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THE HEALTH EFFECTS OF ULTRAFINE PARTICLES

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Abstract

Particulate matter (PM) is a complex mixture of particles suspended in the air that vary in size and composition depending on their sources. Particles from mobile sources tend to fall into a bimodal distribution referred to as nuclei mode and accumulation mode. Nuclei mode particles (or nanoparticles) are less than 50 nm in diameter and are generally made of hydrocarbons, sulfur, or metallic ashes. Accumulation mode particles range in size from about 50 nm to 500 nm and may contain elemental and organic carbon, nitrate, sulfate, and various metallic ashes.

After they have been emitted, particles undergo chemical reaction in the air, so their composition and size distribution vary depending on weather, proximity to sources, and other factors. Ambient particles generally fall into a mass-based trimodal distribution of ultrafine (< 100 nm), fine (between 0.1 and 1um), and coarse (>1 um). Ultrafine PM include nuclei mode and a fraction of accumulation mode PM.

The US Environmental Protection Agency and other agencies around the world regulate the levels (mass) of ambient particles smaller than 10 um in diameter (PM_{10}). Some agencies, including the US EPA, also regulate particles smaller than 2.5 um in diameter ($PM_{2.5}$). Ultrafine PM contribute very little to the mass of $PM_{2.5}$ and PM_{10}, but are present in high numbers. Their level in ambient air is generally determined as number count.

Formation of nanoparticles in mobile source exhaust is very sensitive to testing and sampling conditions, fuels, and after-treatment designs. Analysis of aerosol samples collected at different distances from roadways have shown that nanoparticles can be measured near the road, but disappear with distance from the road. Moreover, different locations within a city have different size distribution of ultrafine particles depending on whether locally generated (nuclei mode) or transported (accumulation mode) aerosols predominate.

A large number of time-series epidemiologic studies over the last decade have reported associations between short-term increases in exposure to PM_{10} and $PM_{2.5}$ and increases in morbidity and mortality, particularly among people with respiratory and cardiovascular diseases.

Recently, epidemiologists have also begun to investigate the association between health outcomes and ultrafine particle number. Effects of nanoparticles are more difficult to assess due to the limitations of current monitoring instruments. Some scientists have proposed that smaller particles may be especially toxic: they have a greater total surface area than larger particles of the same mass, may be more likely to penetrate and interact with cells deeper in the lung than larger particles, and are thought to move rapidly to tissues outside the airways.

Inhaled particles can cause a variety of effects depending on their physico-chemical properties and the characteristics of the host. Endpoints other than mortality and morbidity (such as hospital admissions) that have been measured include changes in respiratory function and respiratory symptoms, airway inflammation, vascular parameters (such as blood coagulability, blood pressure, etc.), and heart function.

There is only one time-series study examining the association between mortality and various PM sizes (Wichmann et al, HEI 2000). The results of this study are reviewed in detail in the presentation of Annette Peters. The epidemiologic studies comparing effects of different sized PM reviewed in this presentation consist of panel studies of children or adults in which repeated measures of lung function, respiratory symptoms, or electrocardiogram changes were taken. Measures of air pollution were collected at stationary monitoring sites. These studies, using multiple exposure metrics and different lag periods, show associations between ultrafine particle number and a decrease in respiratory function, an increase in respiratory symptoms, and ST-segment depression (an electrocardiogram feature characteristic of myocardial ischemia), but these effects are also associated with other pollutants (sulfate, $PM_{2.5}$, PM_{10}.) In summary, the evidence from epidemiologic studies regarding the effectiveness of small size PM in exerting health effects is inconclusive.

A number of experimental studies to determine the role of size and composition have been conducted using laboratory generated ultrafine and fine particles made up of one element (for example carbon or nickel). The primary endpoints measured were changes in markers of airway inflammation (i.e., increased production of reactive oxygen species and increased number of inflammatory cells, especially polymorphs [PMN].) The main conclusions that can be drawn from these studies are that composition and solubility of PM (and perhaps physical parameters such as surface area or surface charge) appear to be the most important characteristic associated with increased inflammation. Size may also play a role and effects of different sized particles of

the same composition may differ. The studies evaluated in this presentation, however, used particle (and element) concentrations much higher than those in ambient air and it is unclear whether these conclusions apply to ambient PM. Additional epidemiologic studies in locations with different types of sources measuring a variety of PM parameters using standardized methods as well as experimental studies comparing different types of PM (both soluble and insoluble) and PM metrics and using more realistic exposure conditions would help in elucidating the role that PM size and composition play in inducing toxic (adverse) health effects.

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The Health Effects of Ultrafine Particles

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7th International ETH-Conference on Combustion Generated Particles
18th –20th August 2003

Overview of Presentation

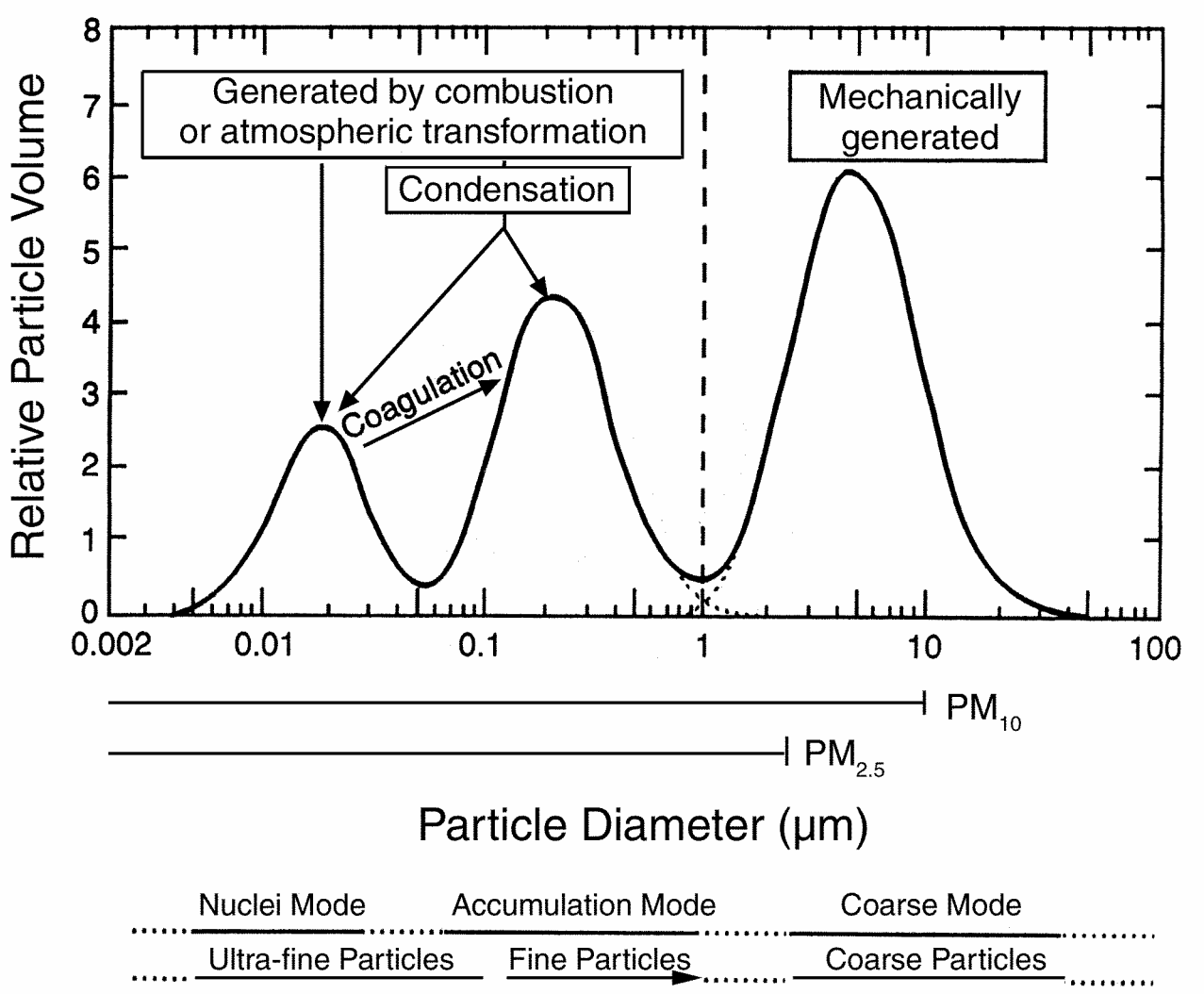
- Considerations on nanoparticles and ultrafine (UF) particles (PM)
- Epidemiologic studies comparing PM of different sizes
- Experimental studies comparing PM of different sizes (fine and UF PM) and composition

The Ambient Particle Mixture

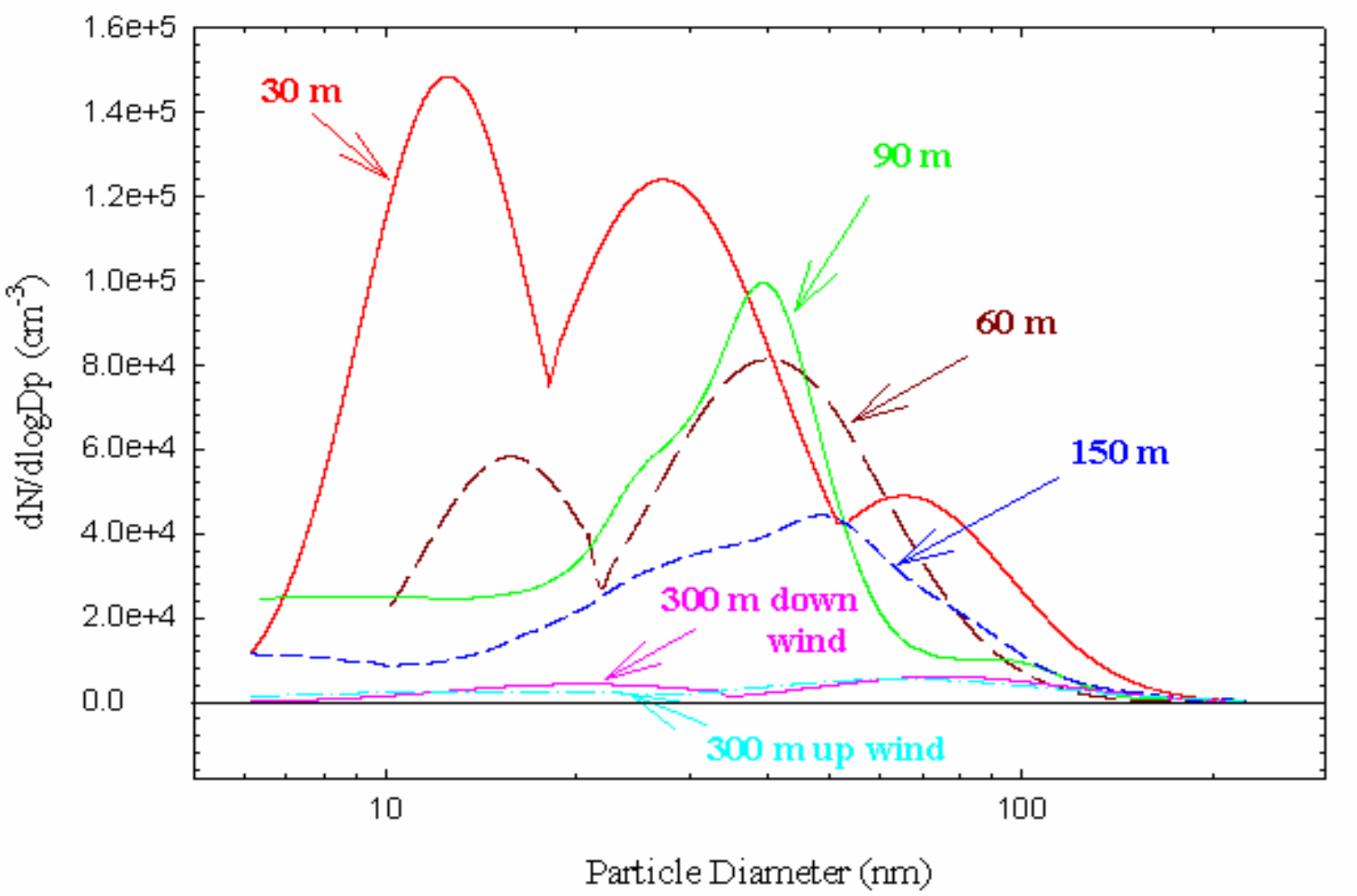
Solid and liquid PM in the air

- Multiple sources
  - Combustion (diesel, gasoline engines; wood-burning stoves; power plants; cooking)
  - Natural (wind blown dust)
  - Secondary particles from chemical transformation in the air
- Vary in size and chemical composition
- Vary from place to place and over time

Distribution of Particles in Ambient Air

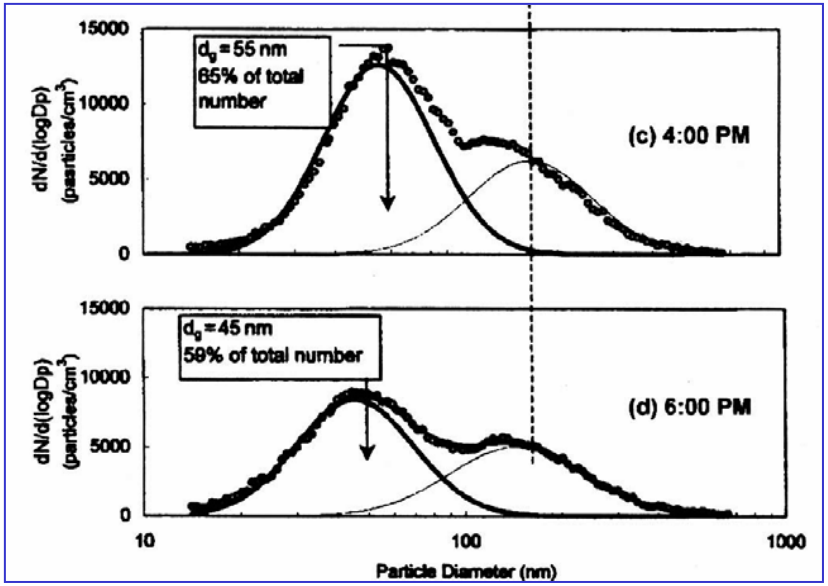


Measurements of Ultrafine (UF) PM Near a California Freeway



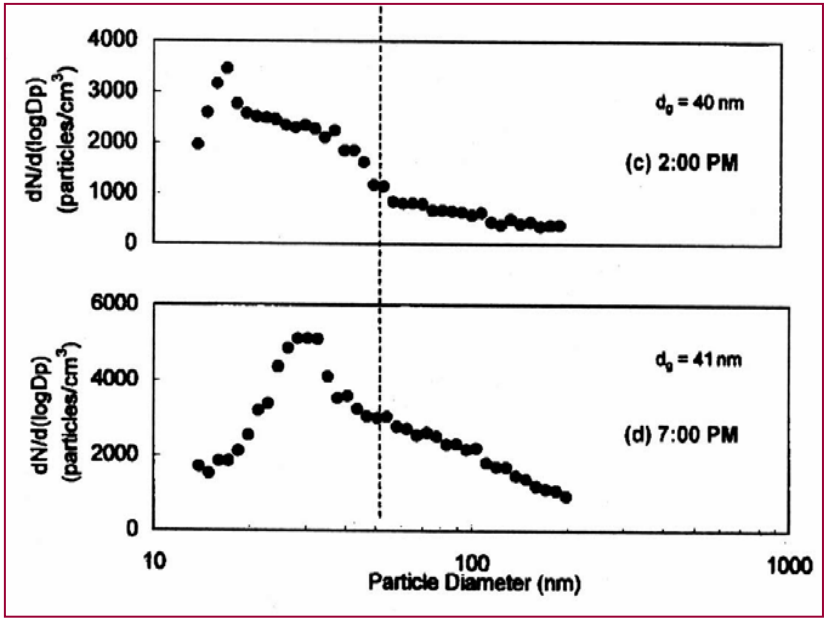
Zhu et al JAWMA Sep 2002

Size Distribution of UF PM in Ambient Air



(SMPS, 15 minutes)

Riverside CA - PM from transport and atmospheric reactions



Downey CA - fresh particles from a freeway(unimodal distribution)

Kim et al JAWMA Mar 2002

Health Effects of Nanoparticles: Special Considerations

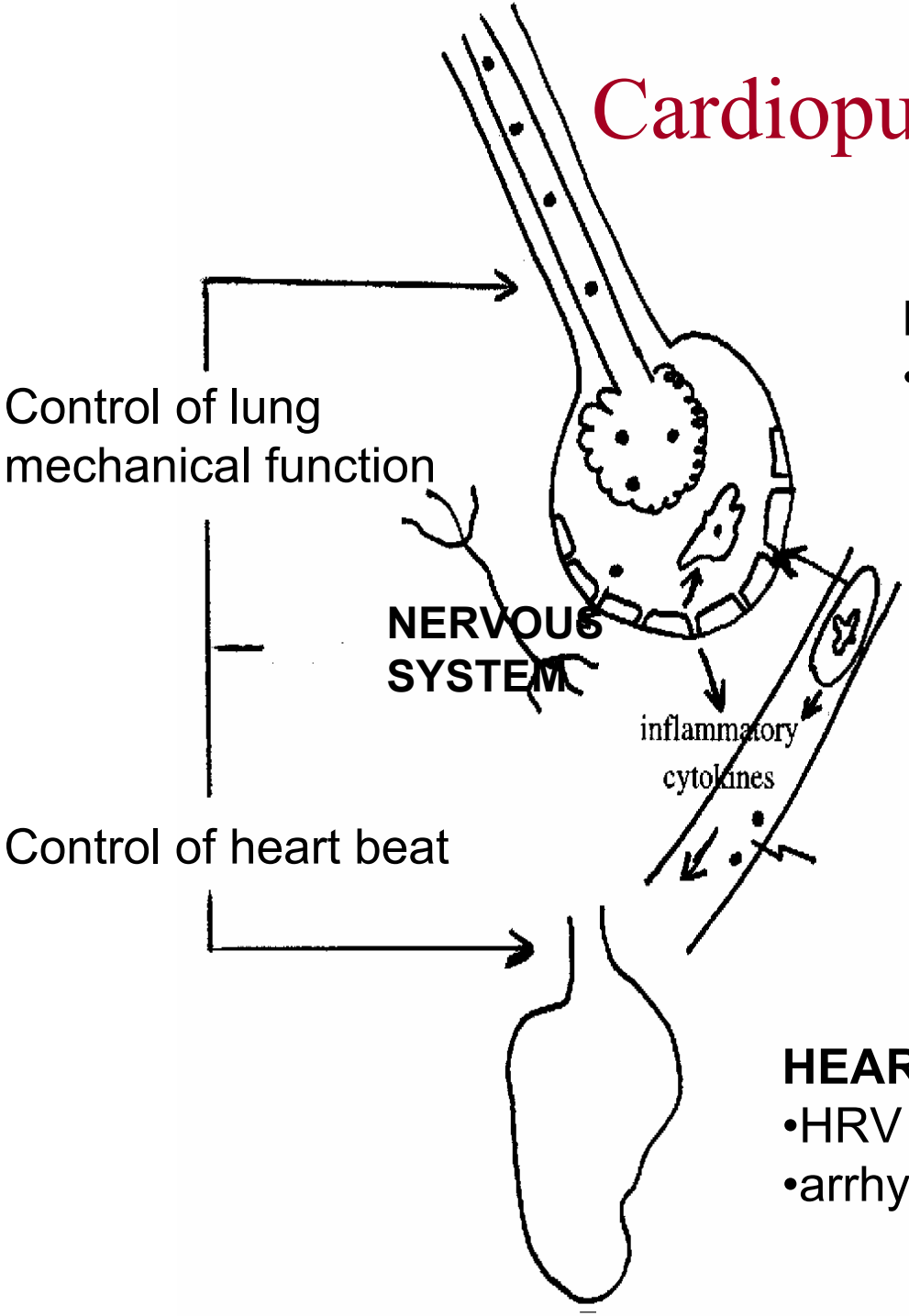
- Nanoparticles are short-lived and tend to disappear with distance from roadways. Levels vary greatly within a city
- No sampler is available to measure personal exposure to nanoparticles. Epidemiologic studies so far have assessed associations with levels (number) of ultrafine (UF) particles (<0.1μm)
- Experimental studies can be designed to test specific hypotheses

Which PM Attributes Are Associated with Toxicity?

- Size/Surface Area

  Smaller particles, especially UF
  - are present in high number, but not mass
  - reach alveolar (gas-exchange) region in deep lung
  - have greater surface area per unit mass for chemical reactions
  - translocate more rapidly out of airways?
  - poorly phagocytized by alveolar macrophages?
- Chemical Composition (e.g. metals, organic compounds, acidity)
- Biological Constituents (e.g allergens, endotoxin)

Cardiopulmonary Effects of PM



LUNG
- airway inflammation
  - cell activation & recruitment
  - ROS and cytokine production

CIRCULATION
- blood coagulability
- systemic inflammation
- blood pressure
- vasoconstriction

HEART
- HRV
- arrhythmia

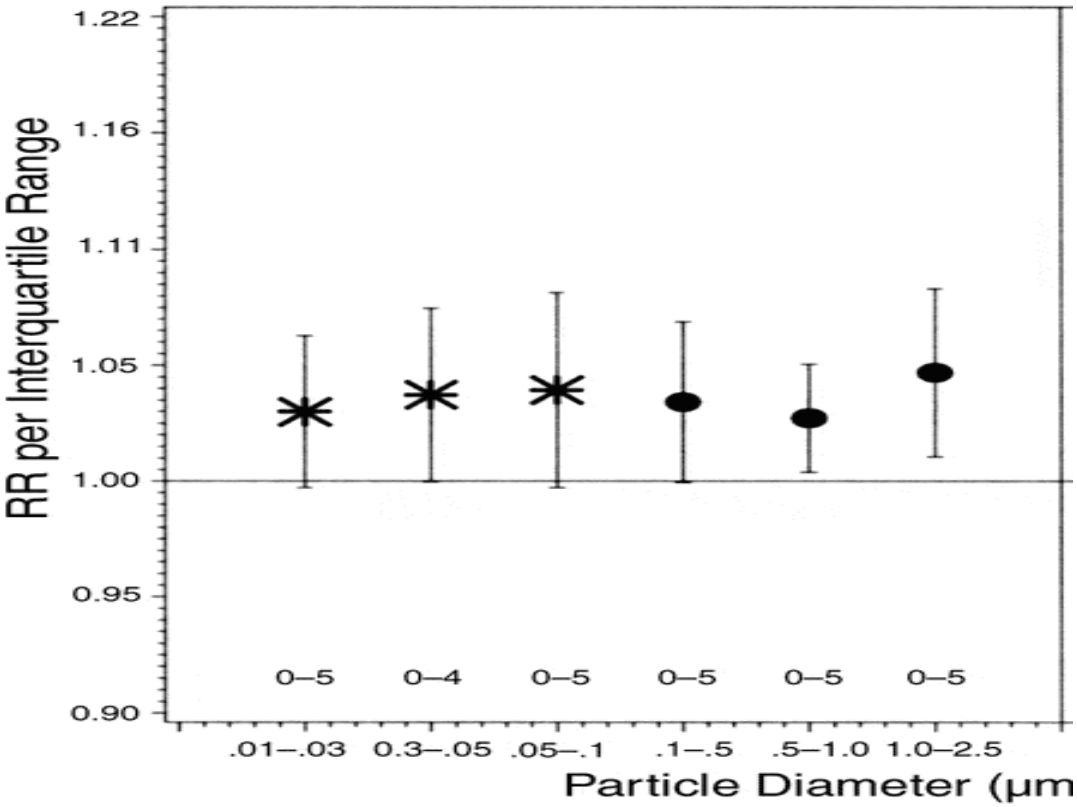
Epidemiologic Studies Comparing PM of Different Sizes

- Time-series studies of mortality

- Panel studies of children or adults with repeated measures of outcomes:
  - Decreased lung function (peak flow)
  - Increases in **respiratory** symptoms
  - ECG changes

Similar Effects of UF and Fine PM on Daily Mortality

Erfurt Germany



Wichmann et al, HEI 2000

Association of UF PM with Symptoms

Study	Results
De Hartog et al Am J Epid 2003 (3 panels of 37-47 elderly with coronary artery disease-ULTRA)	PM2.5(but not PM10 and UF number) were associated with phlegm and shortness of breath
Penttinen et al et al Eur Resp J 2001 (78 adult asthmatics)	No association of any size PM with respiratory symptoms
Tittanen et al Eur Resp J 1999 (49 asthmatic children)	No consistent association of any size PM with decreased peak flow
Peters et al Am J Resp Crit Care Med 1997 (27 adult asthmatics)	All measures of pollution were associated with feeling ill and cough on the same day

Association of UF PM with Decreased Lung Function

Study	Results
Penttinen et al Eur Resp J 2001 (78 adult asthmatics)	UF number (but not fine and coarse PM mass) was associated with decreased peak flow
Osunsaya et al Occup Environ Med 2001(44 adults aged >50 yrs) with asthma or COPD	Neither UF number or PM10 mass were associated with changes in peak flow
Timonen et al Am J Resp Crit Care Med 1997 (229 children with chronic asthma symptoms)	UF and PM2.5 mass (but not PM10) were associated decrease in peak flow (on the same day)
Peters et al Am J Resp Crit Care Med 1997 (27 adult asthmatics)	UF and PM2.5 mass (but not PM10) were associated with same day decrease in peak flow

Association of UF PM with Cardiac Function Changes

Study	Results
Pekkanen et al Circulation 2002 (45 subjects with coronary artery disease-ULTRA)	Association of UF number, PM1, and PM2.5 (but not PM2.5-10) and risk of exercised-induced ST-segment depression

Epidemiologic Studies - Conclusions

- Many studies using multiple metrics and different lags show associations between ultrafines (particle number) and respiratory function or symptoms.
- In the majority of the studies, effect is equivalent to that of $PM_{2.5}$ or PM_{10} mass. Also difficult to separate from effects of other pollutants.

Experimental Studies Comparing Fine and UF PM in Animal Models

Primary endpoint: markers of airway inflammation (in bronchoalveolar lavage or lung tissue):

- ↑ production of reactive oxygen species
- ↑ total cells
- ↑ inflammatory cells especially polymorphs (PMN)
- ↑ total protein
- ↑ inflammatory cytokines

Comparison of Fine and UF Nickel PM in Rats

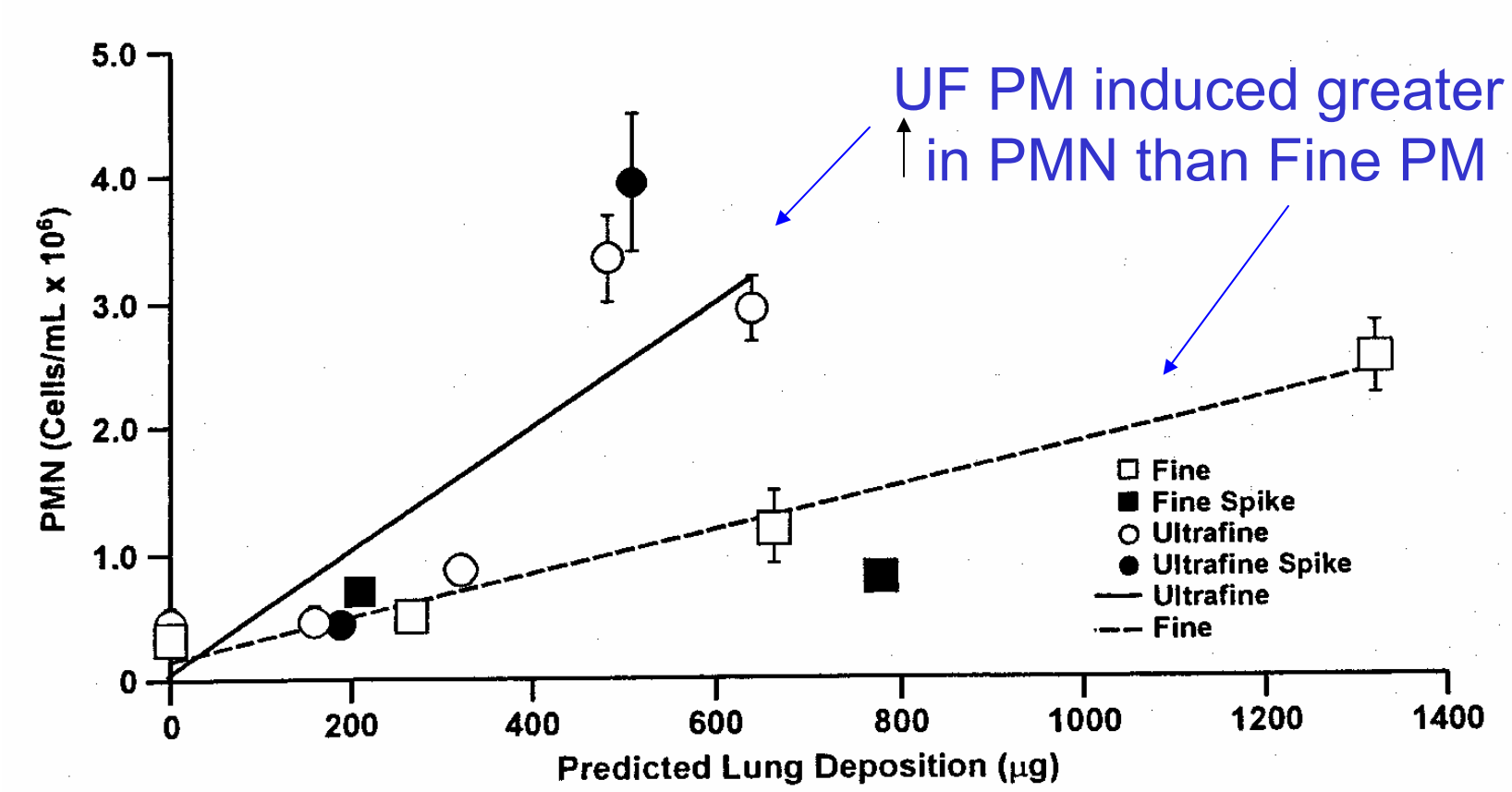
Exposure (72 hr)	Cell No. ($x10^5$)	Protein	Neutrophils (% of total cells)
	% change relative to control		
NiO, 50-60 nm 340 ug/m3	=	=	=
NiSO4, 50-60 nm 420 ug/m3	+90%	+4 fold	+36 fold
NiSO4, 250 nm 480 ug/m3	=	+11 fold	+83 fold

Fine and UF NiSO4 particles increased inflammation.
UF NiO had no effect.
NiSO4 is soluble, NiO insoluble

Leikauf et al, HEI 2001

Comparison of Fine and UF Vanadium (V_2O_5) PM

(aged, endotoxin-treated rats)

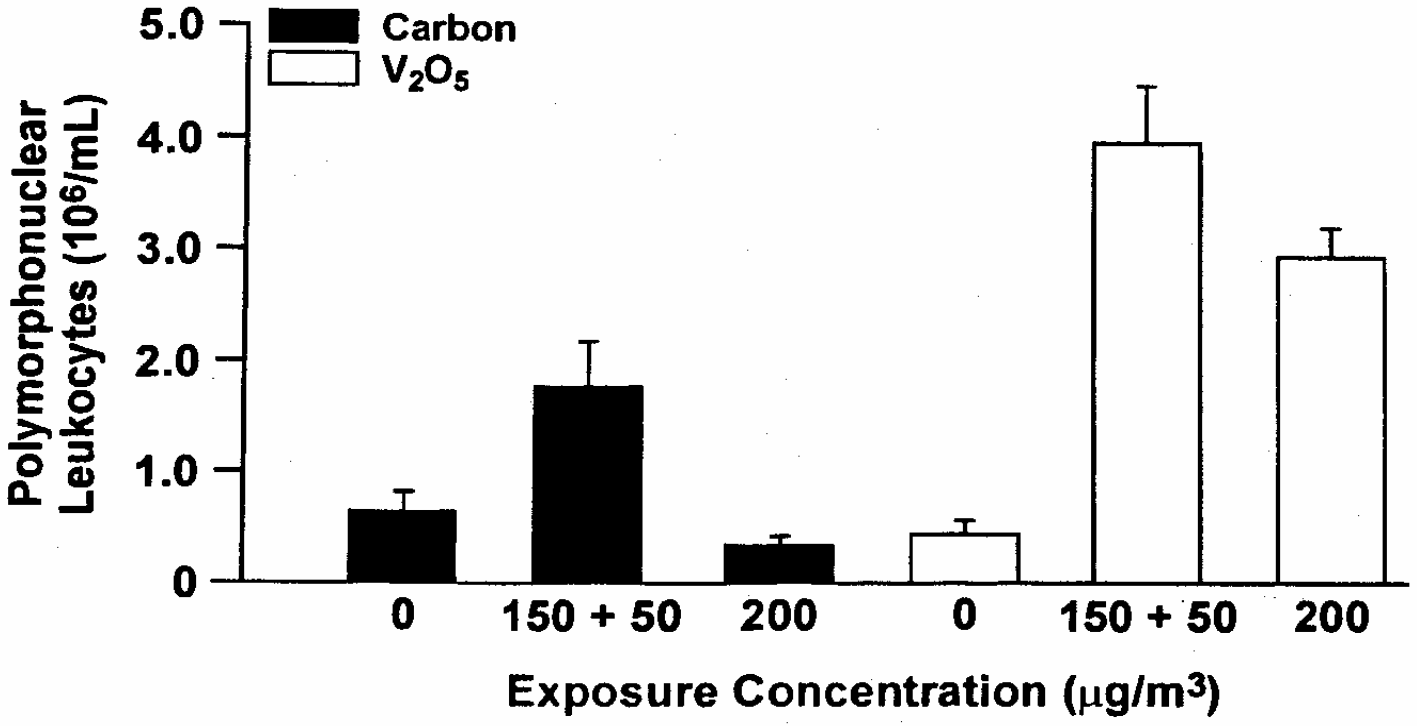


Hahn et al 2002, preliminary data

Comparison of UF Carbon and Vanadium PM

(aged, endotoxin-treated rats)

Both UF vanadium and carbon cause ↑ in response; vanadium more potent



Hahn et al 2002, preliminary data

Comparison of UF Carbon or Platinum PM in Mice

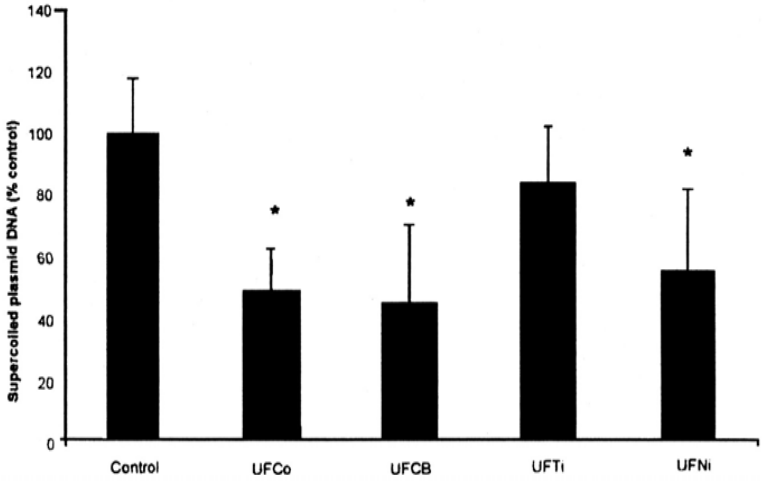
Almost no effects in different animal models

Changes in % neutrophils 22 hrs after inhalation

	Carbon		Platinum	
Animals Tested	Young	Old	Young	Old
Healthy C57BL/6J mice	0.1	0.2	0	–0.2
Healthy rats	0.2	–0.2	NT	NT
Elastase-treated C57BL/6J mice	2.5	2.8	2.7	4.9
Tsk mice	NT	0.7	NT	NT
Tsk mice, endotoxin-preexposed	NT	–2.8	NT	NT
Rats, endotoxin-preexposed	5.1	–5.4	NT	NT

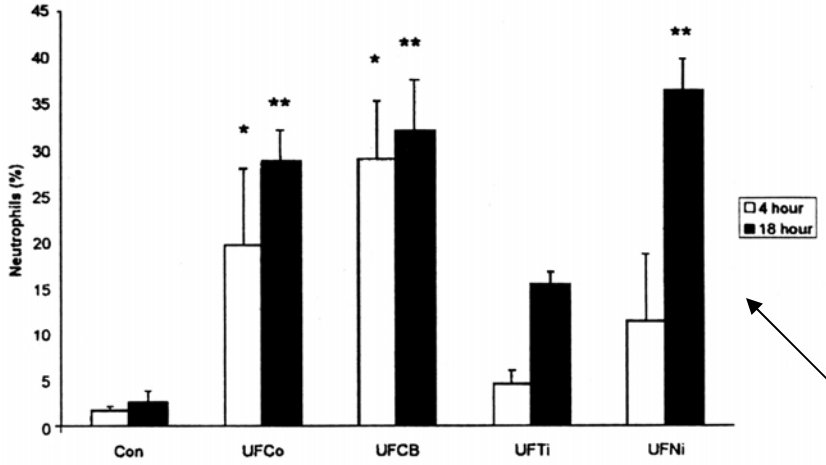
Oberdörster et al, HEI 2000

Comparison of UF Nickel, Carbon, Cobalt, Titanium PM



In vitro

Degree of inflammation appears related to ability to generate ROS and cause oxidative damage

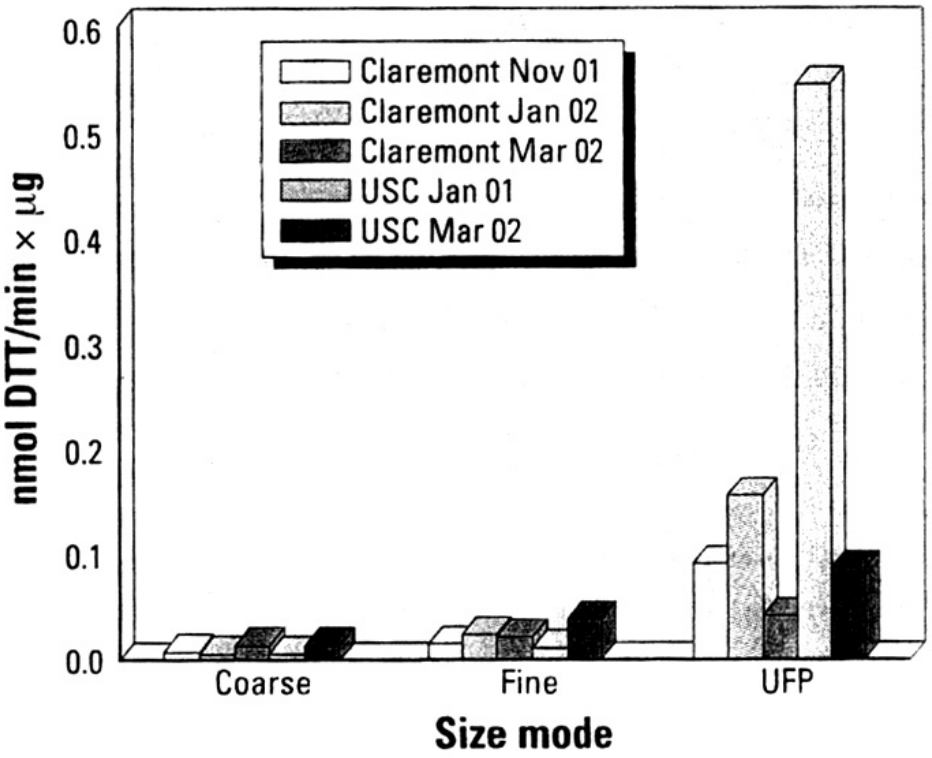


Instillation in rats

Dick et al Inhal Toxicol 2003

Comparison of Different Sized Ambient PM

(in vitro cell lines)



UF PM induced more ROS than other sized PM

UF PM had highest % PAH, Coarse PM had highest % metal

Li et al Environ Health Perspect 2003

Experimental Studies of UF-Summary

- Leikauf et al: UF and fine Ni - greater effects of fine PM compared to UF
- Hahn et al, UF and fine V_2O_5 -greater effects of UF compared to fine PM
- Leikauf et al: UF NiO (insol) and Ni_2SO_4 (sol) - greater effect of soluble compared to insoluble form
- Hahn et al, UF V_2O_5 and C- greater effect of V_2O_5 compared to C
- Oberdörster et al, UF Pt and C – few effects on inflammation; fine PM not evaluated
- Dick et al, UF Ni, C, Co, Ti – different effects on inflammation (effect dependent on ROS generation)
- Li et al, UF, fine, and coarse PM – UF had highest ROS activity, which appeared dependent on PAH content

Experimental Studies of UF PM - Conclusions

- Composition appears to be the most important characteristic of PM
  - Form of metal in PM (soluble versus insoluble, surface area, surface charge, other characteristics?)
  - PAH content
- Size may also play a role
  - Effects of different sized particles of same composition may differ

Research Needs

Epidemiologic studies in locations with different types of sources measuring a variety of PM parameters and using standardized analytic methods.

Controlled inhalation exposure studies comparing different types of particles, both soluble and insoluble.