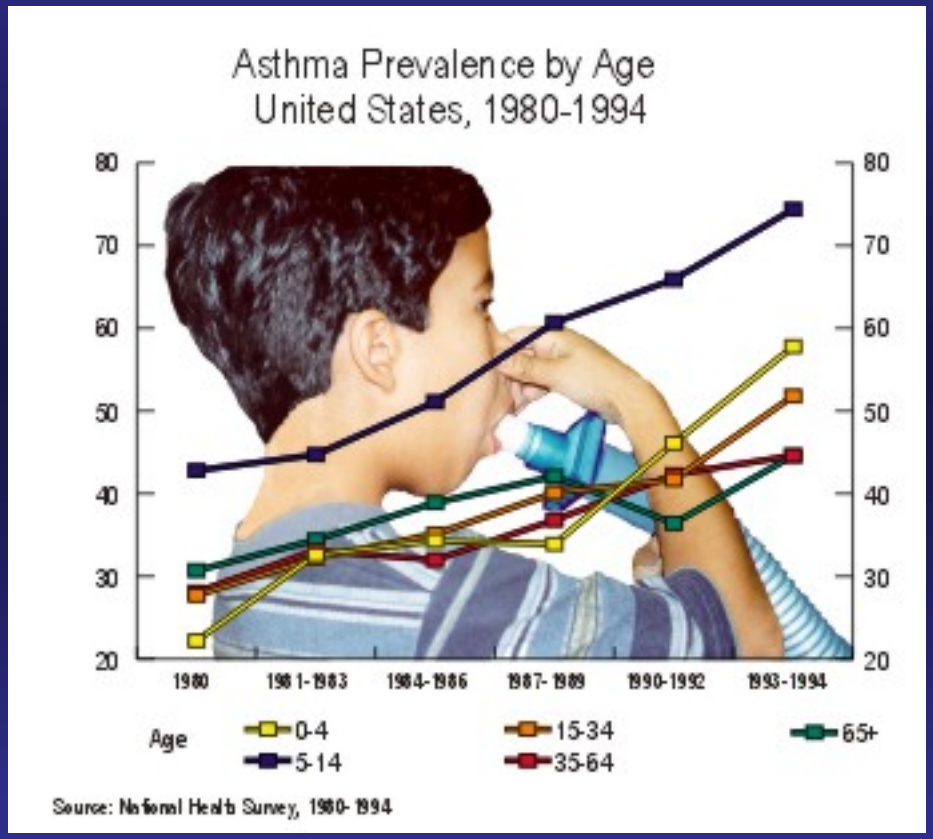
University of California Los Angeles
University of Southern California
Michigan State University
University of California Irvine
University of Wisconsin-Madison

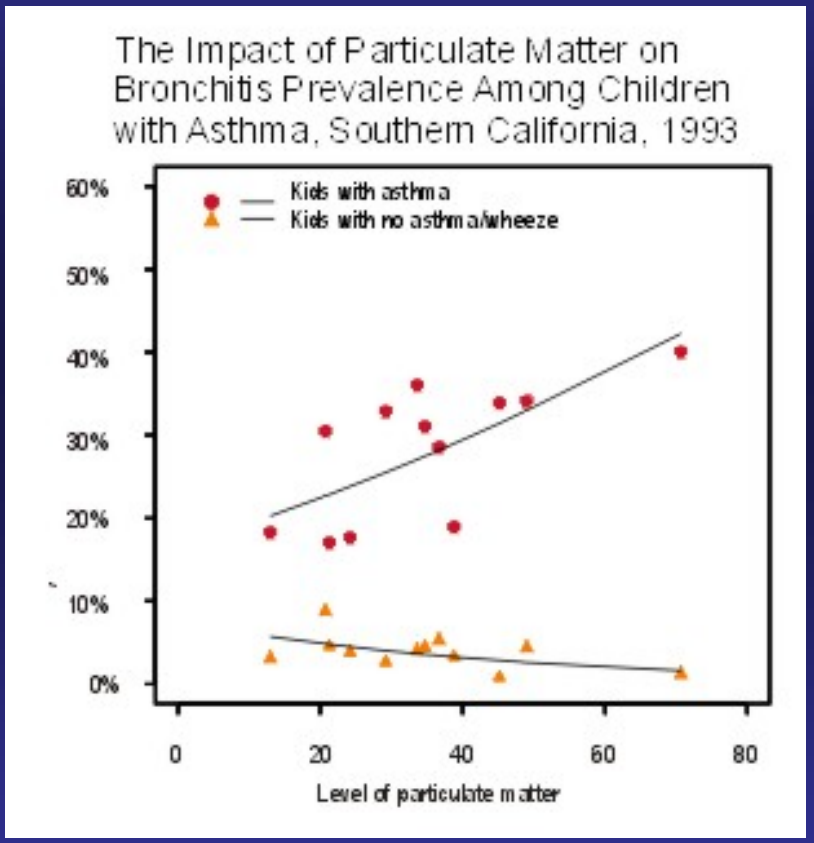
Prevalence of Allergic Disease Since the Industrial Revolution



Saxon et al

The Impact of Air Pollution on Asthma in Children





Source: Southern California Environmental Health Sciences Center, 2007

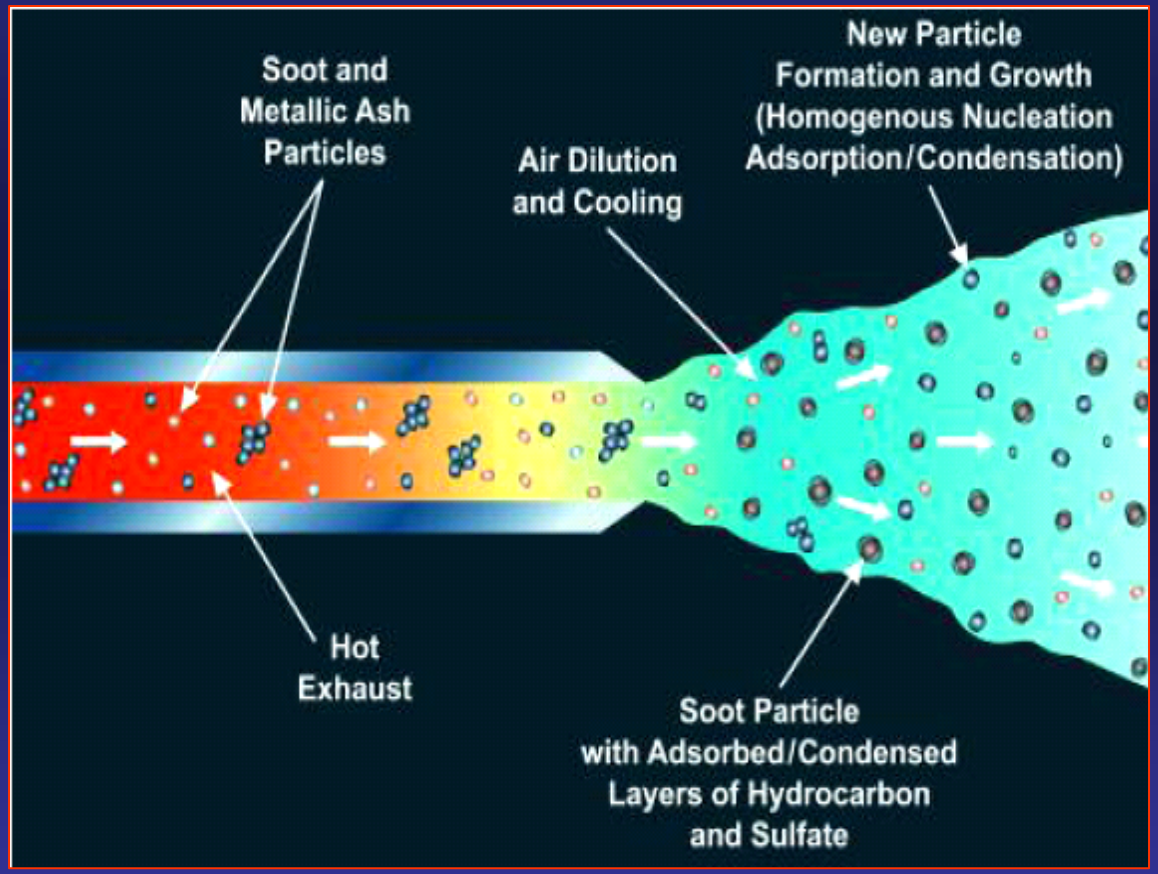
1. Why are pollutant particles dangerous?

2. Is it the particles themselves or their chemical components that cause the damage?

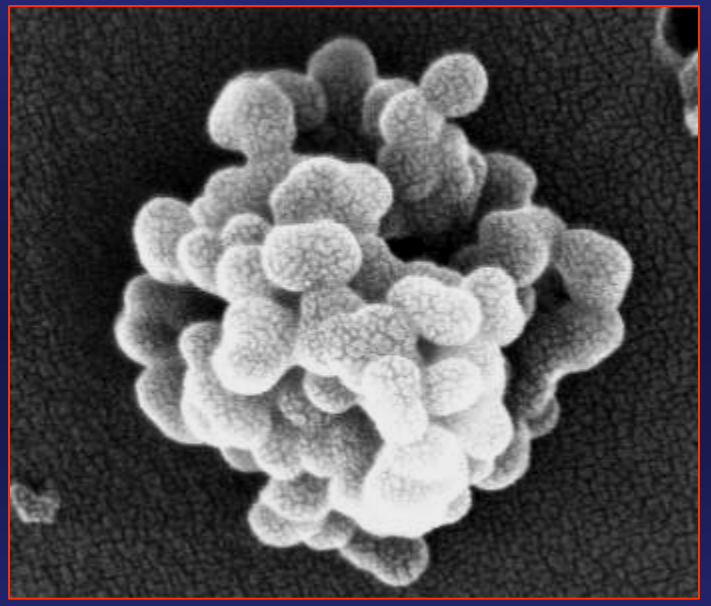
3. What are the potential mechanisms

DEP as a model particulate pollutant

Diesel Exhaust



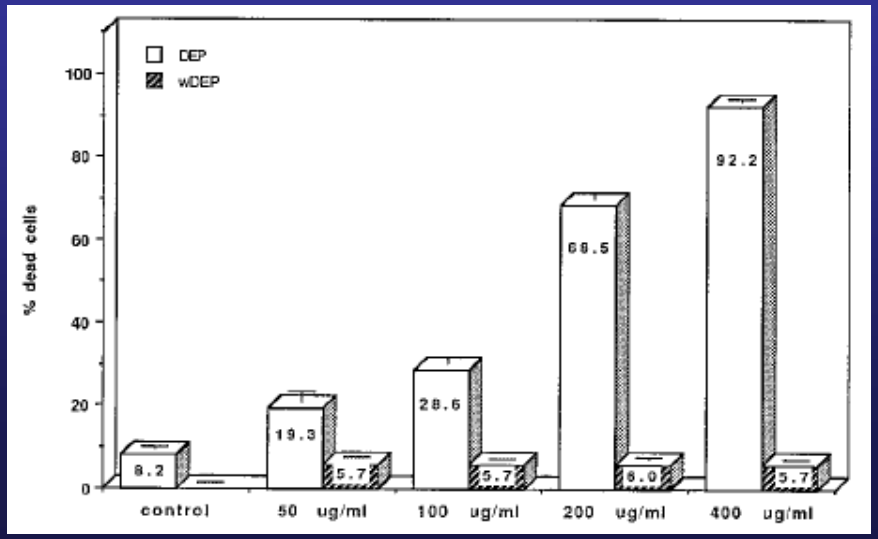
Diesel Exhaust Particles



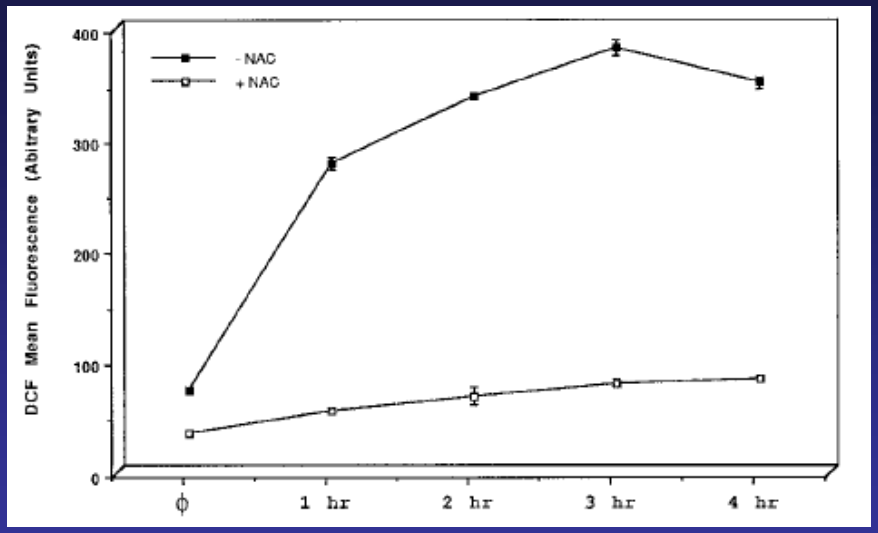
Organic
chemical
& metal
coating

Mouse Macrophage Studies

Cell death



Oxygen radical production



1. DEP toxicity is significantly reduced after the removal of organic chemicals

2. Antioxidant, NAC, could effectively inhibit DEP-induced oxidative stress as determined by the level of intracellular reactive oxygen radicals

3. NAC could effectively inhibit DEP toxicity

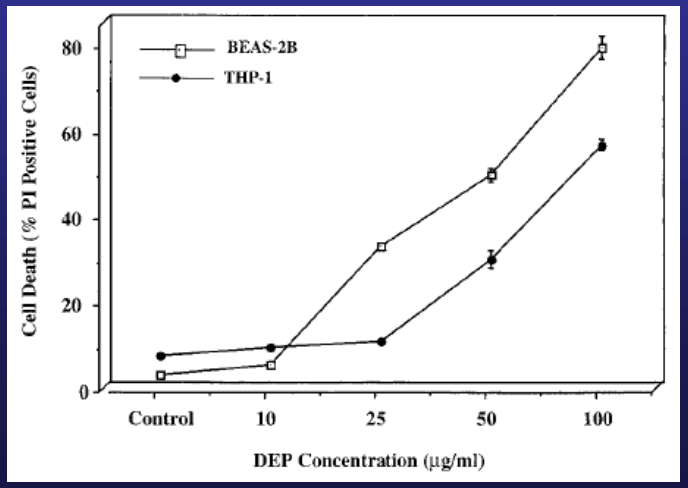
The effect of antioxidant on DEP toxicity

Table III. *The effect of NAC on induction of RAW264.7 cell death*[a]

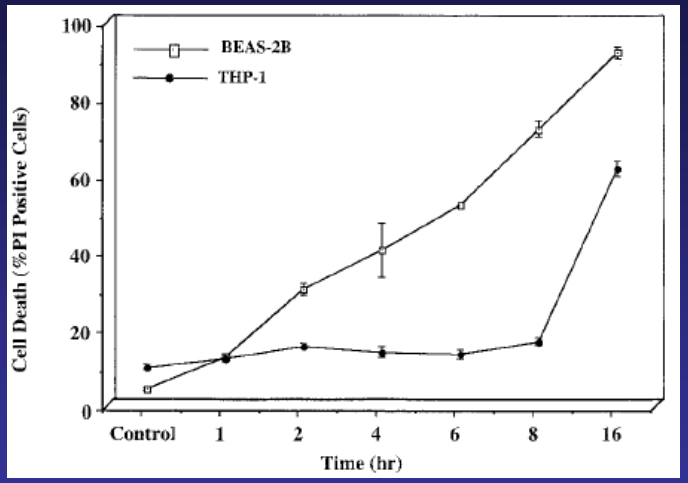
DEP Extract (μg/ml)	Dead Cells (%)	
	− NAC	+ NAC
None	3.8	4.2
30	10.3	6.0
60	42.8	12.1
100	74.7	13.2

Human Bronchial Epithelial Studies

Dose-dependent DEP toxicity

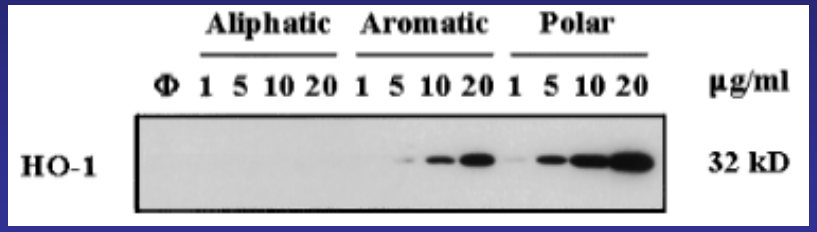


Time-dependent DEP toxicity



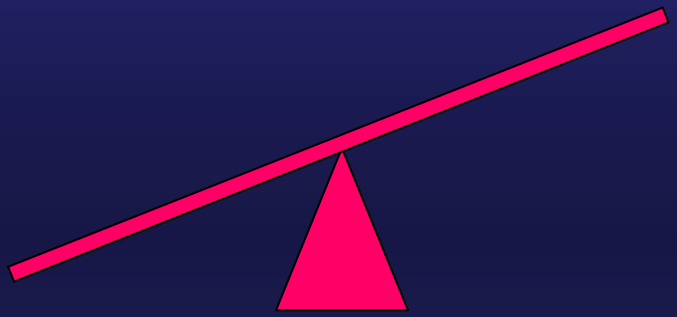
- Organic extract of DEP induced dose- and time-dependent toxicity in human bronchial epithelial cells
- Polycyclic aromatic hydrocarbon-enriched aromatic fraction and quinone-enriched polar fraction are more potent in inducing oxidative stress

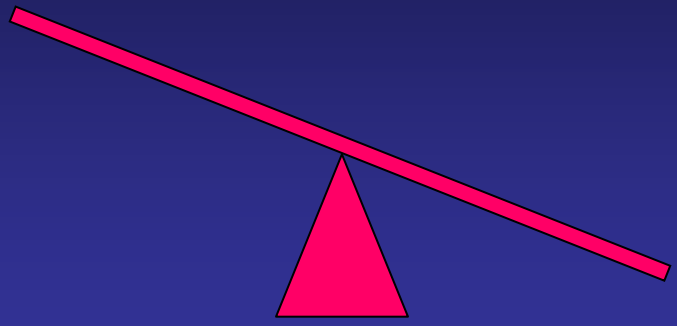
Induction of oxidative stress by organic DEP chemicals



What is oxidative stress?

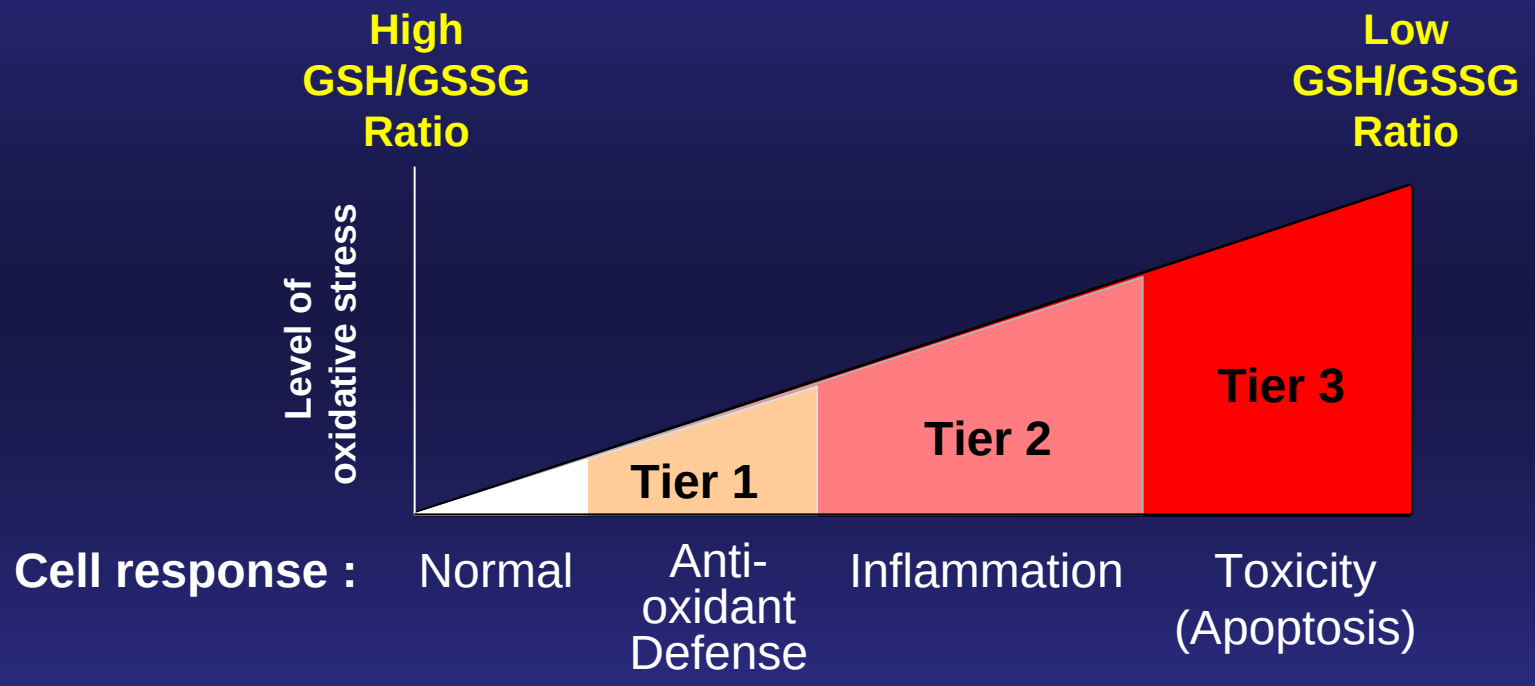
Normal Redox equilibrium





Oxidative Stress

Oxidative Stress Induces a Stratified Cellular Response



Nel, Loo, et al. J. Biol. Chem., 278:50781-90, 2003

DEP Study Summary

Organic DEP chemicals induces adverse biological effects through the generation of stratified oxidative stress response

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Which particle type in the ambient air is most dangerous and why?

….. PM_{10} ?
…... $PM_{2.5}$?
……Ultrafine particles

Transmission Electronmicrograph of a $PM_{2.5}$ Particle

(Courtesy Dr Sheldon Friedlander, UCLA)

$PM_{2.5}$ = aerodynamic diameter < 2.5 micron

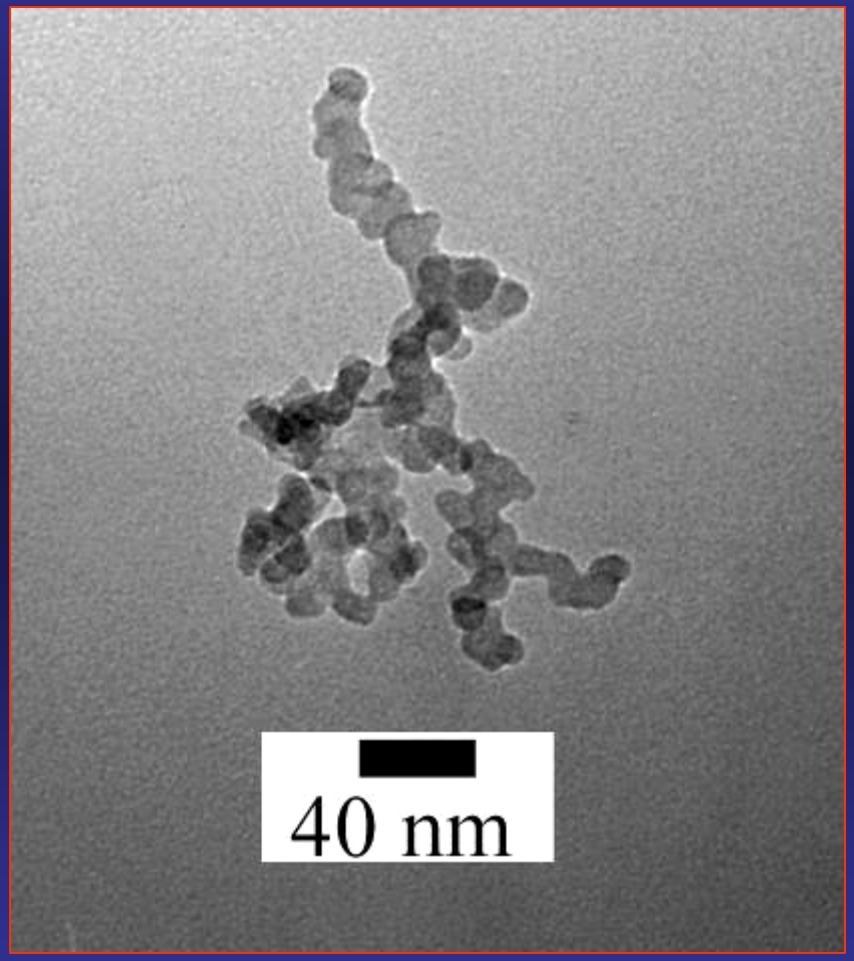
Main sources are soil, crustal elements, sea salt etc.

May contain some emission particles

EPA regulated (mass standard)

Nel. Science, *308*: 804-06, 2005

Transmission Electronmicrograph of Ultrafine Particle



(Courtesy Dr Sheldon Friedlander, UCLA)

Main sources are emission particles or condensation of vapors

Diesel exhaust particles

Not EPA regulated (will require a numbers standard)

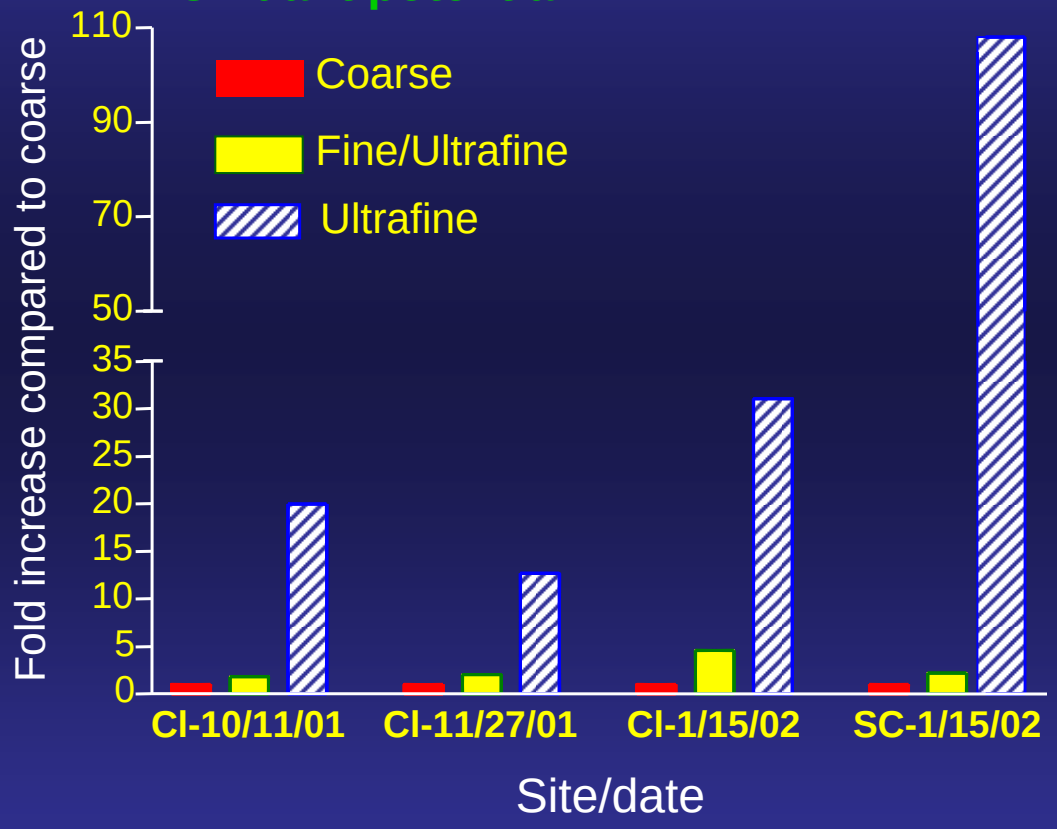
Nel. Science, *308*: 804-06, 2005

Characteristics of Harmful Inhaled Particles

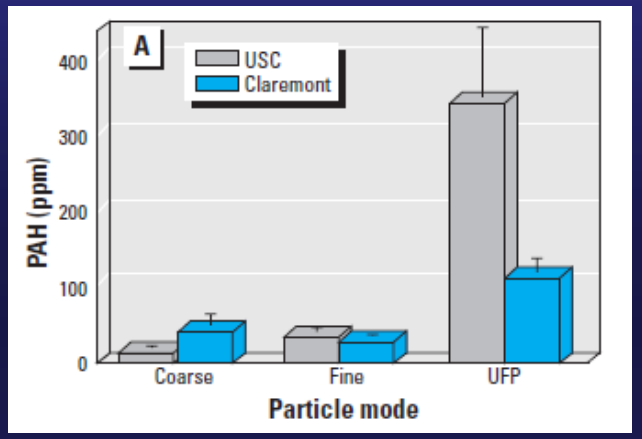
1. Small size
2. Large surface area
3. Ability to be taken up
4. Toxic chemicals

Oxidant Potential and PAH Content of Different Size Particles

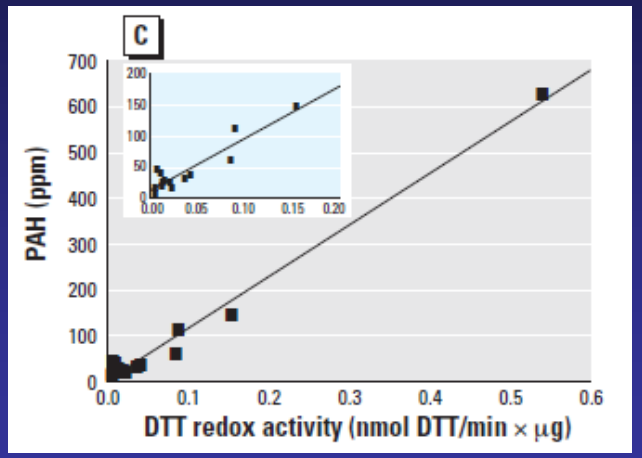
Oxidant potential



PAH content



Correlation



Li et al. Environmental Health Perspectives. 2003

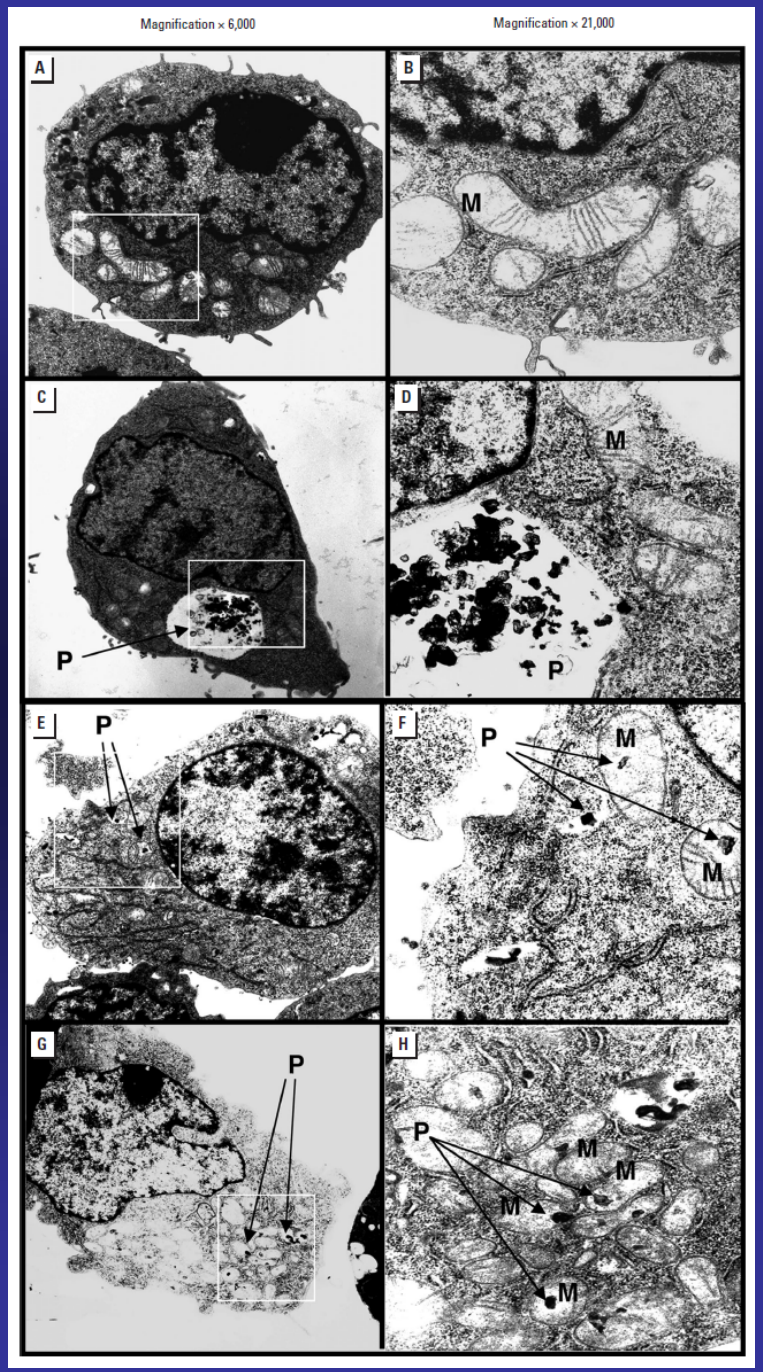
The Cellular Effects of Different Size Particles

Control

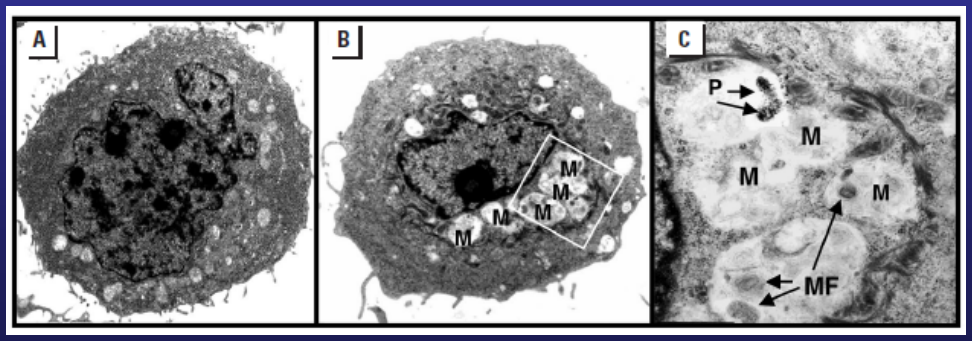
Coarse

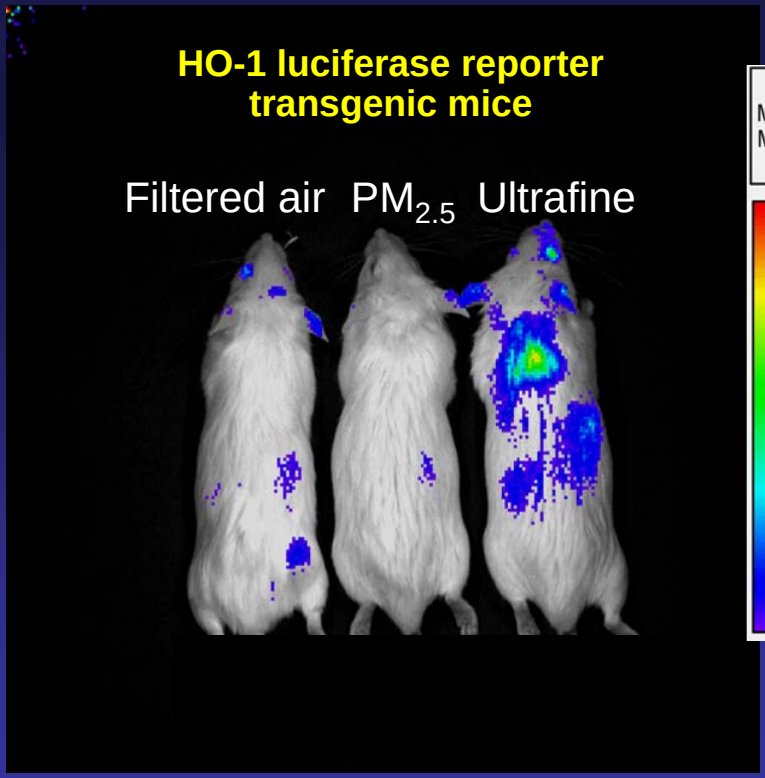
Fine

UFP



Control — UFP





Summary of Particle Size Comparison

Ultrafine particles are more dangerous than coarse and fine particles due to their ability to carry more pro-oxidative organic chemicals and stronger oxidant potential

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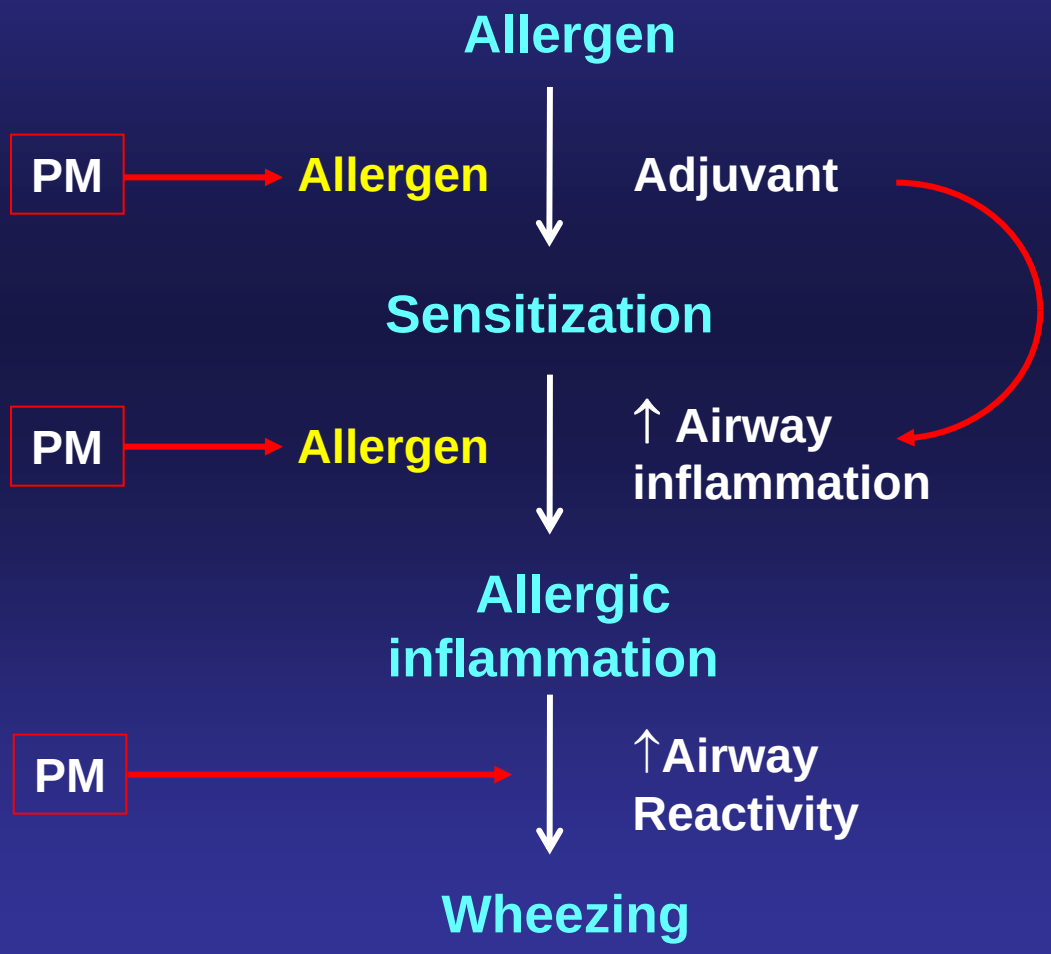
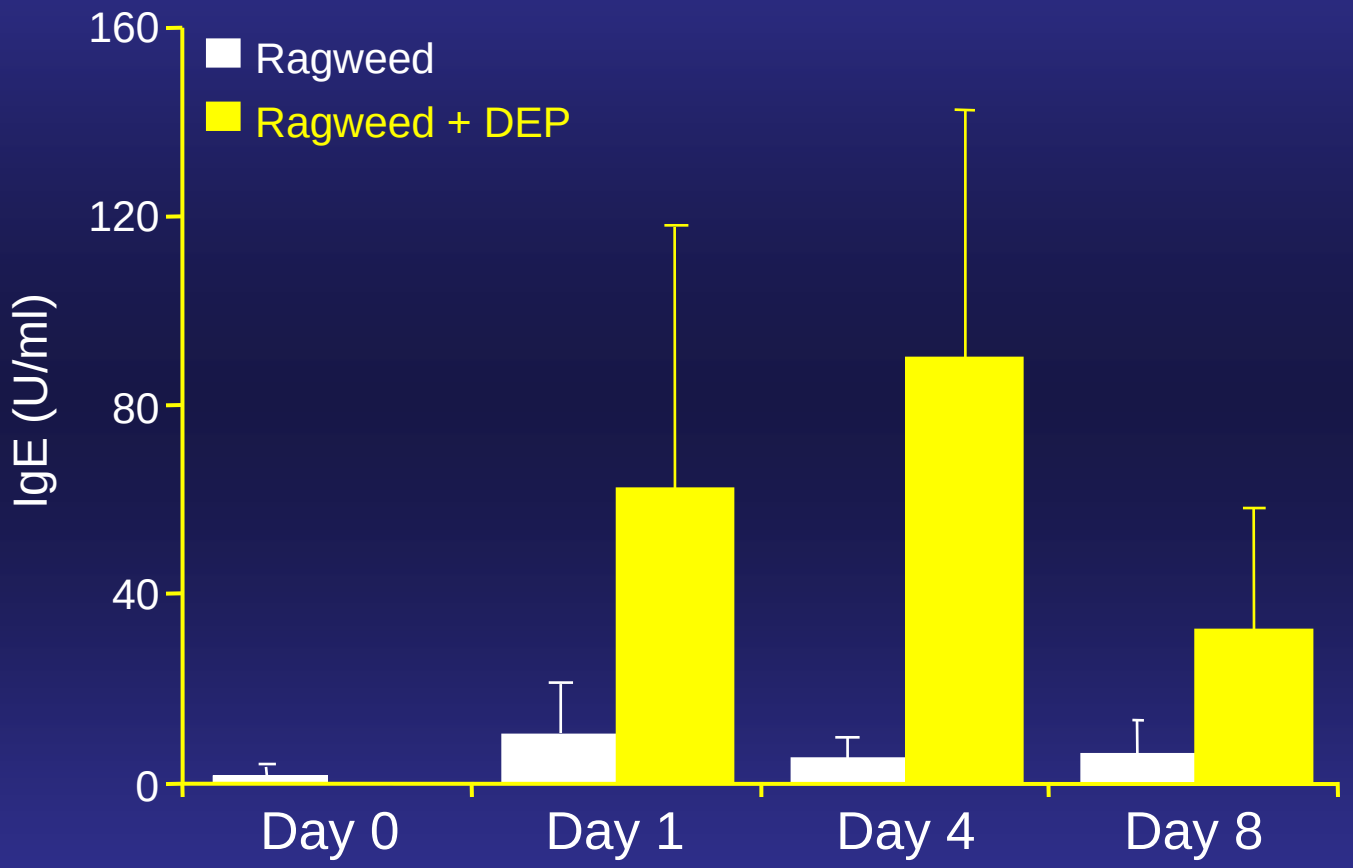
How do ambient particles impact allergic airway inflammation such as asthma?

Experimental DEP Effects on Asthma



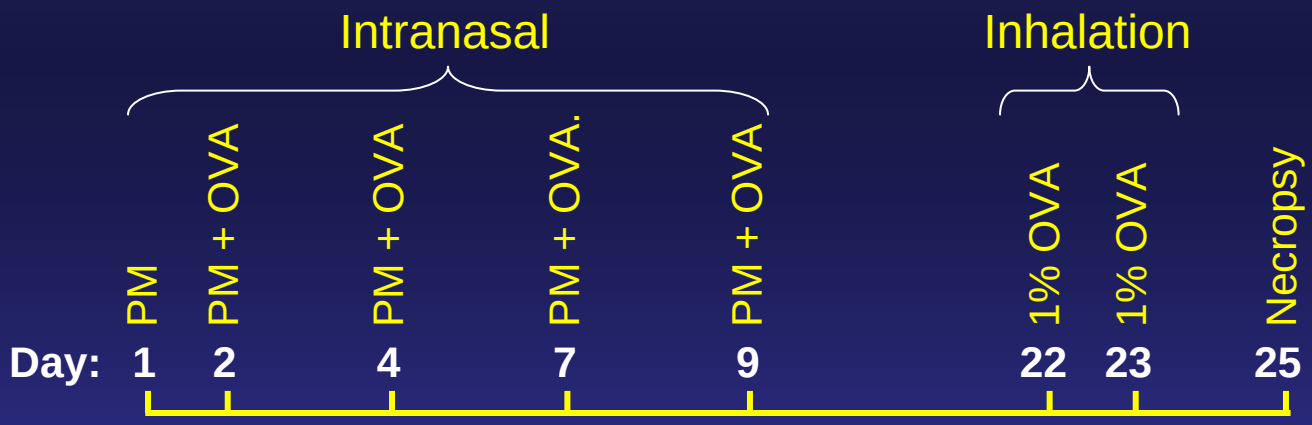
DEP Augments Allergen-specific IgE in Humans



Diaz-Sanchez et al. J. Immunol., 158:2406 -2413, 1997

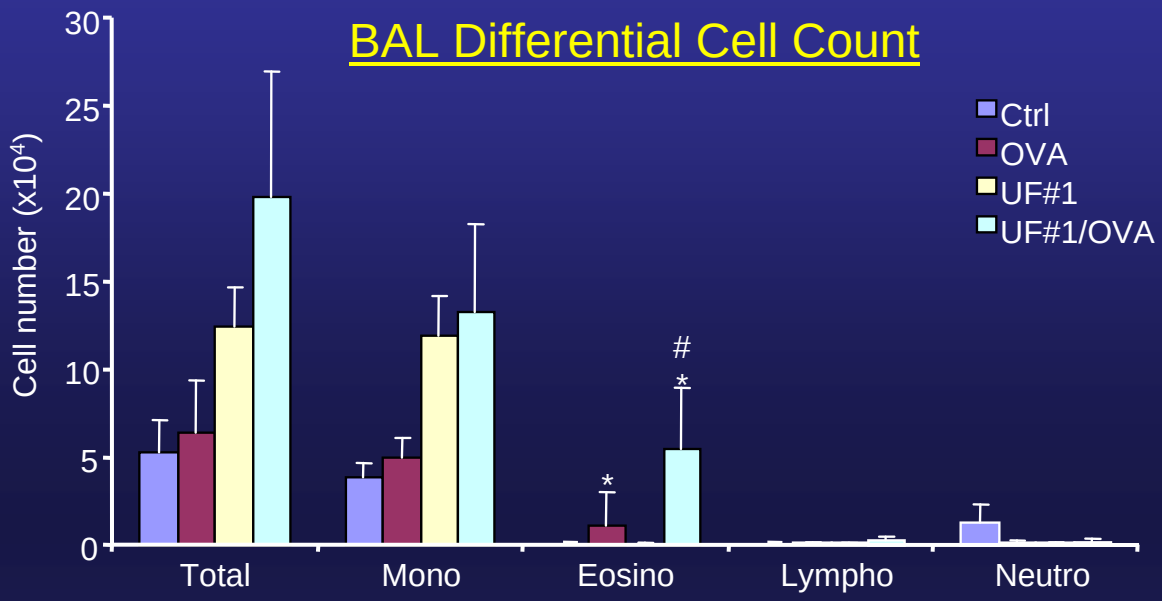
Animal Model to Study PM Effect on Allergic Sensitization

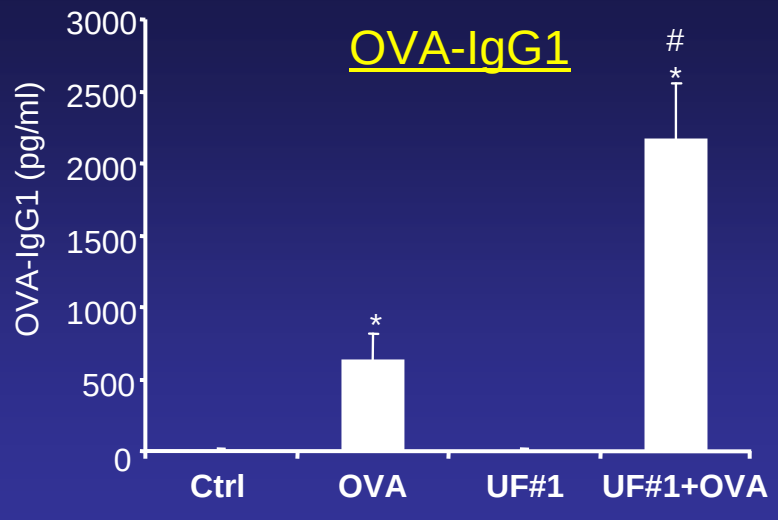
Allergic sensitization protocol

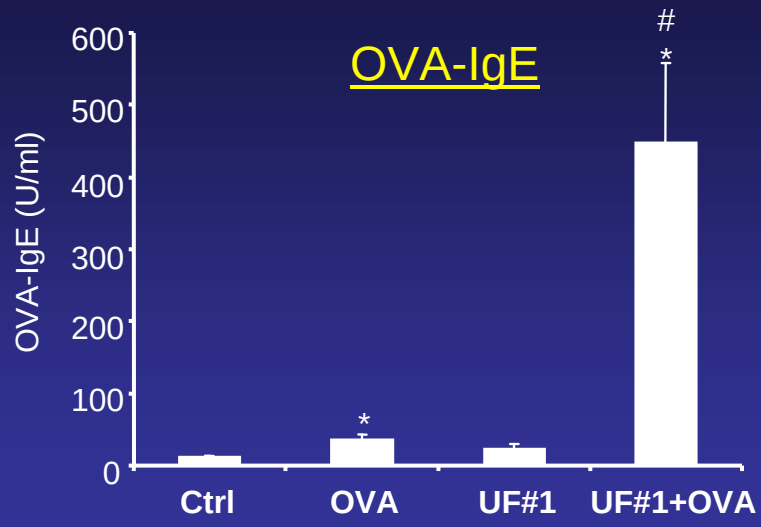


Li et al, Environ Health Perspect, 2009

Ambient UFP enhanced OVA-induced allergic inflammation

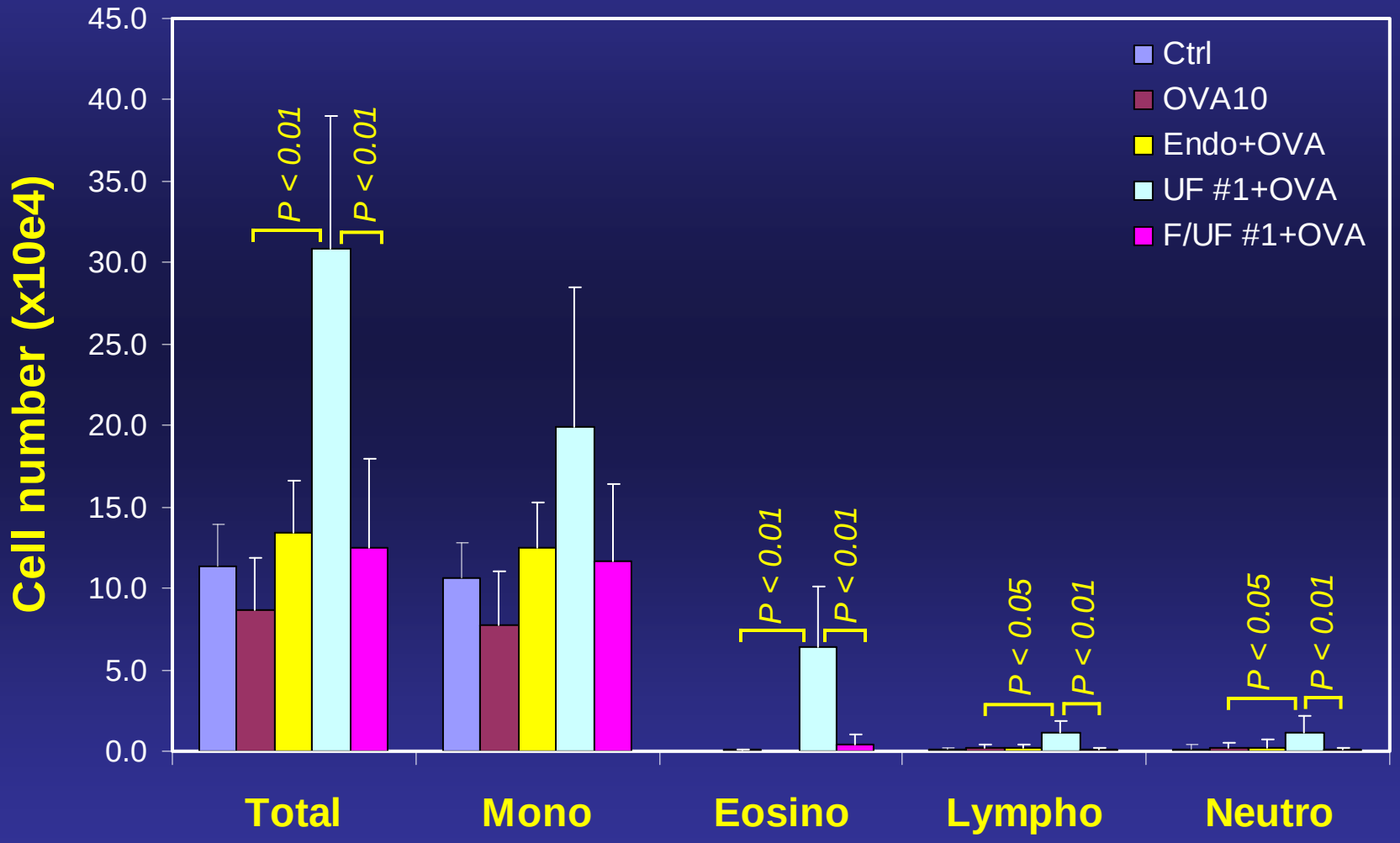




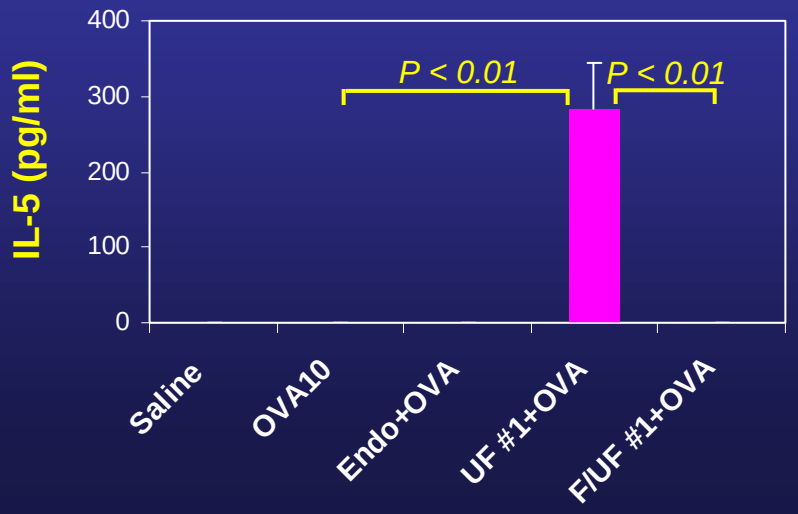


Li et al, Environ Health Perspect, 2009

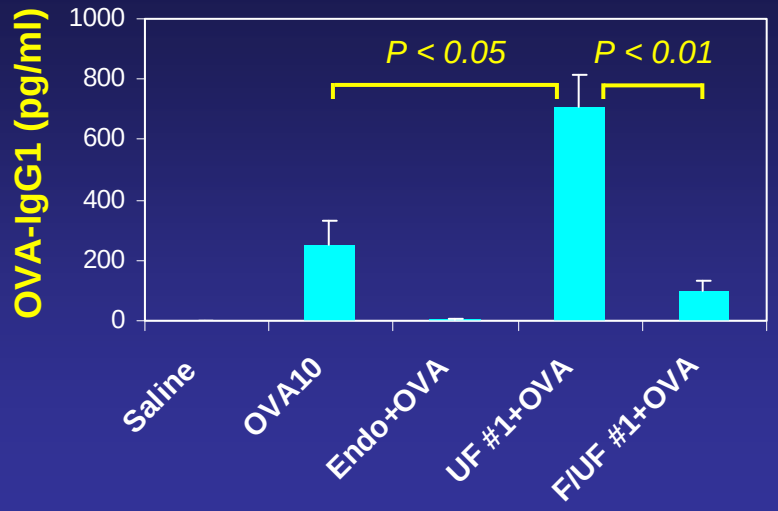
Ambient Fine/UF particles failed to exert an adjuvant effect on OVA sensitization

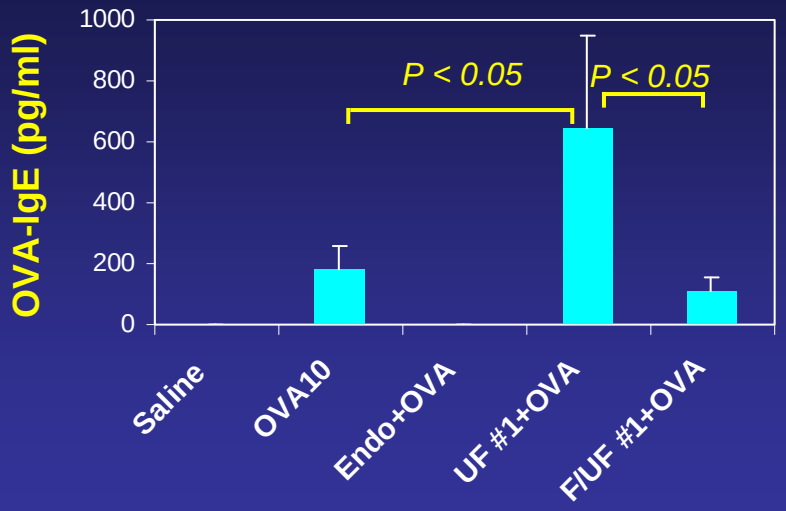


UFP-induced eosinophil infiltration was accompanied by increased IL-5 in BAL

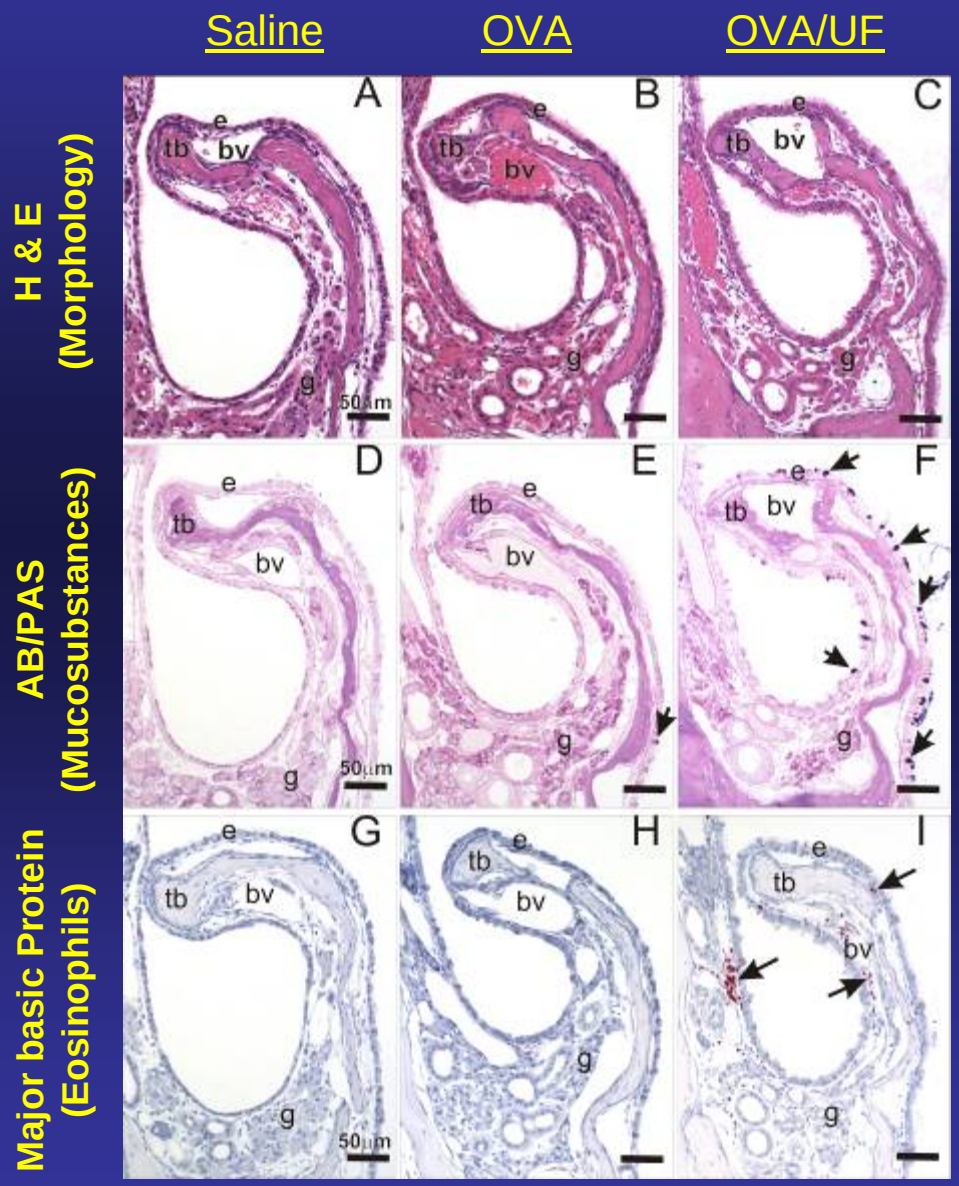


Ambient UFP increased IgG1 and IgE productionIn OVA-sensitized mice

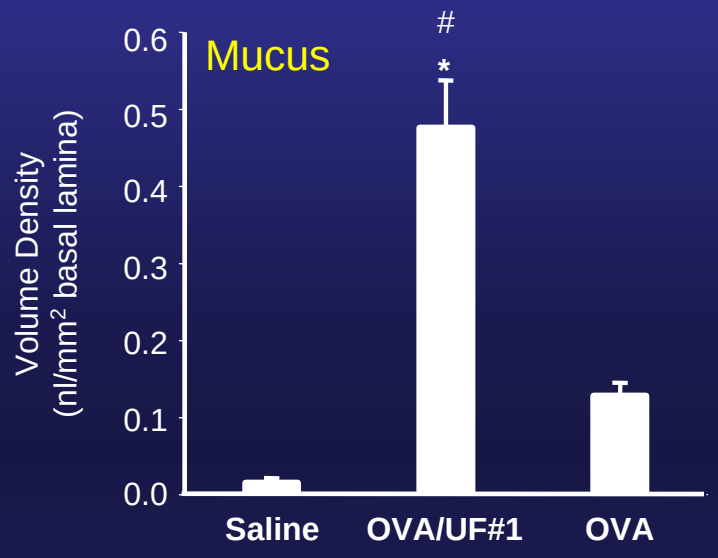


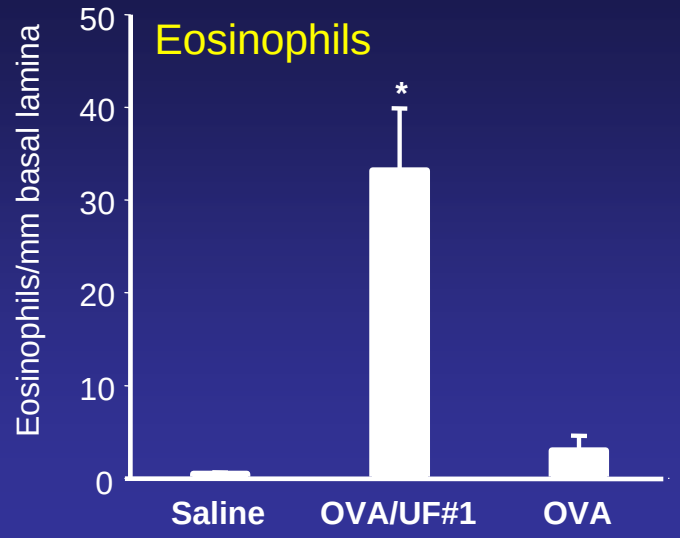


UFP-induced Allergic Inflammation in Nasal Maxilloburbinates



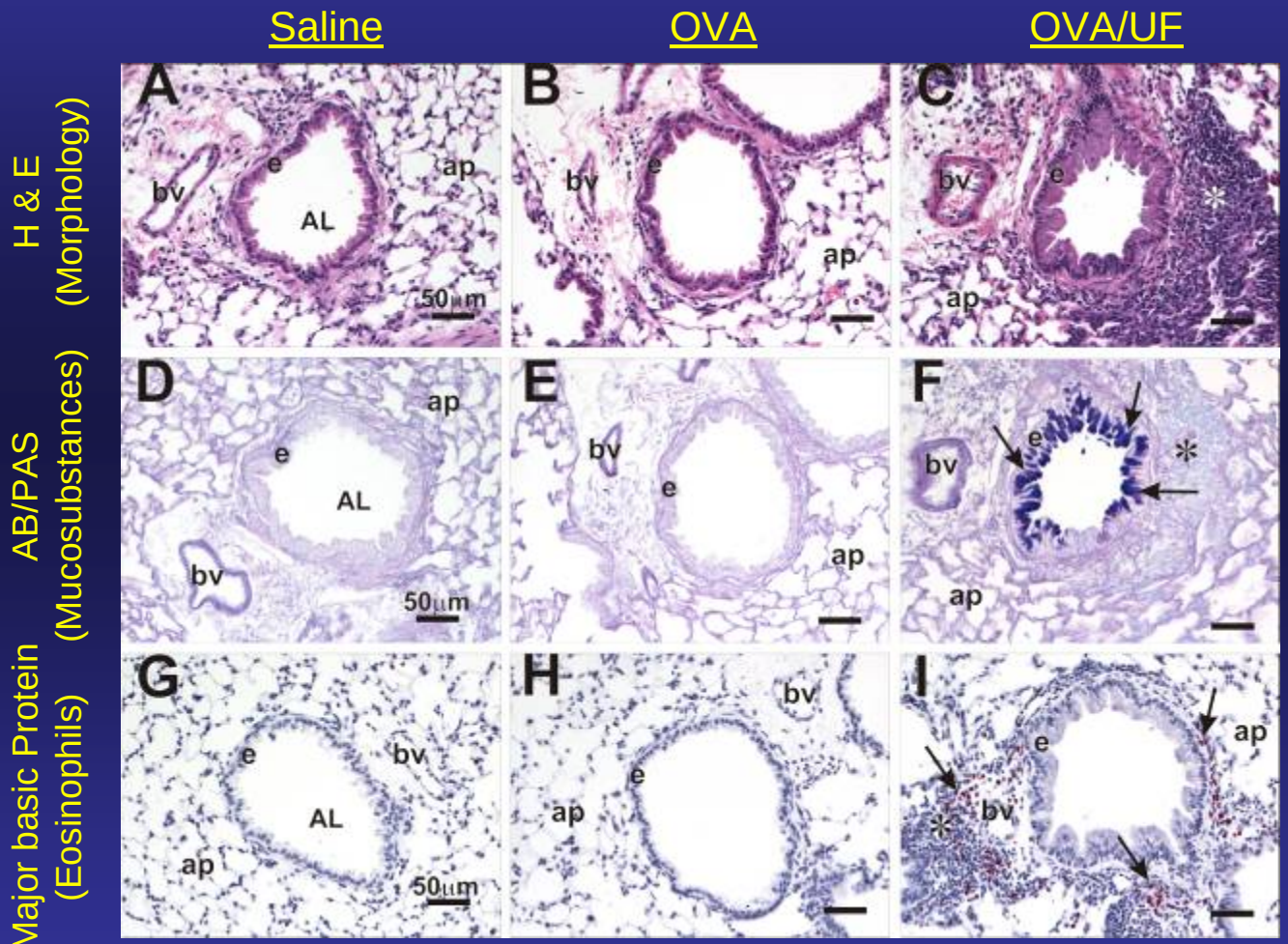
Nasal morphometry



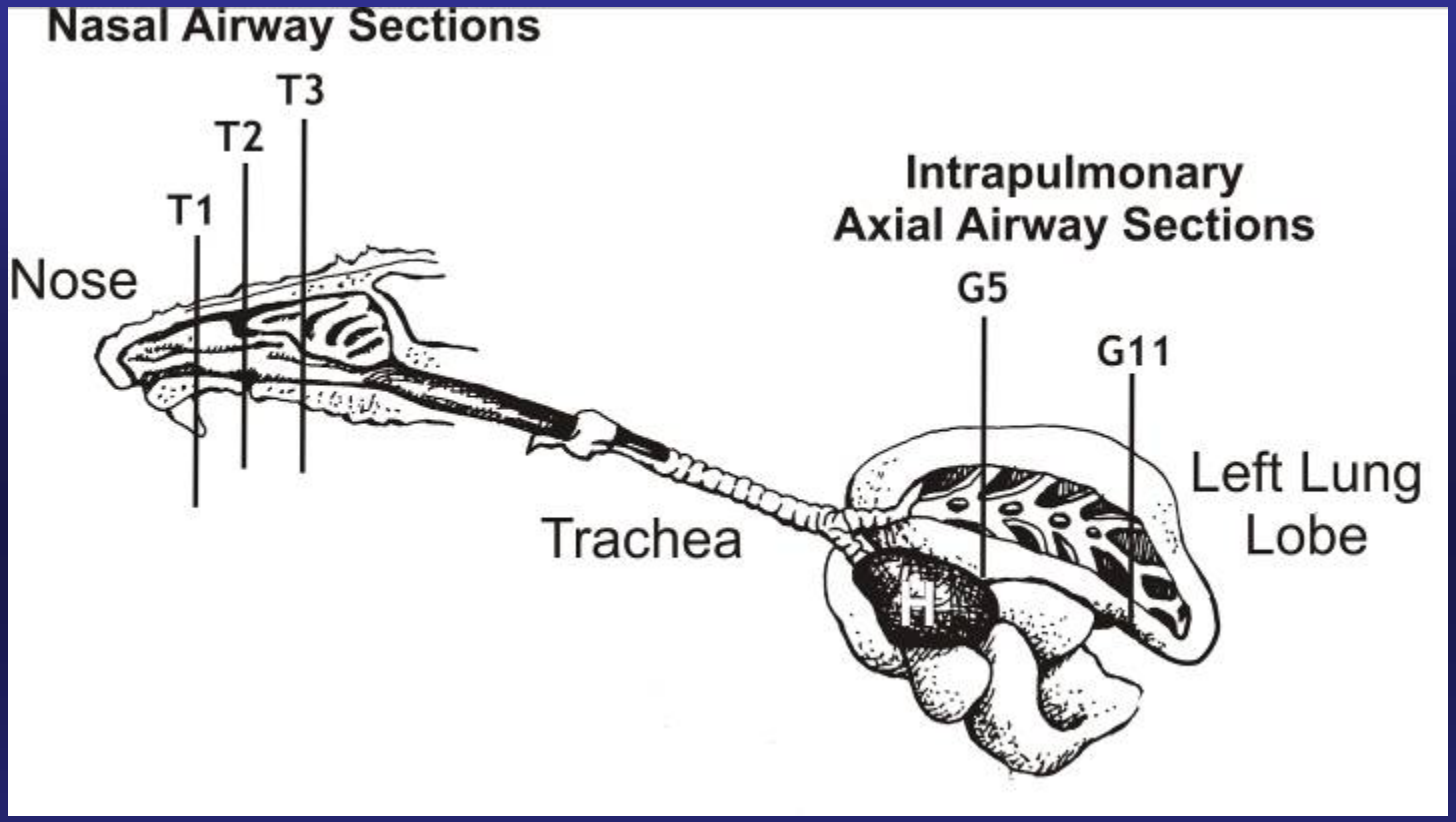


Li et al, Environ Health Perspect, 2009

UFP-induced allergic inflammation in conducting airways



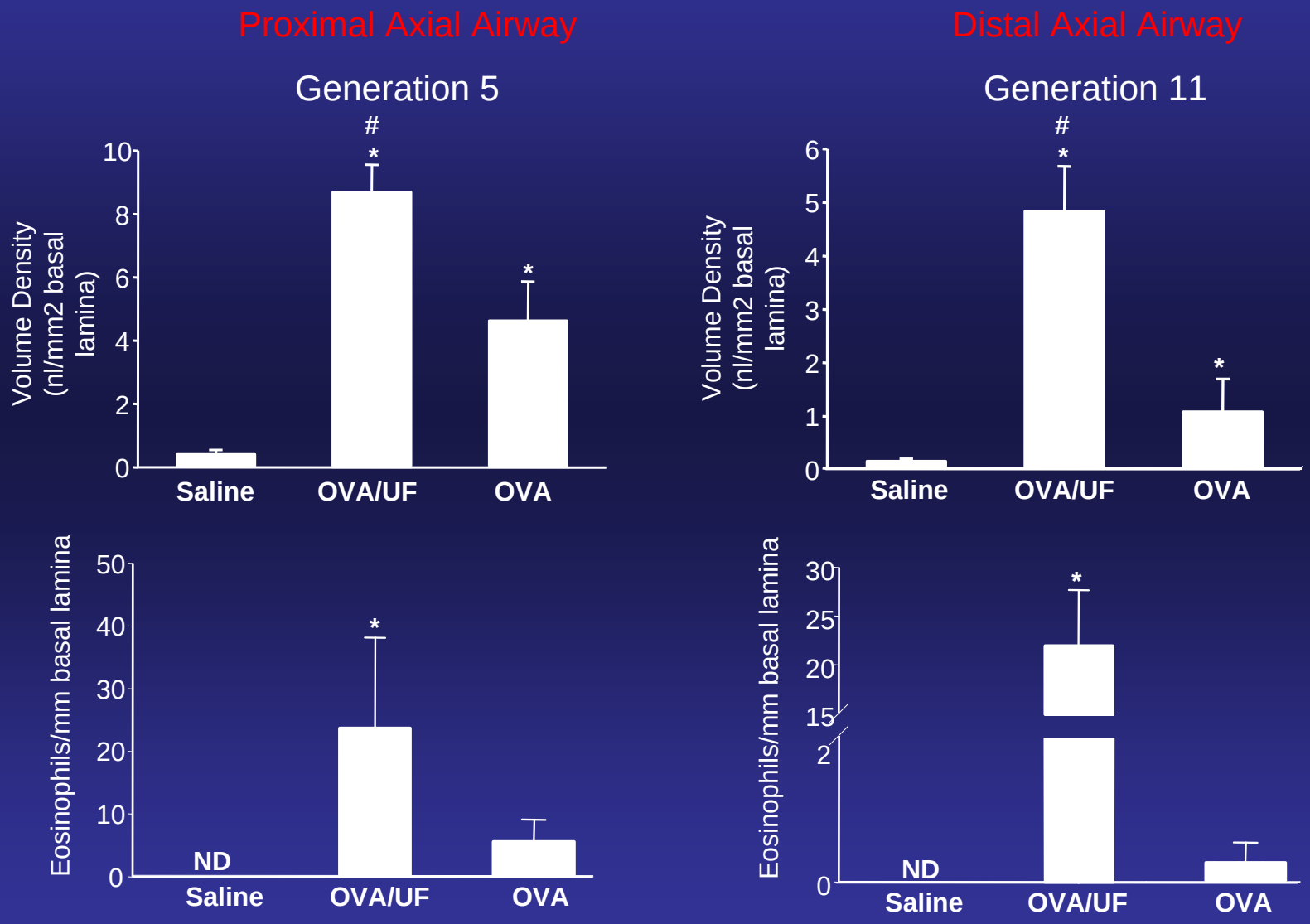
Li et al, Environ Health Perspect, 2009



Schematic drawing of the murine respiratory tract highlighting the intrapulmonary sites where pro-oxidative UFP exert its adjuvant effect on OVA sensitization

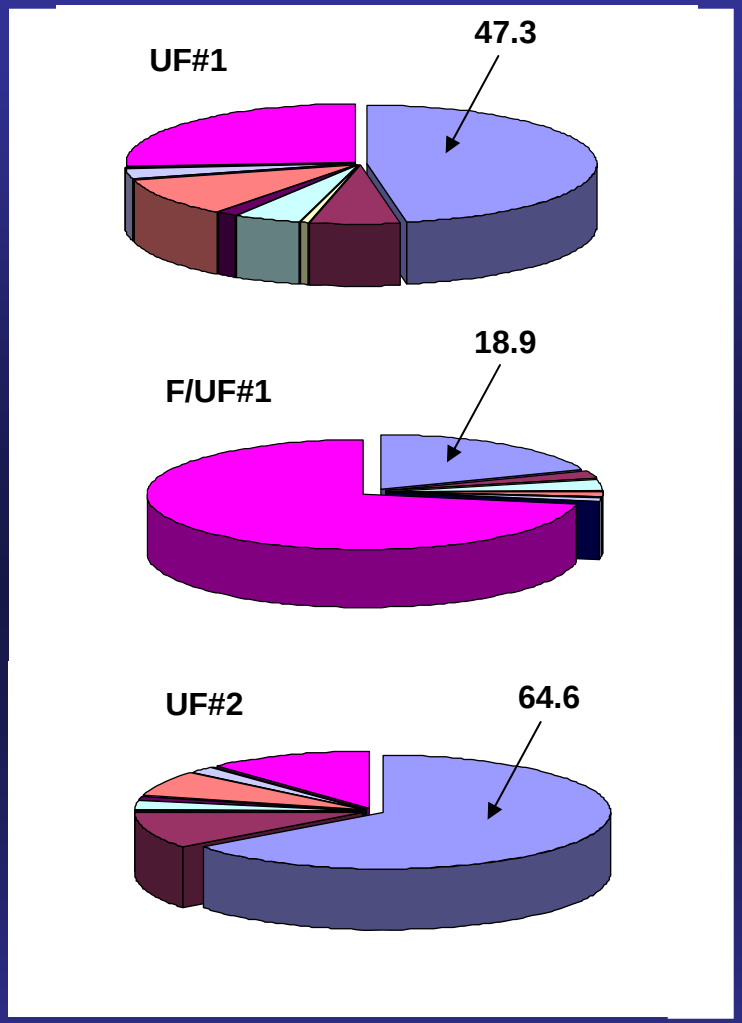
Li et al, Environ Health Perspect, 2009

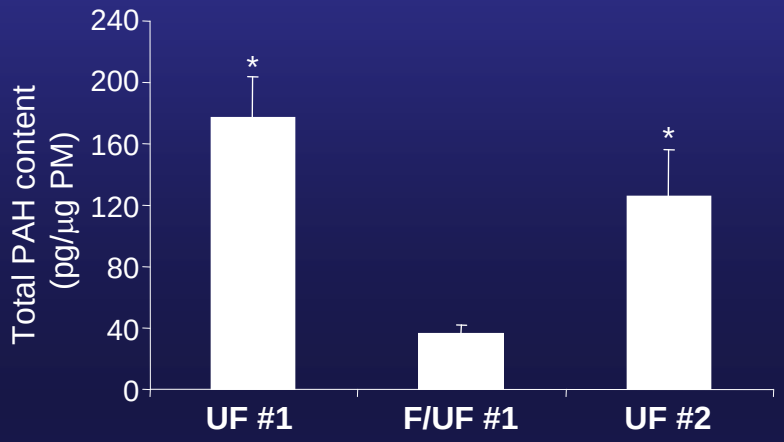
Morphometric Analysis of Mucosubstances and Eosinophils in Proximal and Distal Axial Airway

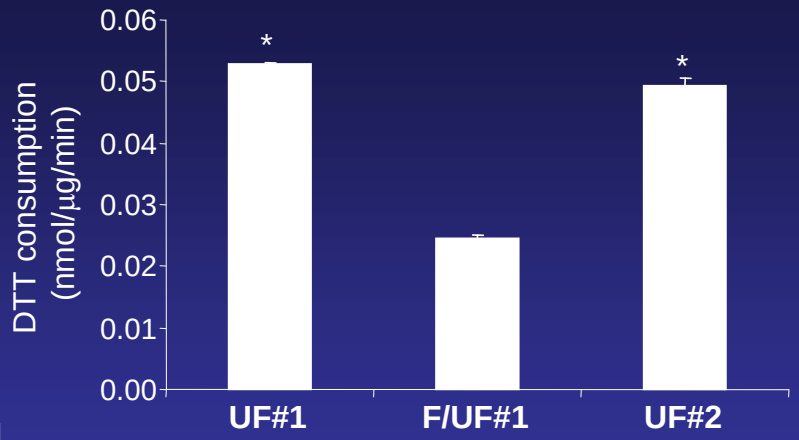


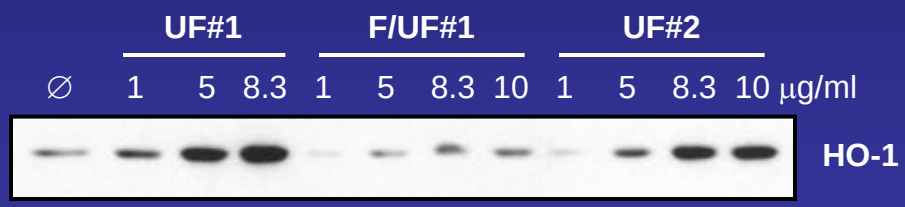
Li et al, Environ Health Perspect, 2009

Analyses of PM chemical composition and redox activity



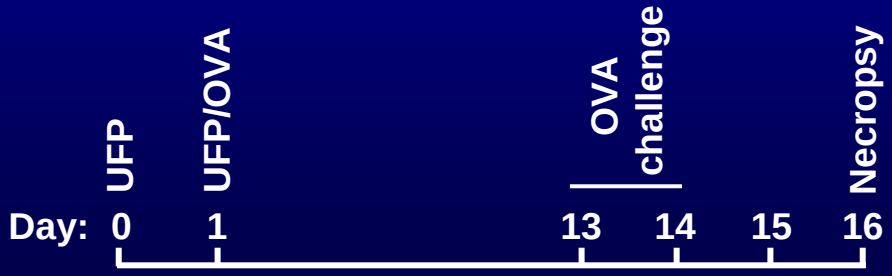


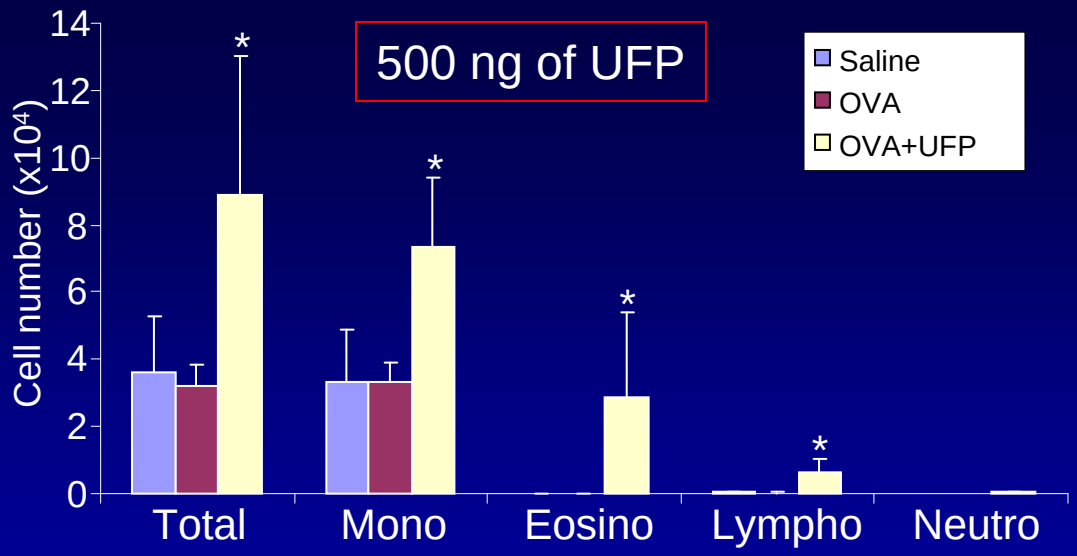


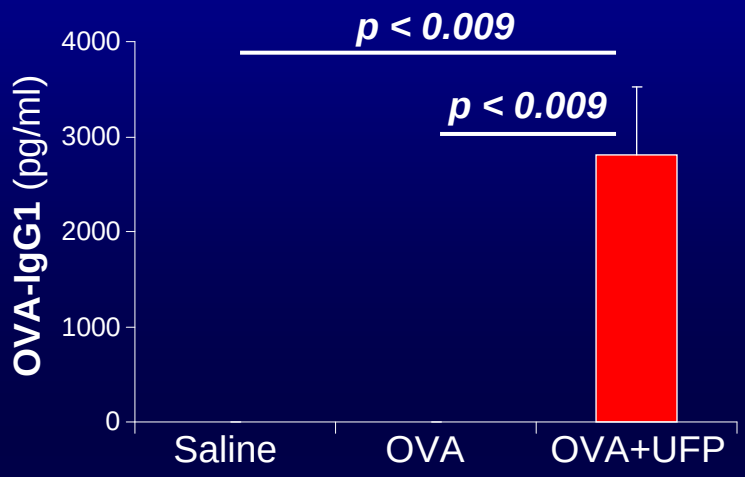


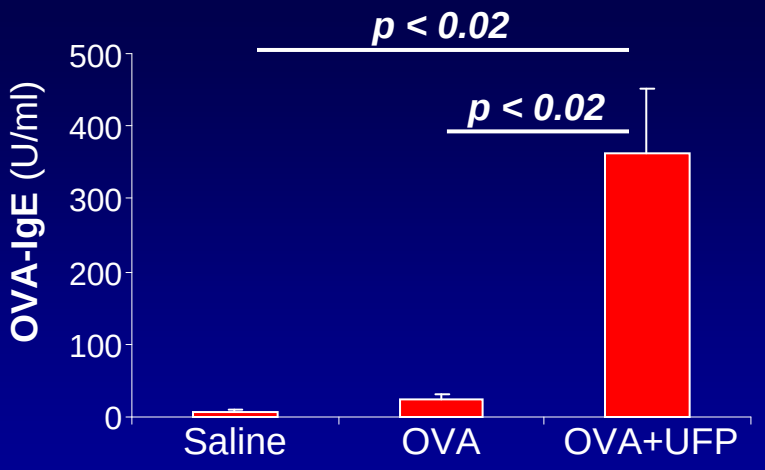
Li et al, Environ Health Perspect, 2009

Single intranasal administration of ng quantities of UFP is sufficient to enhance allergic sensitization to co-administered OVA









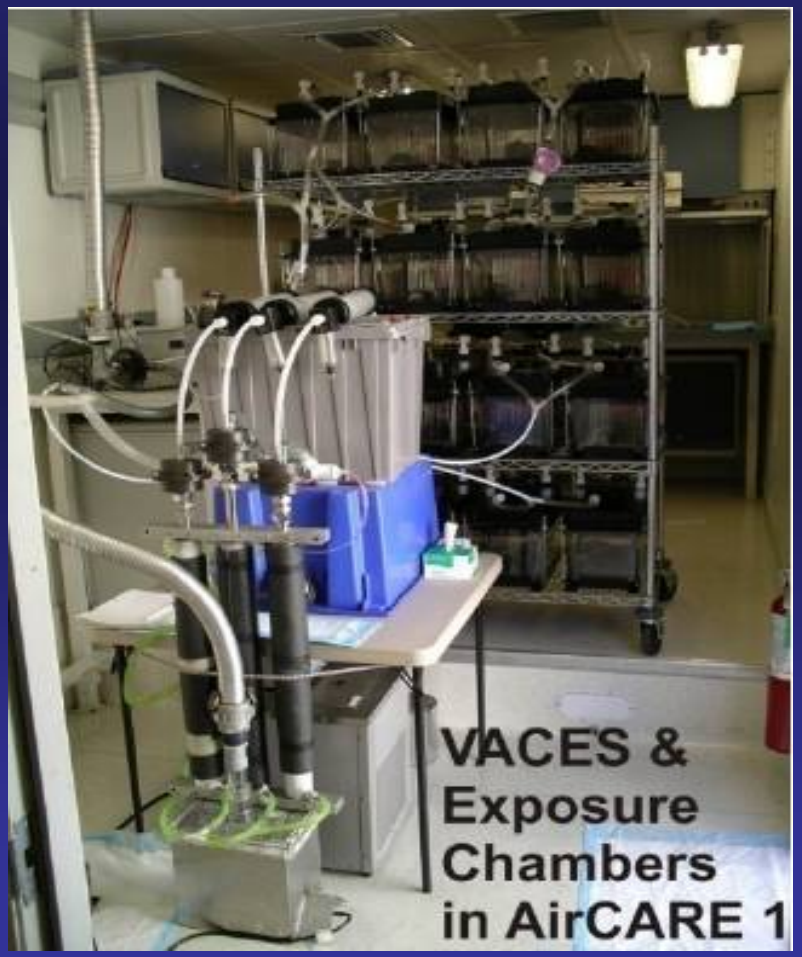
**p < 0.05 compared to Saline and OVA*

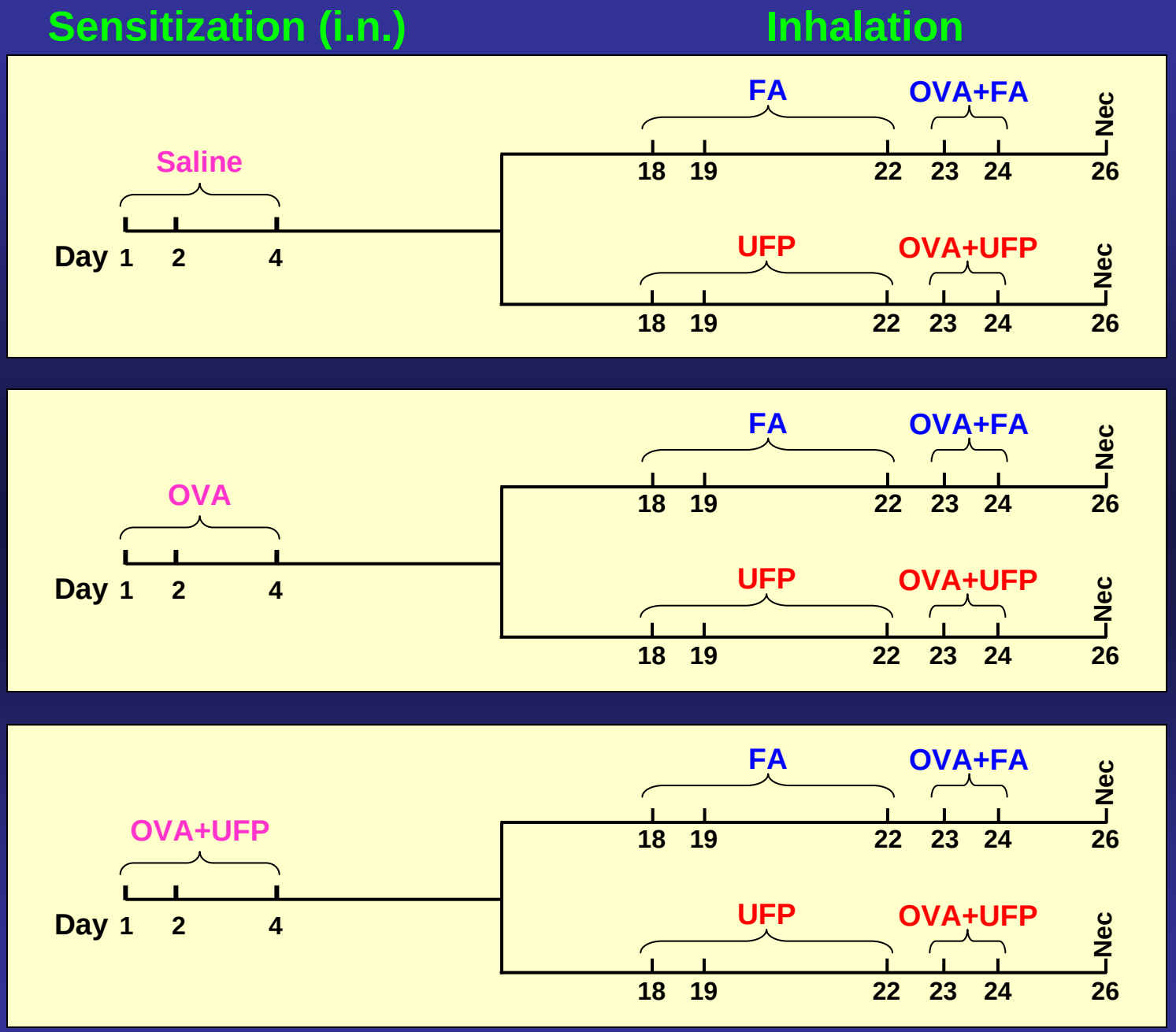
Animal Model to Study PM Adjuvant Effects through Real-time Inhalation of Ambient UFP

i. Primary immune response
ii. Secondary immune response

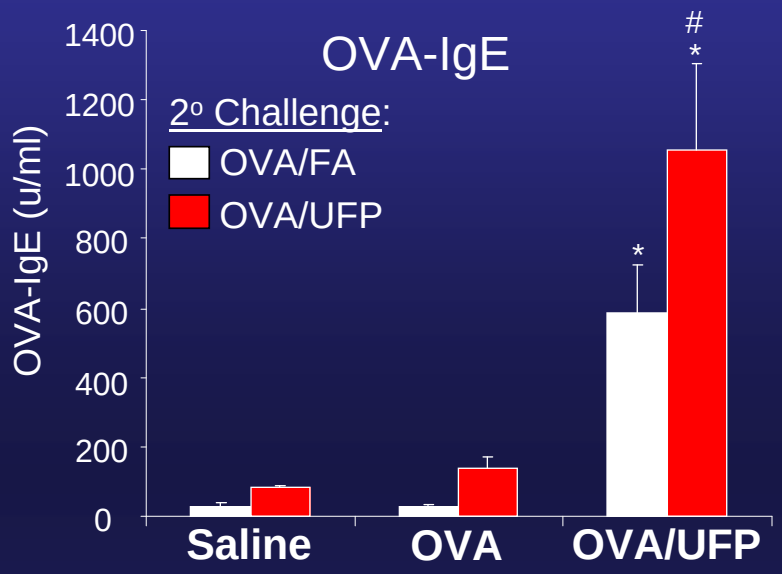
Relevance of the Secondary IR:
Asthma flares in atopics after a sudden surge in ambient PM levels

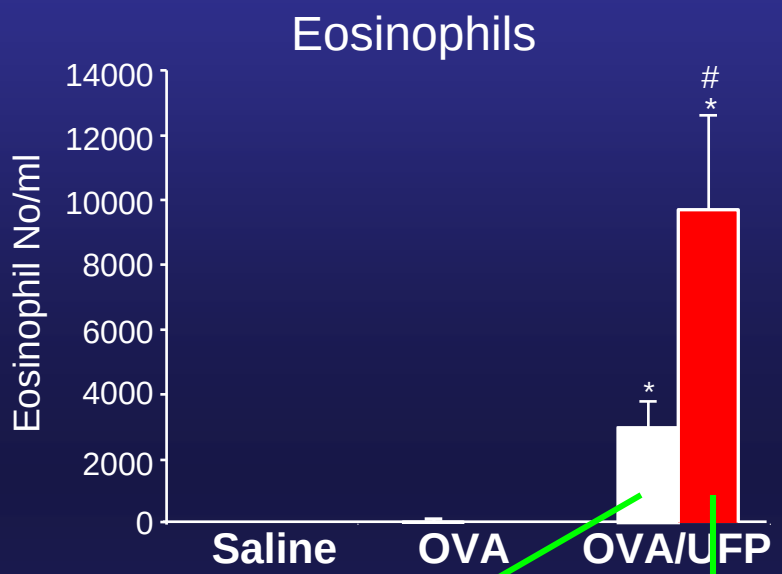
PM Exposure in Mobile Laboratory near 110 Freeway

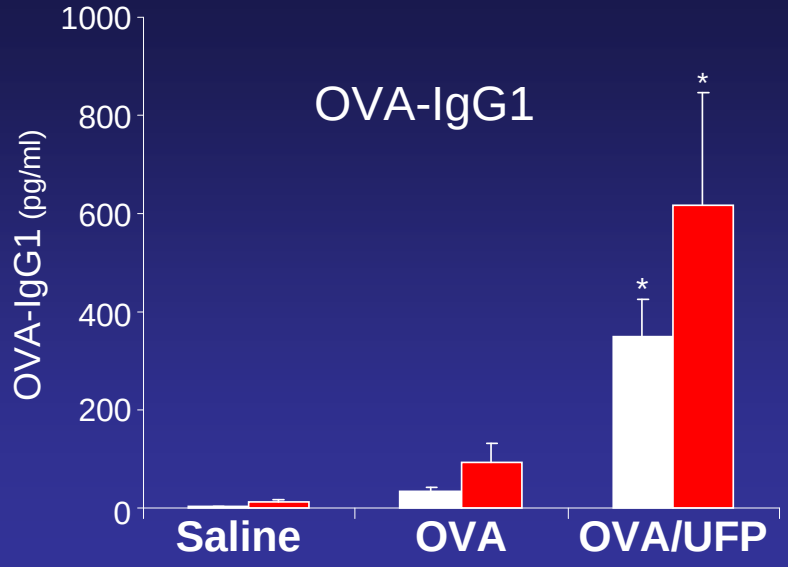


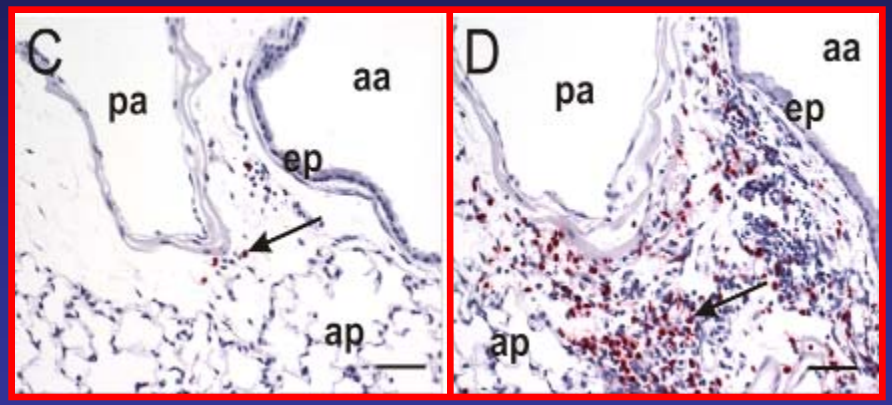

Sensitization (i.n.)
Inhalation
Saline
Day 1 2 4
FA
OVA+FA
UFP
OVA+UFP
18 19 22 23 24 26
Nec
OVA
OVA+UFP

Ambient UFP enhance secondary allergic response in already-sensitized mice

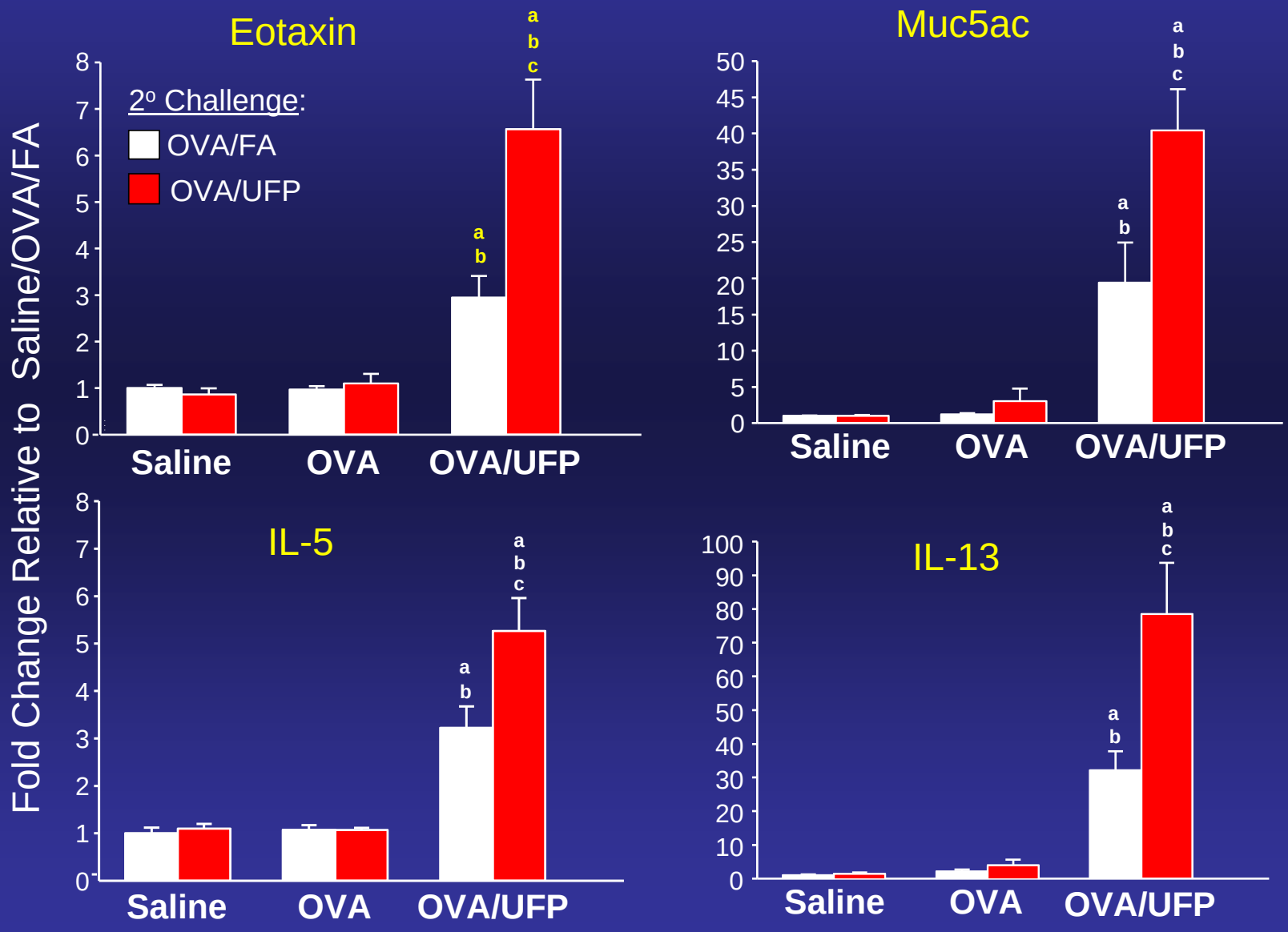




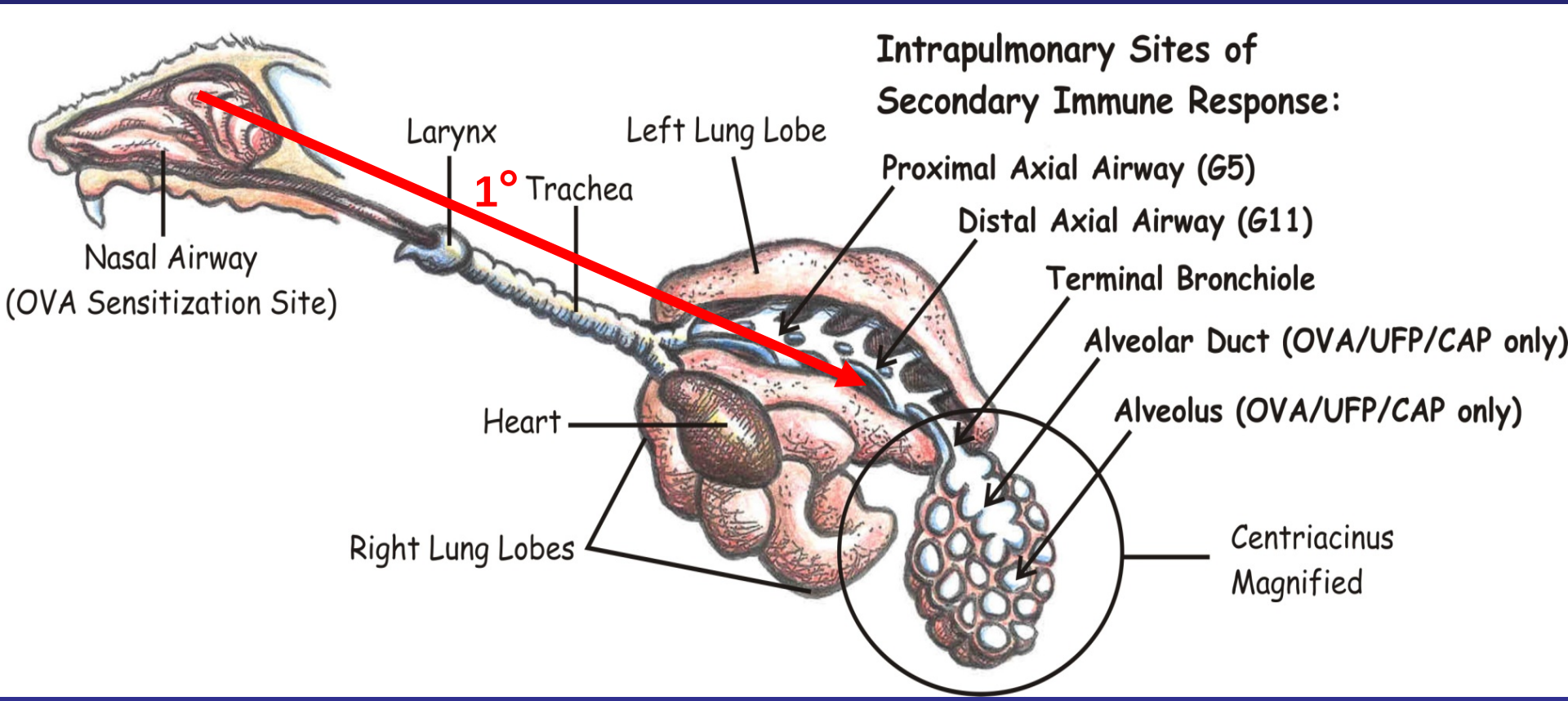




UFP inhalation during the secondary immune response further increased cytokine gene expression in the lung



The target sites of ambient UFP during the primary immune response



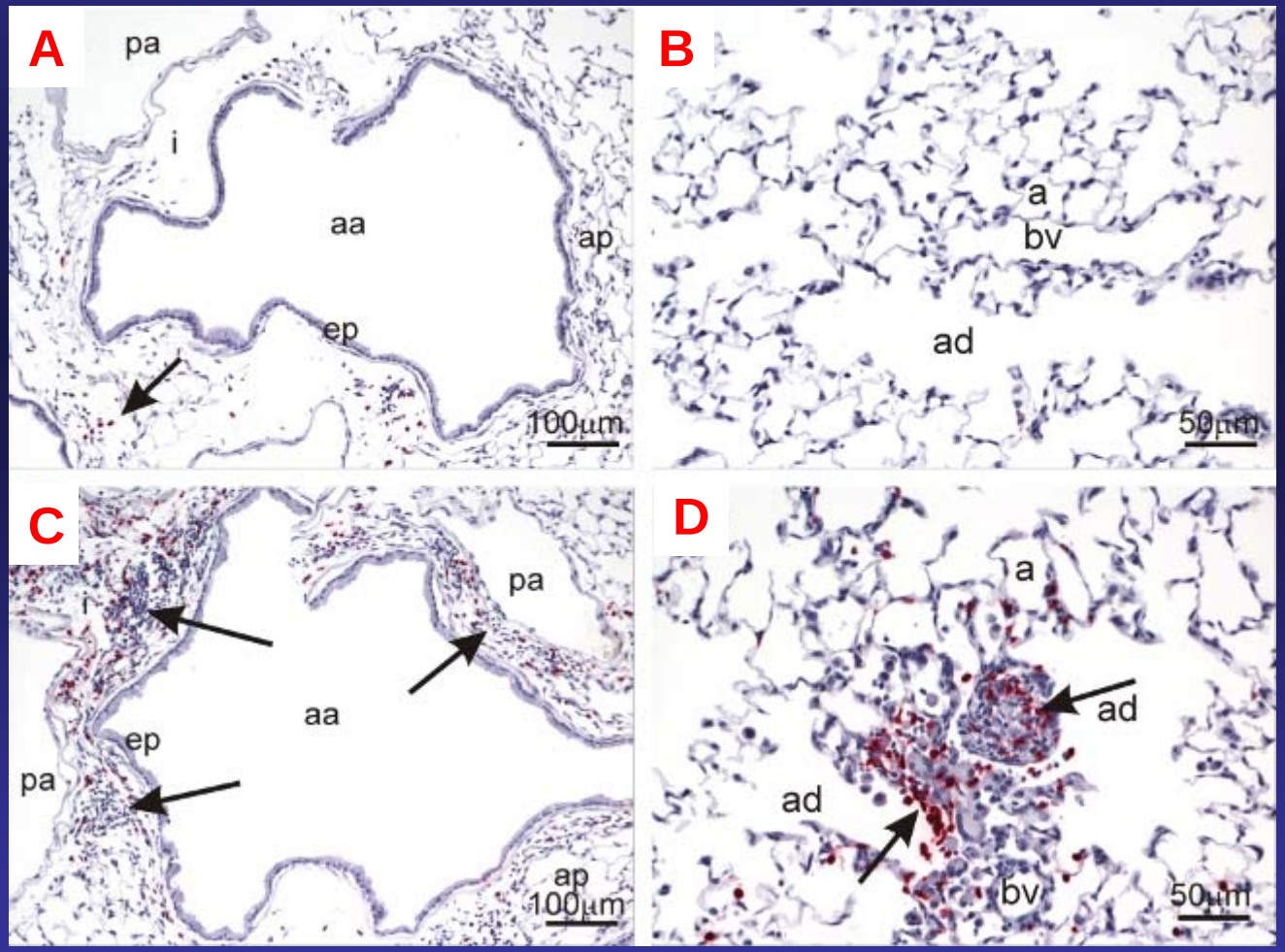
The distal lung is the target of ambient UFP during the secondary immune response

Proximal axial airway (G5) | Distal lung

Challenge

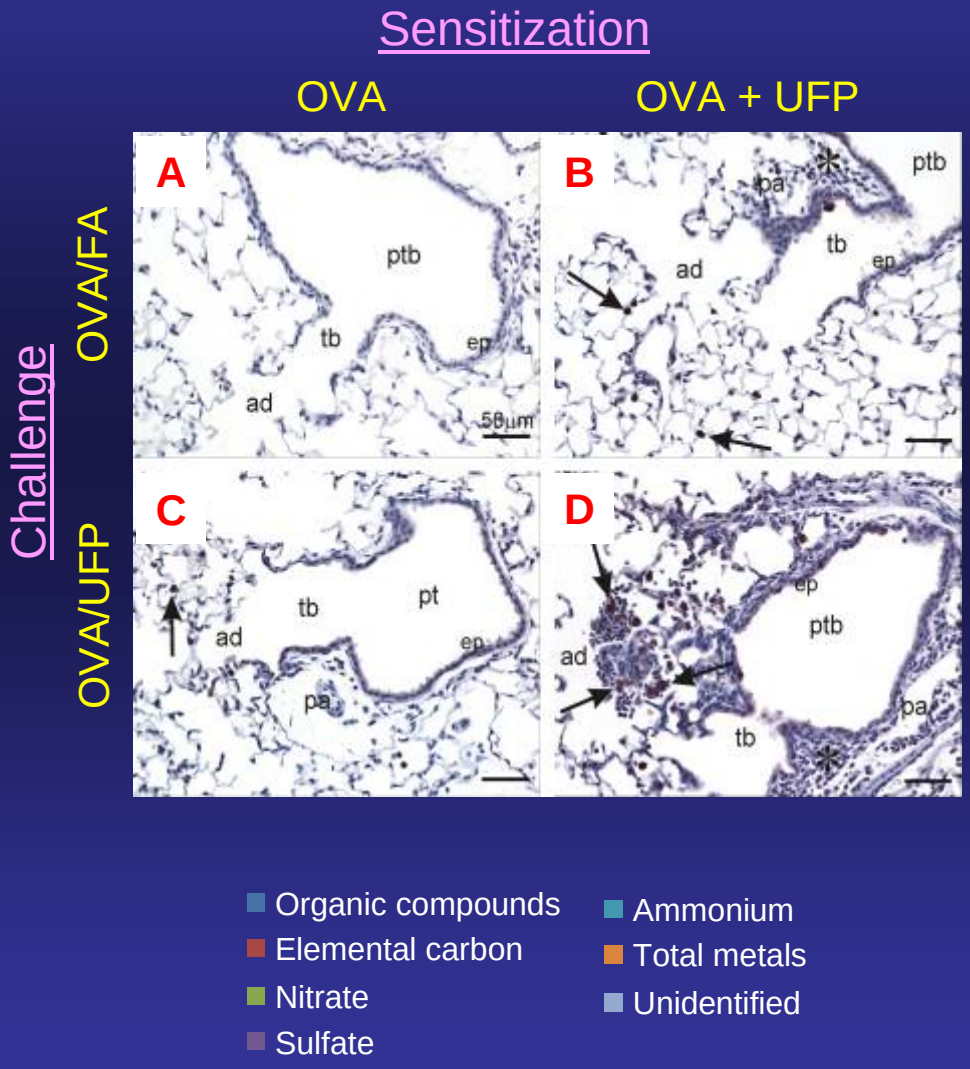
OVA/FA

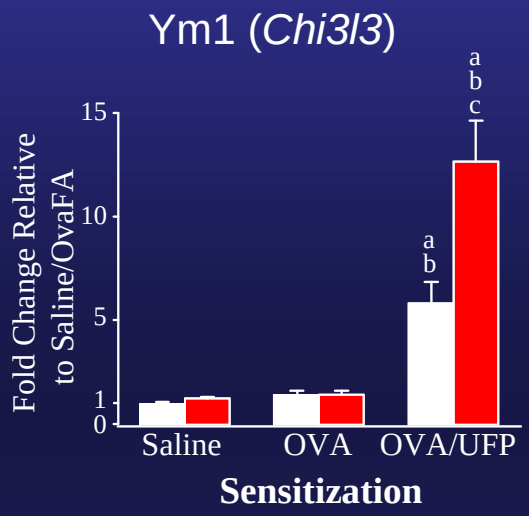
OVA/UFP

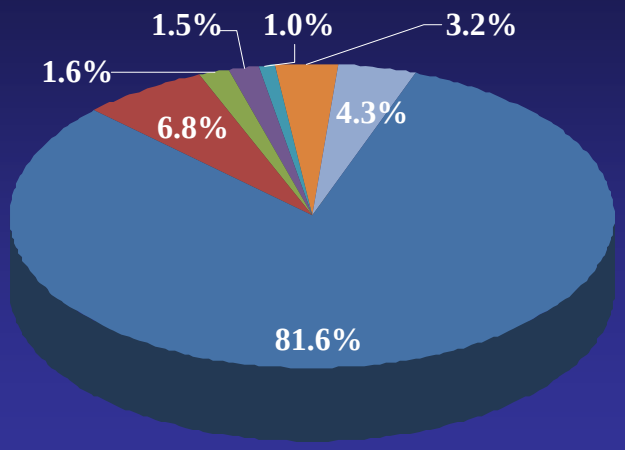


alveolar ducts & alveoli

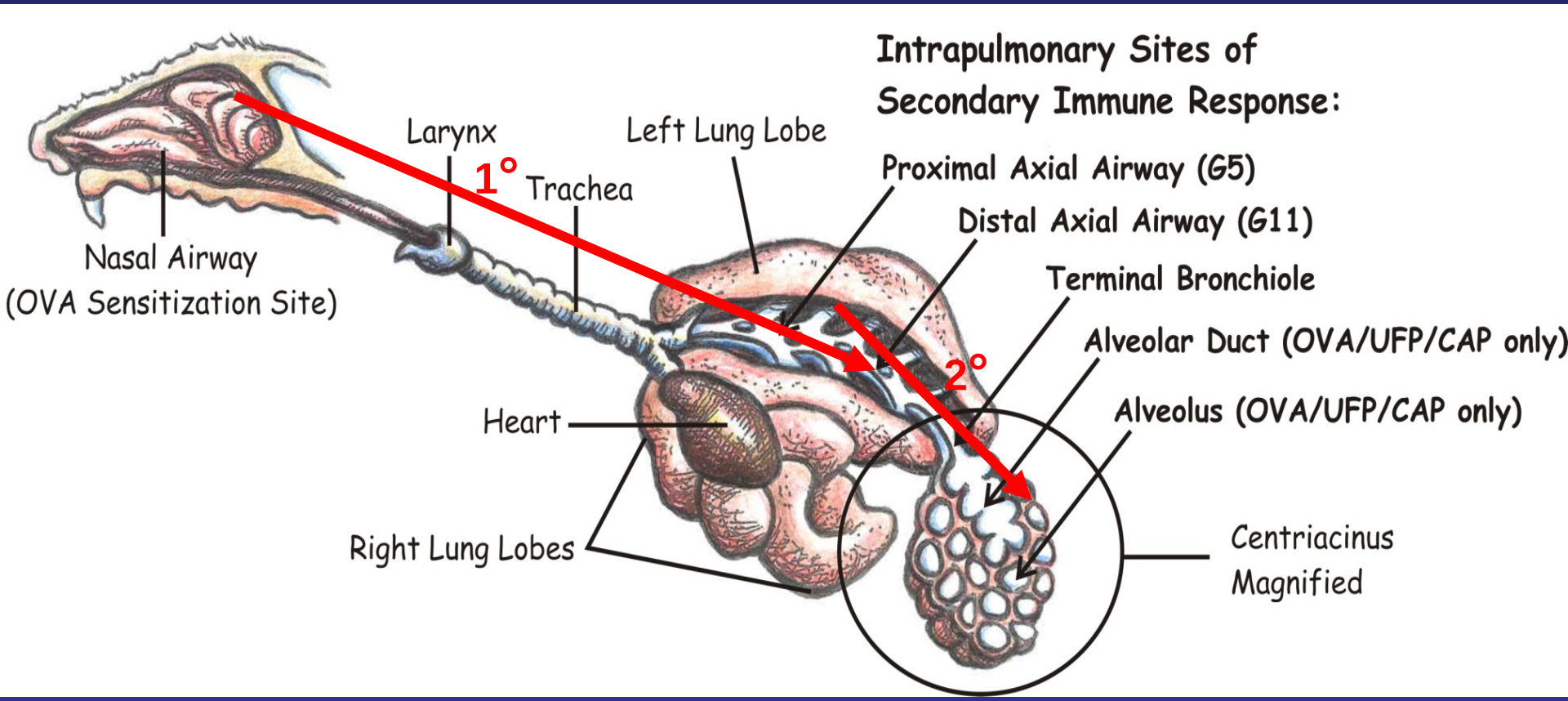
UFP Inhalation-enhanced allergic inflammation in the distal lung is accompaned by oxidative stress







The target sites of ambient UFP during the secondary immune response



Summary of Animal Studies

- Ambient UFP are capable of acting as an adjuvant to enhance immune response to experimental allergen
- UFP are able to interfere with both primary and secondary immune response
- There is a close correlation between the adjuvant effect of PM and particulate redox-active organic chemical content
- Real-life inhalation of pro-oxidative UFP during allergen challenge could lead to a profound allergic inflammation deep in the lung in already-sensitized animals

Overall Summary

- Induction of oxidative stress by particle-associated organic chemicals plays an important role in the adverse health effects of particulate pollutants
- UFP are more dangerous than coarse and fine particles
- UFP are capable of enhancing both primary and secondary immune response to an experimental allergen
- The adjuvant effect of PM is closely correlated to particles' organic chemical content and oxidant potential
- Real-life inhalation of UFP during secondary allergen exposure could lead to a profound allergic inflammation deep in the lung in prior sensitized animals
- Relevance to human: The boosting effect of UFP inhalation on the secondary immune response may provide an explanation for the asthma flares after a sudden surge in ambient PM level

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