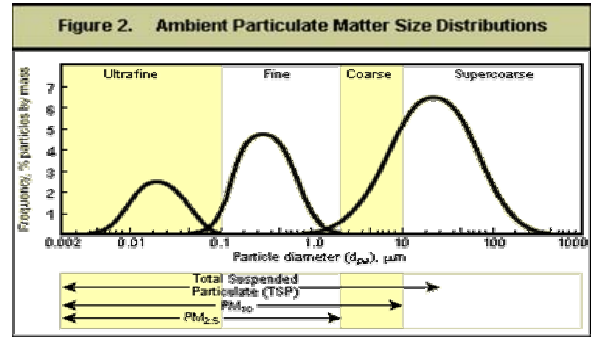


Effects of Coarse Particles

Michael Lipsett, M.D.

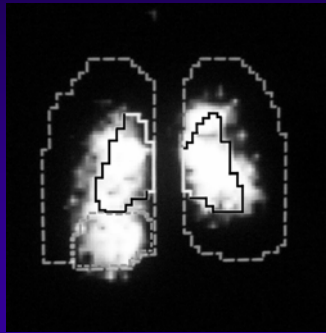
Particle Size Distributions



U.S. EPA, Basic Concepts in Environmental Sciences, <http://www.epa.gov/eogapti1/module3/category/category.htm>

Coarse Particle (CP) Deposition

- Particle deposition modeling suggests most CP deposit by inertial impaction in the first 3-8 airway generations (Asgharian et al. J Aerosol Med 2004;17:213)



SOURCES OF CP

- Crustal material (soils, dust)
- Traffic (resuspended road dust, brake linings, tire debris)
- Abrasion, crushing or grinding materials (e.g., demolition, construction, mining)
- Coal and oil fly ash
- Biological materials (bacteria, mold, pollen fragments)
- Sea salt (ocean spray)



CP – An Underappreciated Pollutant

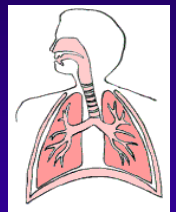
- 1997 – EPA PM Standards downplayed health concerns of CP – 2 relevant epi studies
- 2005 - EPA's Proposed CP Standard
 - Proposed 24-hr standard $70 \mu\text{g}/\text{m}^3$
 - Urban particles only
 - Specific exemptions for mining (including metals) and agriculture

Many PM Effects Thought to be due to Inflammation and Oxidative Stress

Oxidative stress occurs when production of reactive oxidant species (ROS) exceeds anti-oxidant defenses

Pollutant sources of ROS include particles (metals and PAHs) and oxidant gases

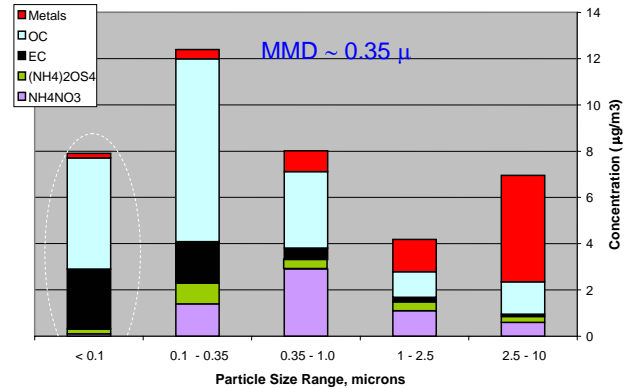
Can be amplified by **inflammation**



Chemical and Biological Constituents of PM Linked with Inflammation

- Transition metals - e.g., Fe, V, Ni
- Organic compounds, including PAHs
- Endotoxin (and other biological compounds)

24-h Average PM10 Mass and Chemical Composition of Various PM Subfractions in Downey, CA



Source: Singh et al Atmos Environ 2002;36: 1675

Comparison of Soluble Transition Metals in Weekly Composites of Urban and Rural Coarse Particles (µg/L)

Metal	Borken (rural)	Duisberg (urban)
Fe	136.4	59.3
Cu	66.1	65.2
V	3.3	4.6
Ni	141.0	32.9
Cr	2.5	2.0
Al	319.9	61.7

(Schins et al. Toxicol Appl Pharmacol 2004;195:1)

Endotoxin Characteristics

- Essential component of Gram negative bacterial cell walls
- Ubiquitous in soils
- Associated primarily with coarse fraction
- Recognized by mammalian cells via Toll-like receptors (TLR), stimulating innate immune response
- Causes airway inflammation



CP Toxicology – Major Points

- CP cause greater inflammatory responses than FP in both alveolar macrophages and bronchial epithelial cells in vitro and in animal experiments
- While some of CP-associated toxicity is due to endotoxin (e.g., inflammatory response in AM), some effects are endotoxin-independent
- Gene expression in human airway cells after CP exposure is startlingly different than after FP or UFP exposure

Findings from Selected Studies of CP Effects on Alveolar Macrophages (AM)

- CP >>> FP in proinflammatory cytokine (IL-8, IL-6, TNF-α) induction due mainly to endotoxin (and other microbial products) in insoluble fraction
- Decreased AM function
 - ↓ phagocytosis and oxidant generation (both independent of endotoxin and metals)

(Soukup and Becker, Toxicol Appl Pharmacol 2001; Monn and Becker, Toxicol Appl Pharmacol 1999)

Other Toxicological Studies of With Greater Effects of CP than Fine PM

- *In vitro* cell injury and cytokine production (summer) (Pozzi et al. *Toxicology* 2003), but not winter (Pozzi et al. *Environ Res* 2005)
- Oxidative DNA damage *in vitro* (Greenwell et al. 2002)
- Reduced alveolar macrophage function, not related to endotoxin or iron (Kleinman et al. *Toxicol Lett* 2003)
- Potentiation of allergic responses in a mouse model of allergy, including pathological changes in the lung, not likely due to endotoxin (Steerenberg et al. *Toxicol Appl Pharmacol* 2004)

Coarse Particle Epidemiology – Major Points

- Most time-series studies of daily mortality tend to show greater effect of FP than CP, though there is some evidence of CP effect, especially in arid areas
- Respiratory hospital admissions studies provide evidence for associations with CP as strong or stronger than with FP
- Few studies of CP and long-term mortality and morbidity – little or no evidence of a CP effect

(Brunekreef and Forsberg; *Eur Respir J* 2005)

Epidemiological Analyses of PM: Sources of Exposure Measurement Error

- Theoretically greater spatial heterogeneity for CP than FP - likelihood of exposure measurement error and effect estimates biased towards the null
- Many studies have not measured CP directly, rather this metric has generally been estimated by PM_{10-2.5}, creating at least two sources of instrumental measurement error
- CP tend not to penetrate indoors as efficiently as FP; outdoor measurements tend to systematically overestimate exposures

Most studies of daily mortality show greater effect of FP

- **FP > CP**
 - Harvard six cities (Schwartz et al. 1996, 2003)
 - 8 Canadian cities (Burnett et al. 2000, 2003)
 - Santiago, Chile (winter) (Cifuentes et al 2000)
 - Santa Clara, CA (Fairley et al. 1999, 2003)
- **CP > FP**
 - Mexico City (Castillejos et al. 2000)
 - Coachella Valley, CA (Ostro et al. 2000)
 - Santiago, Chile (summer) (Cifuentes et al 2000)

CP and Wind Events

- Studies suggest no increase in mortality during wind events with high PM₁₀ (and high CP)
 - Schwartz et al. *Environ Health Perspect* 1999 (Spokane, WA)
 - Pope et al. *Environ Health Perspect* 1999 (Salt Lake City, UT)
- One implication is no effect of crustal coarse particles on mortality
- However, behavioral change might affect exposures during such events

CP and Cardiovascular Outcomes

- Hospitalizations for ischemic heart disease
 - Detroit (Ito 2003)
 - Toronto (Burnett et al. 1997 – summer; 1999)
- Cardiovascular mortality
 - Coachella Valley (Ostro et al. 2000, 2003)
 - Phoenix (Mar et al. 2000, 2003)
 - Mexico City (Castillejos et al. 2000)

CP, FP and Respiratory Hospital Admissions

Study	Outcome; Location	Popul'n Ages	RR or OR CP (95% CI)	RR or OR FP (95% CI)
Lin et al. EHP 2002	Asthma hosp Toronto	6-12	1.17 (1.03 – 1.33)	0.92 (0.83 – 1.02)
Sheppard et al. HEI 2003	Asthma hosp Seattle	< 65	1.02 (0.99-1.04)	1.03 (1.01 – 1.06)
Yang et al. 2004	1 st resp hosp admit, Vancouver	< 3	1.22 (1.02, 1.48)	NS (OR not provided)
Lin et al. 2005	Resp infection, Toronto	< 15	1.17 (1.06-1.29)	0.90 (0.76 – 1.07)
Chen et al. Inhal Tox 2005	Resp hosp readmission, Vancouver	> 65	1.14 (1.05-1.24)	0.98 (0.92 – 1.05)

Long-term Mortality Explained Better by Fine Particles than Coarse

- Long-term cohort studies find little association between mortality and coarse particles
 - American Cancer Society cohort (*Pope et al. JAMA 2002*)
 - Six Cities Study (PM_{15-2.5}) (*Dockery et al. NEJM 1993*)
 - Adventist Health Study (*McDonnell et al. J Expo Anal Environ Epidemiol 2000*)
- Possibility of differential measurement error not explored

What About Those Rural Particles?

- Very little research
- *Schins (2003)* rural and urban CP comparable cytotoxicity (LDH release) and inflammatory responses (IL-8) in cultured AM and epithelial cells; CP significantly > FP
- *Schins (2004)* – rural CP > urban CP (and both >> FP (rural or urban) in inflammatory effects in human whole blood assay and in rats instilled with PM.
 - Inflammatory effects not correlated with metal content
- Coachella Valley studies – association with cardiovascular mortality and decreased heart rate variability
- Not really enough information to draw a principled distinction between rural and urban particles

Conclusions

- PM size cuts are associated with different chemical, biological and physical properties, effects on gene expression and toxicity.
- CP cause significant inflammatory effects; some related to endotoxin, some not
- Ambient CP has been associated with increased daily mortality in some areas, including cardiovascular mortality, and its effects can exceed those for FP for respiratory hospitalizations
- Not much evidence for effects of chronic CP exposure on mortality or morbidity