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Toxic and Carcinogenic Effects of Fine Particles - Observations and Hypotheses

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Introduction

The reason that I will not limit my presentation only to ultrafine particles (< 0.1 μm) is that a considerable part of the information on health effects is originating from fine (< 2.5 μm) or bigger particles. This means if I would limit my presentation only to ultrafine particles we would not understand the relevance which is behind the current political discussion on health effects of emissions from combustion processes.
Ultrafine particles coagulate in the air. There are observations that aggregates of ultrafine TiO_2 can separate in the lung again into ultrafines by dispersion in water and surfactant. If this happens also to carbonaceous particles is not known. A possible disaggregation back again into ultrafines could be significant for health effects. This means that in the environment particles are measured as fines but in the lung they could act as ultrafines.
The definitions of the particles fractions found in the environment according to their diameter are presented in a figure (see copy of overhead).
In the last decade epidemiologic studies were performed to investigate the effect of ambient particles on health effects. These investigations led to the question which component of the ambient air or which other parameter is responsible for these effects (e.g. climate influence).

Non-carcinogenic effects after acute and chronic exposure to environmental aerosols.

The question arises whether the observed increase in mortality is due to environmental aerosols. If yes, which fraction of the aerosol is responsible for health effects, e.g. chemical components or diameter fraction of aerosol ? How is the mechanism of pathogenesis ?

Oberdörster et al. (1998) proposed various hypotheses which fractions of ambient aerosols could be responsible for the observed effects. These hypotheses were 1) acidic particles, 2) transition metals in the particles like vanadium, 3) ultrafine particles, 4) ultrafine particles may act as carrier for acids, metals or gases, 5) bioaerosols like spores, pollen, bacteria, viruses, endotoxins. Up to now the mechanism why air pollution is leading to an acute mortality is not known. The composition of ambient aerosols is very complex and very heterogeneous. This is one of the reasons that the finding of a causal relationship is difficult.
Many epidemiological studies have shown a relationship of mortality and an increased hospitalization with air pollution.
The conclusions of Pope & Dockery (1999) in regard to non-carcinogenic effects in humans were:

- Acute exposure studies suggest that each 10 $\mu g/m^3$ increase in PM_{10} is associated with a 0.8 % increase in daily mortality.

- Total mortality increase is generally observed to be associated with chronic exposure to particulate air pollution by approximately 2 - 4 % per 5 $\mu g/m^3$ increase in $PM_{2.5}$.

For the subject of this workshop the epidemiological studies are not very helpful to identify whether solid carbonaceous particles or acid aerosol are of primary importance to reduce emissions of combustion processes.
One of the reasons that ultrafine particles are thought to be of special importance is that the alveolar deposition fraction is increasing dramatically for particles with a diameter from 0.1 to 0.01 μm. An epidemiological study of Peters et al. (1997) is pointing in the direction that ultrafine particles are of special importance for acute respiratory effects.
Schwartz et al. (1999) investigated episodes with high exposure to coarse particles. The authors concluded that coarse particles from windblown dust are not associated with mortality risk.

Further evidence for an important impact of ultrafines comes from animal experiments in which pulmonary effects of fine versus ultrafine particles were investigated. Ultrafine carbon black is much more efficient in inducing inflammatory reactions in the lung than fine carbon black (MacNee and Donaldson, 1999).

Carcinogenic effects of diesel motor exhaust

Data from humans
Cohen and Nikula (1999) recently published a meta-analysis of diesel exhaust exposed workers. The studies of occupational exposure to diesel exhaust and lung cancer have consistently observed elevated lung cancer rates among exposed workers that cannot be readily attributed to known sources of bias or confounders. Unfortunately, no current study provides quantitative estimates of the past exposure of study subjects to any constituent of diesel exhaust; therefore the dose-response relation cannot be estimated with great accuracy from the available epidemiological data.

Animal data
Driscoll et al. (1995) correlated for various chronic studies in which carcinogenic effects of solid particles were investigated the tumour incidences with the retained mass or the retained surface area of the particles. This analysis showed a better correlation with the surface. For titanium dioxide chronic rat studies were done with ultrafine and the larger pigment grade particles (Heinrich et al., 1995 and Lee et al., 1985). If the exposure is normalized to the cumulative dose the data show clearly a higher carcinogenicity of the ultrafine TiO_2.

Conclusions

Consequences for strategies to reduce critical components of emissions of combustion processes:
- Reduction of carbonaceous particles
- Sulfates are probably only of secondary importance for health effects (Heyder et al. 1999)

There is some evidence that fine and ultrafine particles play a significant role in the pathogenesis of the mentioned diseases.
Therefore, for future epidemiological studies beside mass concentration 1) particle surface area 2) particle number 3) particle diameter (down to 10 nm) should be measured for environmental aerosols.

Toxic and Carcinogenic Effects of Fine Particles - Observations and Hypotheses

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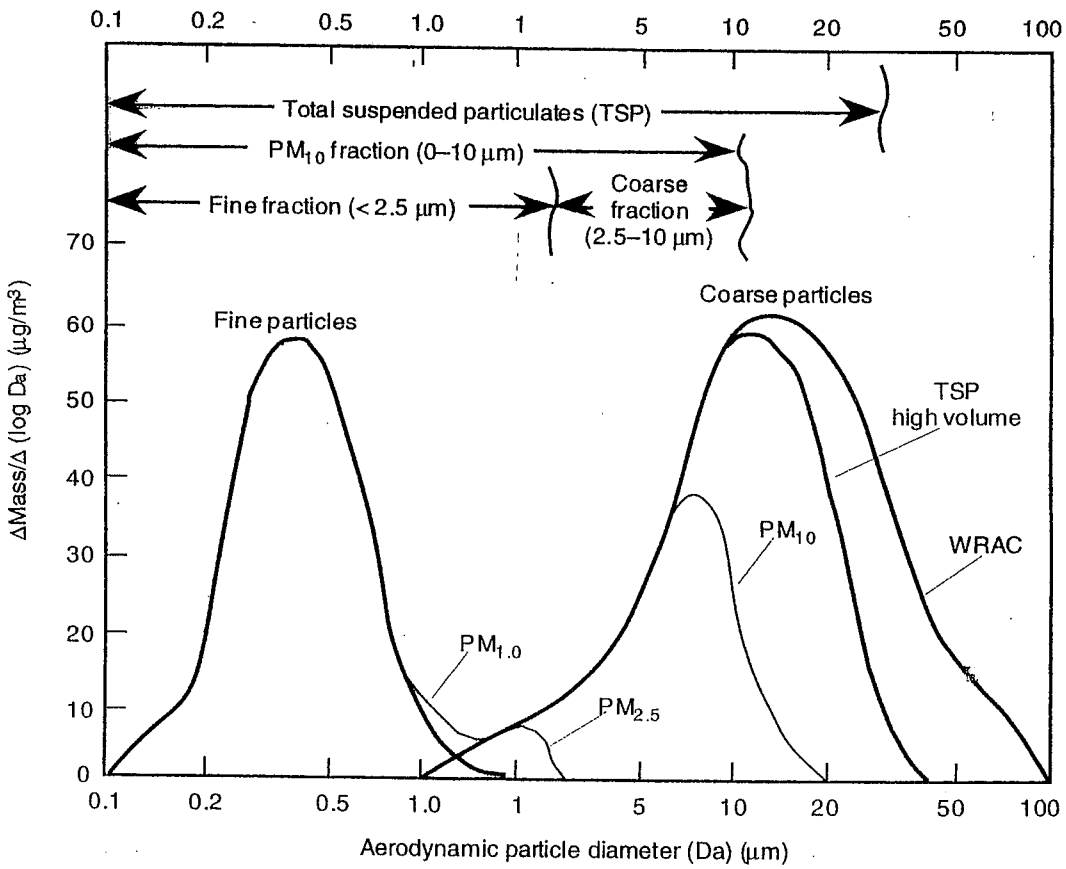
Outline

- **Non-carcinogenic effects after acute and chronic exposure to environmental aerosols**
  - **humans**
  - **animals**
  - **hypotheses of mechanisms**
- **Carcinogenic effects of diesel motor exhaust**
  - **humans**
  - **animals**
  - **hypotheses of mechanisms**
- **Conclusions**



The interrelationship between different parameters used to describe the size distribution of airborne particulate matter. (Adapted from Wilson and Suh, 1997.)

Association between increased concentration of airborne particulates and daily mortality in London during December 1952. (Adapted from Schwartz, 1994a.)

AIR POLLUTION AND DAILY MORTALITY

The nonparametric smoothed plot of the relative risk of death in Philadelphia versus TSP from the Generalized Additive Model. This pattern is seen after controlling for the nonparametric fit to the potentially nonlinear dependence of mortality on temperature, humidity, and time. No evidence is seen for a threshold.

Acute Effects of Environmental Aerosols on Humans

- **Are these effects caused by aerosols?**
- **Which fraction of the aerosol is responsible for health effects, e.g.**
  chemical components
  diameter fraction of aerosol ?
- **How is the mechanism of pathogenesis**

Particle-induced acute pulmonary effects: *hypotheses*.

- Acidic particles
- Transition metals
- Ultrafine particles (<50 nm)
- Ultrafines as carriers:
  acids, metals, gases
- Bioaerosols
  (spores, pollen, bacteria, viruses, endotoxin)

Oberdörster et. al. 1998

Fractional semiquantitative chemical composition of an urban (Cardiff) PM_{10} sample. (a) Major fractional components of an urban PM_{10} sample. (b) Composition of water-soluble fraction. (c) Composition of inorganic material associated with carbon-based fraction. (d) Composition of inorganic fraction after removal of other components from the sample.

Pooley & Milne, 1999

Stylized summary of acute exposure studies, per cent change in health end-point per 10 $\mu g/m^3$ change in PM_{10}.

Pope & Dockery, 1999

Conclusions: Non-Carcinogenic Effects in Humans

- Acute exposure studies suggest that each 10 $\mu g/m^3$ increase in PM_{10} is associated with a 0.8 % increase in daily mortality.

- Total mortality is generally observed to be associated with chronic exposure to particulate air pollution by approximately 2 - 4 % per 5 $\mu g/m^3$ increase in $PM_{2.5}$.

(Pope & Dockery, 1999)

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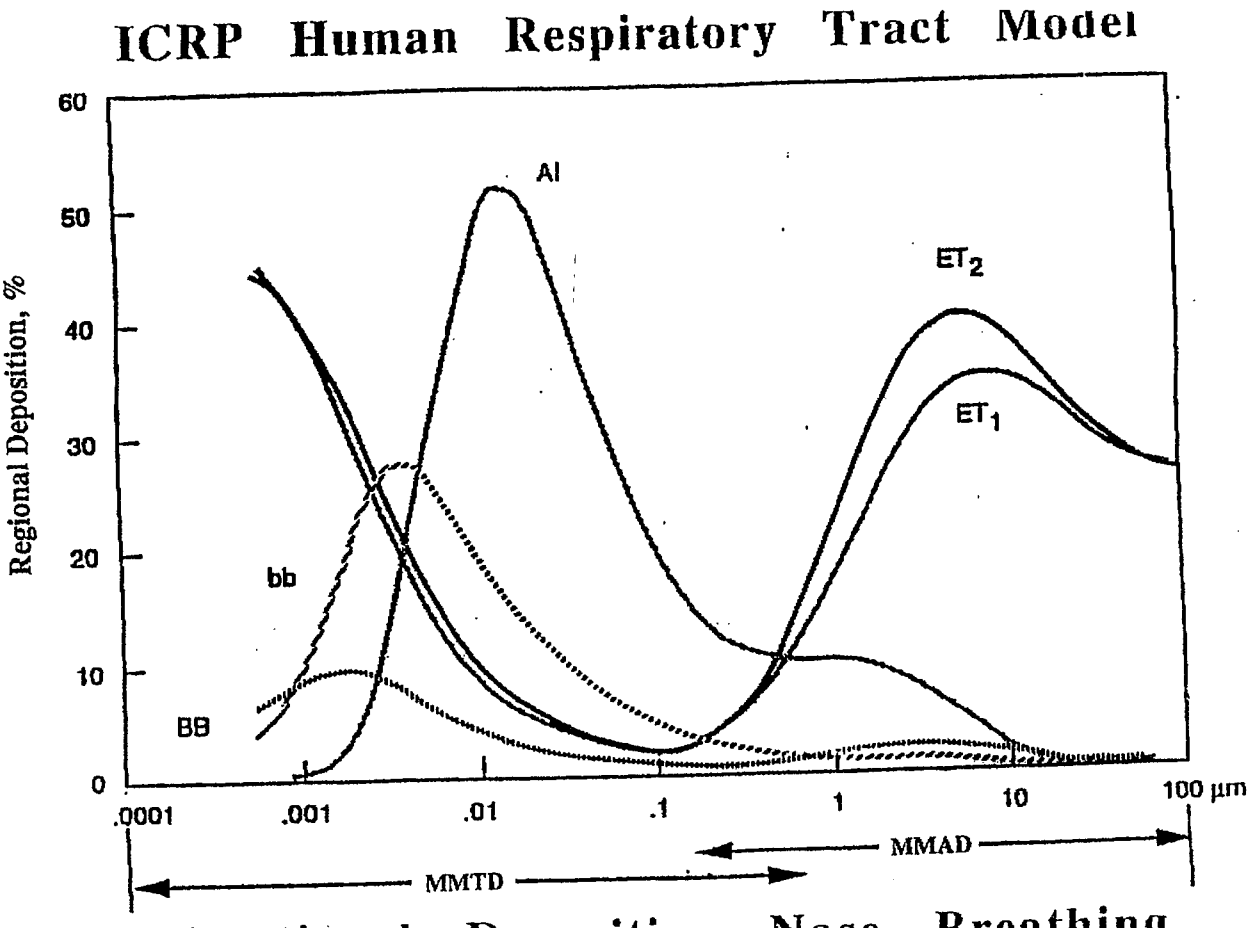

Respiratory Effects Are Associated with the Number of Ultrafine Particles

ANNETTE PETERS, H. ERICH WICHMANN, THOMAS TUCH, JOACHIM HEINRICH, and JOACHIM HEYDER

Institut für Epidemiologie und Institut für Inhalationsbiologie, GSF-Forschungszentrum für Umwelt and Gesundheit, Neuherberg; Lehrstuhl für Epidemiologie, Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie, Ludwig-Maximilians Universität, München, Germany

The association between fine and ultrafine particles and respiratory health was studied in adults with a history of asthma in Erfurt, Eastern Germany. Twenty-seven nonsmoking asthmatics recorded their peak expiratory flow (PEF) and respiratory symptoms daily. The size distribution of ambient particles in the range of 0.01 to 2.5 μm was determined with an aerosol spectrometer during the winter season 1991–1992. Most of the particles (73%) were in the ultrafine fraction (smaller than 0.1 μm in diameter), whereas most of the mass (82%) was attributable to particles in the size range of 0.1 to 0.5 μm. Because these two fractions did not have similar time courses (correlation coefficient r = 0.51), a comparison of their health effects was possible. Both fractions were associated with a decrease of PEF and an increase in cough and feeling ill during the day. Health effects of the 5-d mean of the number of ultrafine particles were larger than those of the mass of the fine particles. In addition, the effects of the number of the ultrafine particles on PEF were stronger than those of particulate matter smaller than 10 μm (PM_{10}). Therefore, the present study suggests that the size distribution of ambient particles helps to elucidate the properties of ambient aerosols responsible for health effects. **Peters A, Wichmann HE, Tuch T, Heinrich J, Heyder J. Respiratory effects are associated with the number of ultrafine particles.**

AM J RESPIR CRIT CARE MED 1997;155:1376–1383.

Episodes of High Coarse Particle Concentrations Are Not Associated with Increased Mortality

Joel Schwartz,[1] Gary Norris,[2,3] Tim Larson,[2,3] Lianne Sheppard,[2,3,4] Candis Claiborne,[5] and Jane Koenig[4]

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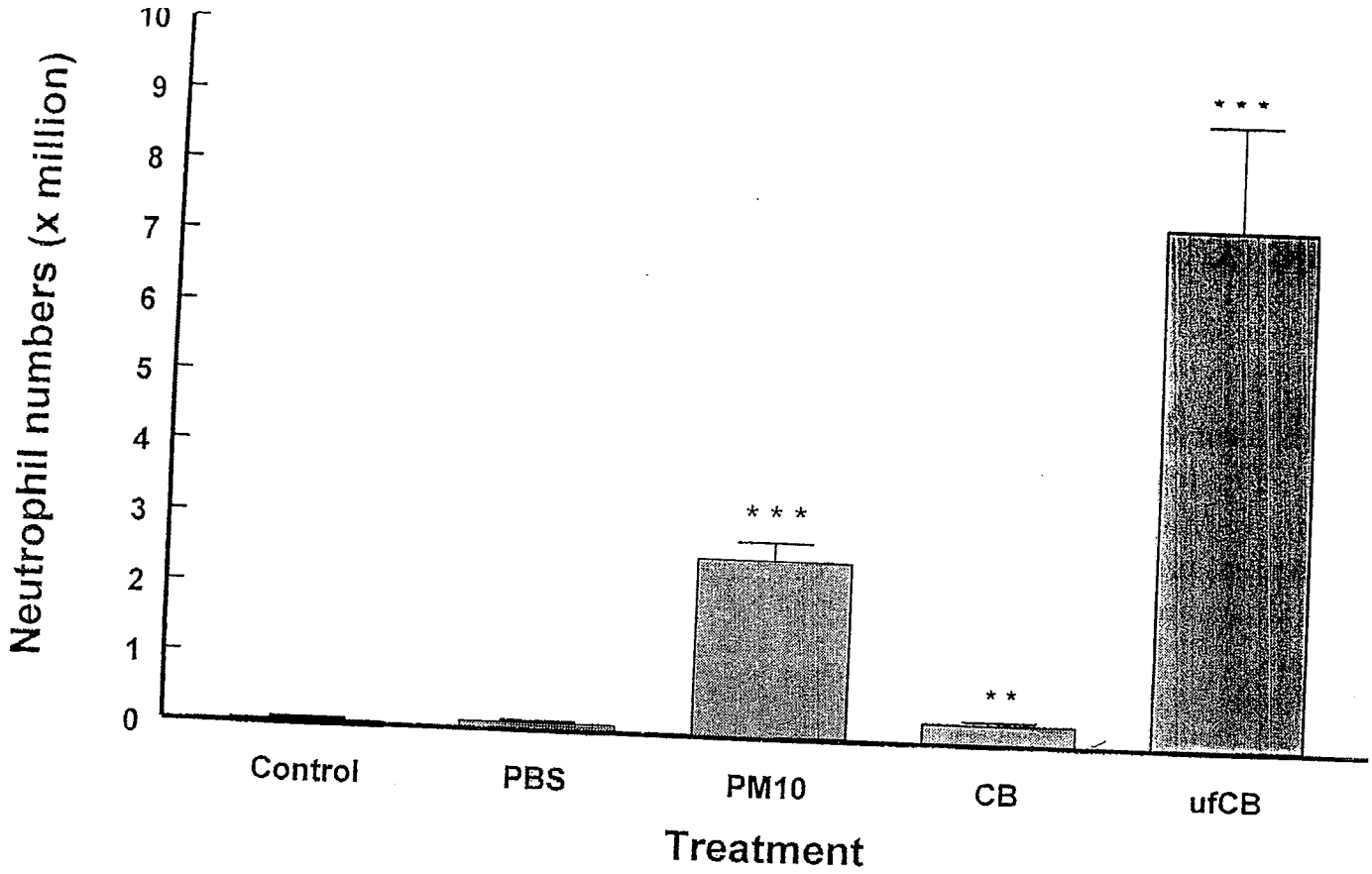
[2]Departments of Civil and Environmental Engineering, [3]Biostatistics, and [4]Environmental Health, University of Washington, Seattle, W 98195 USA; [5]Department of Civil and Environmental Engineering, Washington State University, Pullman, WA 99163 USA

Fine particle concentration (i.e., particles <2.5 μm in aerodynamic diameter; $PM_{2.5}$), but not coarse particle concentration, was associated with increased mortality in six U.S. cities. Others criticized this result, arguing that it could result from differences in measurement error between the two size ranges. Fine particles are primarily from combustion of fossil fuel, whereas coarse particles (i.e., particles between 2.5 and 10 μm in aerodynamic diameter) are all crustal material, i.e., dust. One way to determine if coarse particles are a risk for mortality is to identify episodes of high concentrations of coarse, but not fine, particles. Spokane, Washington, is located in an arid area and is subject to occasional dust storms after crops have been harvested. Between 1989 and 1995, we identified 17 dust storms in Spokane. The 24-hr mean PM_{10} concentration during those storms was 263 μg/m^3. Using control dates that were the same day of the year in other years (but with no dust storm on that day) and that had a mean PM_{10} concentration of 42 μg/m^3, we compared the rate of nonaccidental deaths on the episode versus nonepisode days. There was little evidence of any risk [relative risk (RR) = 1.00; 95% confidence interval (CI), 0.81–1.22] on the episode days. Defining episode deaths as those occurring on the same or following day as the dust storm produced similar results (RR = 1.01; CI, 0.87–1.17). Sensitivity analyses, which tested more extensive seasonal control, produced smaller estimates. We conclude that coarse particles from windblown dust are not associated with mortality risk. *Key words:* air pollution, dust storms, mortality, particulates. *Environ Health Perspect* 107:339–342 (1999). [Online 23 March 1999]

seen at more common levels are causal, p
ticularly because they appear to lie on t
same dose–response curve (*9*).

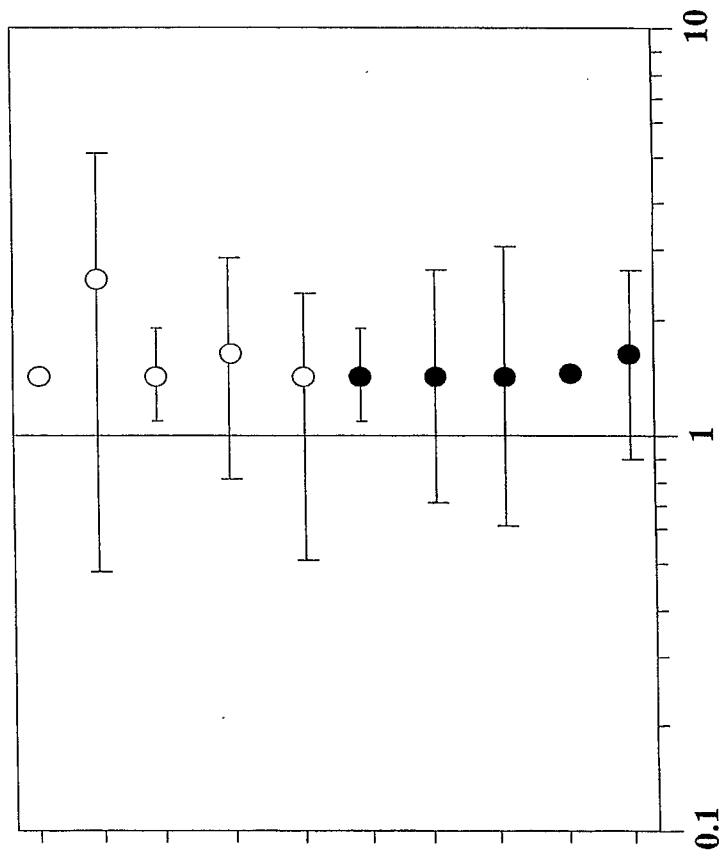
Similarly, assessment of the health effe
of coarse particles could be aided by exam
ing episodes of high concentrations of coa
particles. Indeed, for coarse particles, episc
studies have a major advantage. Episodes
high concentrations of combustion partic
are characterized by low wind speed and
low-lying inversion layer, which leads
increases in other combustion-related pol
tants as well as particles. Hence, the stud
pinpoint combustion pollution as a risk f
tor for mortality, but it is more difficult
determine which species of the combusti
mix is responsible.

In contrast, episodes of high coarse m
particles are generally associated with d



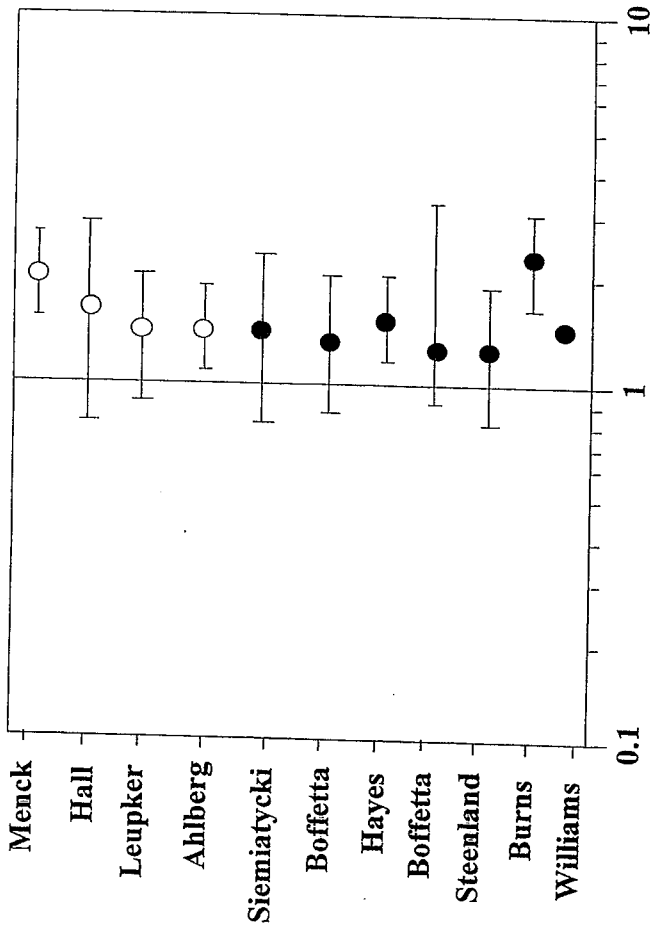
The number of neutrophils in bronchoalveolar lavage (BAL) from rats 6 h after no instillation (control) or intratracheal instillation with PBS, PM_{10}, fine (CB) or ultrafine (ufCB) carbon black (n = 3–5, $^{**}p<0.01$, $^{***}p<0.001$ compared with phosphate-buffered saline (PBS).

MacNee & Donaldson, 1999



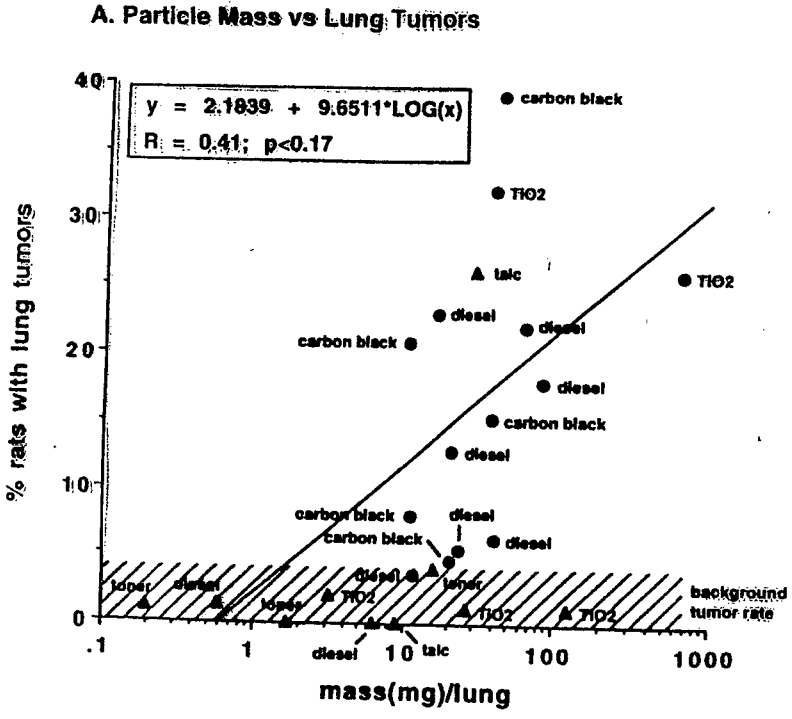
Lung cancer and exposure to diesel exhaust in railroad workers. ●, RR adjusted for cigarette smoking; R not adjusted for cigarette smoking. Error bars show upper and lower 95% confidence intervals (CIs). For the two ies by Howe and Williams, CIs were not reported and could not be calculated. References cited are: Howe *et al* 3), Hall and Wynder (1984), Garshick *et al* (1987), Boffetta *et al* (1988), Schenker *et al* (1984), Garshick *et al* 8), Burns and Swanson (1991), Siemiatycki (personal communication), Williams *et al* (1997), Boffetta *et al* (1990).

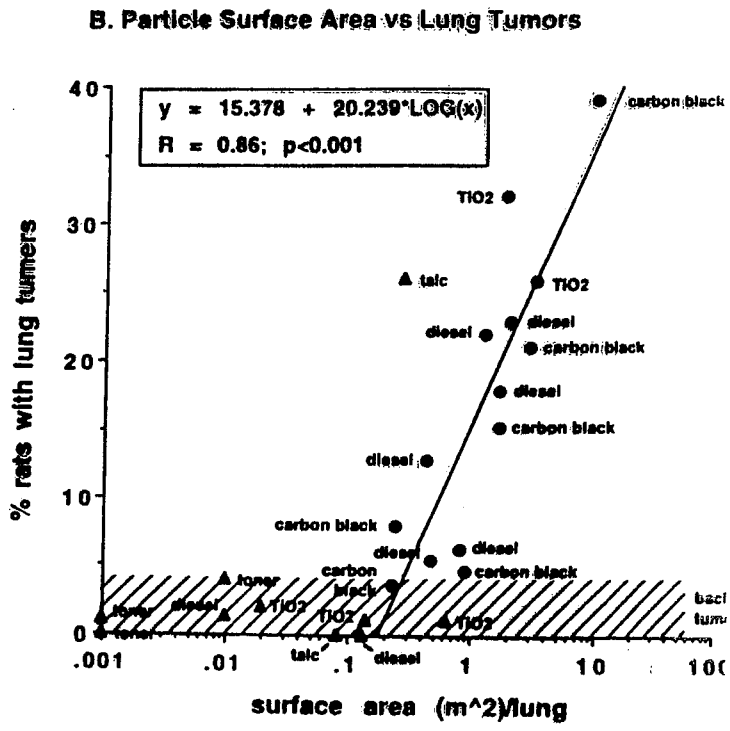
Cohen & Nikula, 1999



Lung cancer and exposure to diesel exhaust in truck drivers. ●, RR adjusted for cigarette smoking; ○, RR not adjusted for cigarette smoking. Error bars show upper and lower 95% confidence intervals (CIs). For the two studies by Williams (1977), CIs were not reported and could not be calculated. For the study by Steenland (1990), the results were those based on union records for long-haul truckers. For the study by Boffetta (1988) the results were based on self-reports of diesel truck driving. For the Siemiatycki study the results were based on self-reports of heavy-duty truck driving (personal communication). Other references cited are: Menck and Henderson (1976), Hall and Wynder (1984), Leupker and Smith (1978), Ahlberg *et al* (1981), Hayes *et al* (1989), Boffetta *et al* (1990), Burns and Swanson (1991).

Cohen & Pikula, 1999





(Driscoll, 1995)

Lung tumor incidence in rats after two years of inhalation exposure to ultrafine TiO_2 (Heinrich *et al.*, 1995) and larger-sized pigment grade TiO_2 (Lee *et al.*, 1995).

Conclusions

Consequences for strategies to reduce critical components of emissions of combustion processes:

- **Reduction of carbonaceous particles**
- **Sulfates are probably only of secondary importance for health effects (Heyder et al. 1999)**

There is some evidence that fine and ultrafine particles play a significant role in the pathogenesis of the mentioned diseases.
Therefore, for future epidemiological studies beside mass concentration
particle surface area
particle number
particle diameter (down to 10 nm)
should be measured for environmental aerosols.

Comparison Working Place / Environmental Aerosol

Occupational exposure limit to diesel exhaust : 100 $\mu g/m^3$ (8 hr/day) (in Germany)
This is a technical derived exposure limit. It reflects the currently achievable technical safety.

This value cannot directly be compared to environmental aerosols.
- **These are much more complex in their chemical composition.**
- **Sensitive subpopulations are also exposed in the environment. This is an important difference to occupational exposure („healthy worker effect“)**