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## **The health risk of solid particle diesel engine emissions**

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### 1. Introduction

About 5 or 6 decades ago, the occurrence of PAH (polycyclic aromatic hydrocarbons) was confirmed in diesel engine exhaust gases. Prior toxicological data on PAH initiated suspicion that diesel engine exhaust gas could be carcinogenic. Hence, many subsequent investigations scrutinized the composition of the diesel engine exhaust gas, the carcinogenic potency of the individual constituents and the entire mixture. Analyses showed that the exhaust gases were a complex heterogeneous blend of gases, vapors, mono- and oligo-molecular substances and solid particles.

The particles consist of a carbon core covered with hydrocarbons, metals, and metal oxides, as also nonmetallic inorganic substances. The combustion of diesel fuel creates "primary particles", whose diameter is about 20 - 30 nanometer (1 nanometer = 1/1000 micrometer = 1/1'000'000 mm; symbol for nanometer = nm, symbol for micrometer =  $\mu\text{m}$  or  $\mu$ ). The primary particles can coalesce into larger particles (mostly 100 - 200 nm, some even 1  $\mu\text{m}$  or larger), which however easily disintegrate (e.g. through heat, weather and in living tissue).

Because the diesel soot particles are so small, the inhaled air entrains these into the innermost peripheral regions of the respiratory lung structures, i.e. into the alveoli "lung sacs" where the gas exchange with the blood occurs. The inlets to the alveoli are respiration dependent about 2 - 7  $\mu\text{m}$  diameter. The particles are partially expelled with the expiratory air, but some are deposited on the alveolar walls. The macrophages ( $\phi\alpha\gamma\epsilon\iota\nu$  is Greek for eat) ingest the deposited particles. Foreign bodies mobilize the autonomous macrophages that migrate from the blood, or the pulmonary interstitium, into the alveoli [Lehnert et al. 1994].

The smallest particles, however, partially escape detection by the much larger macrophages and are not ingested. The alveoli dilate and contract through respiratory pulsation. The pulsation expels some of the particles into the bronchiole, possibly after prolonged retention in the alveoli. Unfortunately, these particles could also penetrate, through the narrow interalveolar pores, into the pulmonary interstices (the interstitium). There the lymphatic fluids can capture and transport the particles to the regional lymph nodes. The soot particles do not decompose easily. Hence, these are retained for several weeks, months or years in the interstitium and in the lymph nodes. The lymph nodes are thus colored dark gray. The particle accumulations are mutational and / or tumor inducing threats. The particles are partially dissolved and transported to various organs, where they were found during medical investigations. (Mutation = change in the cellular genetics; during subsequent cell divisions malformation of the daughter cells can occur.)

If the macrophages succeed in ingesting the particles, then the particle coating is partially stripped. Larger particles decompose into smaller particles or their primary constituents. Under favorable circumstances, the macrophages with the ingested particles exit the alveoli into the respiratory airways and are expelled up into the throat (see below). Alternatively, the macrophages either revert through the alveolar wall into the pulmonary tissue, or decompose in the alveoli. Reverting macrophages transport the particles, as previously described, into the interstitium or into the lymph nodes. Decomposing macrophages augment accumulation of particles and macrophage debris in the alveoli. Prolonged high concentrations of particles in the respiratory air cause alveolar overload, i.e. the particle invasion overwhelms the scavenging mechanisms. The decomposing macrophages then release inflammatory substances that can damage the alveolar walls.

Naturally, during inhalation or exhalation the diesel soot particles are partially deposited also in the nose, throat (pharynx), in the large airways (trachea) or in the bronchia. The walls of the trachea, the bronchia and up to the very fine passages (bronchiole) are covered with undulating hairs (cilia) and a mucous coating. The particles stick to the mucous and the motile cilia – waving like a cornfield in the wind – expel the mucous encapsulated particles into the pharynx. Subsequently, these are expectorated or swallowed.

## 2. Particle induced diseases

### Tumors

The possible carcinogenicity of diesel engine exhaust gas was investigated on rats. Lung tumors were observed after intense exposure of the respiratory tract to solid particles. A big surprise was tumors occurring even without hydrocarbons on the particles, i.e. solely carbon particles. This phenomenon was confirmed also for otherwise non-toxic, non-irritating (so-called inert) substances [Heinrich U et al. (1982), Heinrich U et al. (1989)]. The processes, through which diesel soot and other particles induce tumors, is yet incompletely understood. The hypothesis is that the adhesion of diesel soot particles, on animal and human tissue, yields carcinogenic precursor substances.

Several epidemiological studies evaluated the human tumor risk of diesel engine exhaust gas. High incidences of exhaust gas induced tumors, particularly among residents of vicinities and streets exposed to large traffic volumes. Among the vulnerable occupational groups are workers in bus garages or mines, and drivers of heavy duty vehicles or diesel locomotives [Dasenbrock C et al. (1996), Gustavsson P et al. (1990), Heinrich U et al. (1982), Heinrich U et al. (1989), Heiskel H et al. (1998), IARC (1989), Lipsett M (1999), Säverin R et al. (1999), Stayner L et al. (1998)]. The research findings prompted many regulatory authorities, particularly in Europe and the USA, to promulgate directives and legislation that limit pollutant emissions and workplace concentrations.

### Other health damage

Many scientific investigations found non-tumorous health damage caused by diesel engine exhaust gas. Some examples are:

Allergies, especially allergic rhinitis [Brändli O (1997), Chambellan et al. (2000), Knox RB et al. (1997), Kobayashi T et al. (1995), Peters A et al (1997), Pekkanen J et al (1997)];

Chronic bronchitis [Ulvestad B et al. (2000)];

Diminished respiratory volume [Ulfvarson U et al. (1991)];

Cardiac diseases [Godleski JJ et al (2000)]; and

Increased mortality [Oberdörster G et al. (1995)].

These findings are very significant for the population. There is also a financial aspect because of the consequent medical expenses.

### The role of ultrafine solid diesel particles

The ultrafine solid diesel particles (UF), i.e. those smaller than 100 nm, are specially significant [Anderson PJ et al. (1990), Brändli O (1996), Donaldson K et al. (1999), Ferin J (1994), Gradón L et al. (2000), MacNee W et al. (2000), Oberdörster G et al. (1992), Peters A et al. (1997)]. The UF are more toxic than larger particles. The reasons are:

The diesel engine exhaust gas contains many more UF than larger particles.

UF are mostly deposited in the pulmonary alveoli. The UF are not intercepted in the bronchi, where the cilia could effectively expel them. Larger particles, unlike the UF, are mostly deposited ahead of the alveoli, where the organism can easily eliminate them from the respiratory system. (Particles larger than 10 µm do not normally reach the alveoli.)

The macrophages do not detect some or all of the UF. Thus, the UF mostly evade the alveolar scavenging mechanism.

UF are so microscopic that they intrude between alveoli walls directly into the pulmonary interstitium and dwell there for long periods.

UF have, in comparison with larger particles, several orders of magnitude greater total surface area.

Hence, they have many more free radicals that can directly or indirectly incite inflammatory reactions and tumors.

Moreover unlike larger particles, the UF directly interfere the Calcium-3 flow to the pulmonary cells and thus impede the cell functionality.

Animal experiments indicate that even short exposures to UF can increase the blood coagulation factor VII, and thus hasten coronary and cerebral thrombosis.

**Conclusions** about the health effects of ultrafine solid particles in diesel engine exhaust gases.

Diesel engine exhaust gas should not only contain the least possible mass of solid soot particles, but also have the smallest possible count of ultrafine particles.

Clean Air legislation and occupational health directives presently still specify pollutant limits as maximum particulate mass in diesel engine exhaust gas. This metric is unsatisfactory from a toxicology perspective and must be supplemented or substituted with limits for particulate count. Instruments are available for field measurement of particulate count. Thus, the particle count can be monitored and compliance verified.

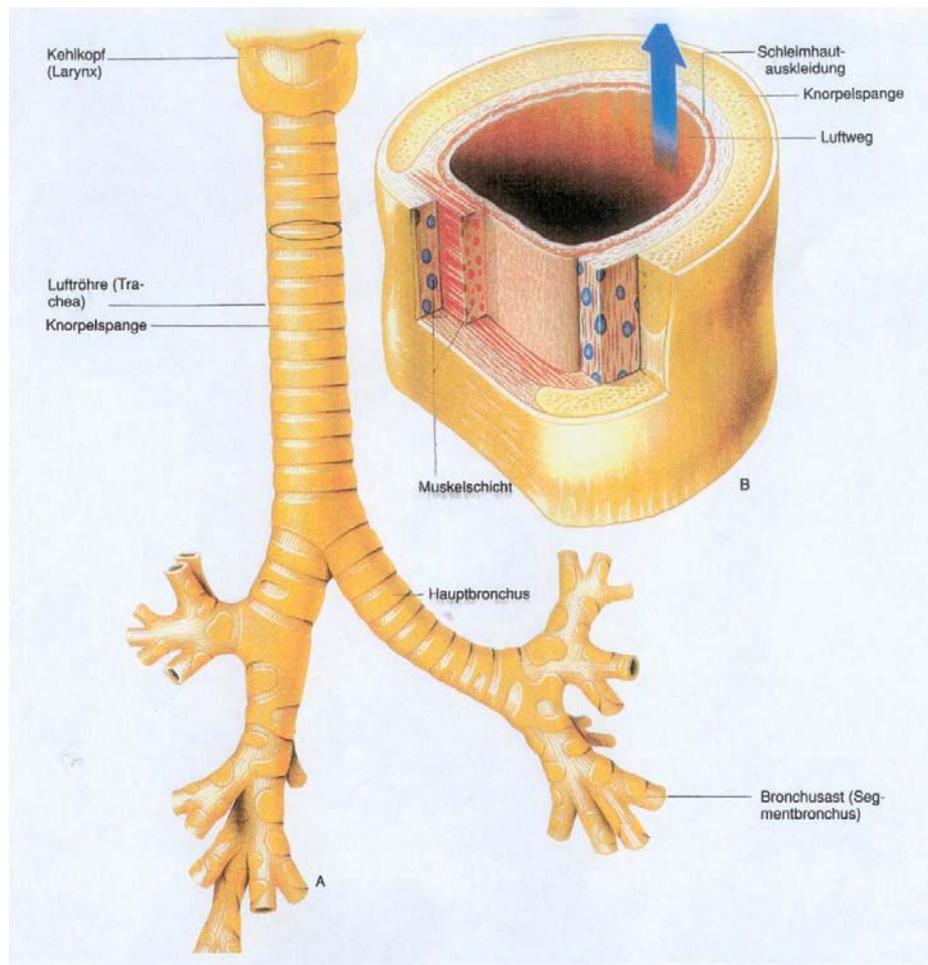
Diesel engines, emitting too many ultrafine solid particles, should be fitted with traps that can also intercept the ultrafine solid particles.

### **3. Figures: The diesel-soot particle trajectory into the lungs**

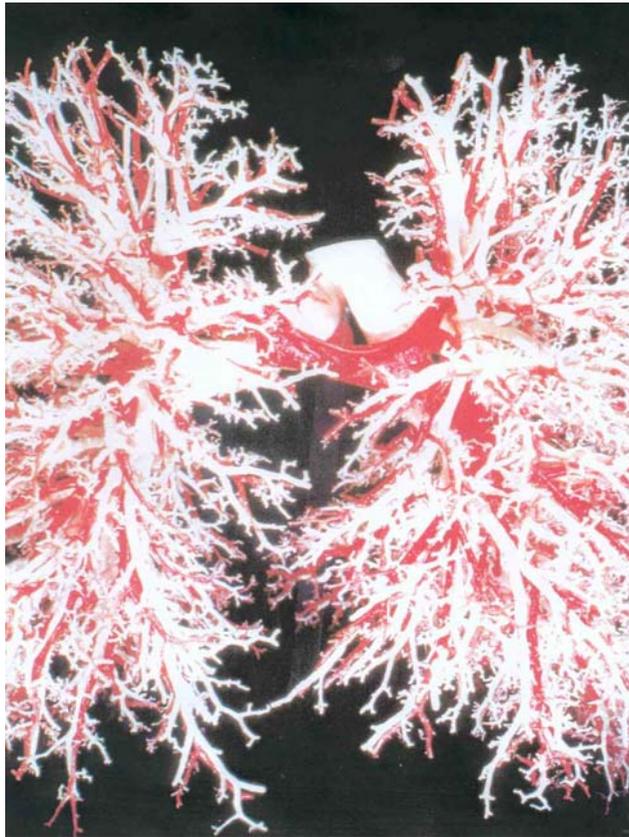
#### **General caption for all figures**

The diesel-soot particle trajectory into the lung

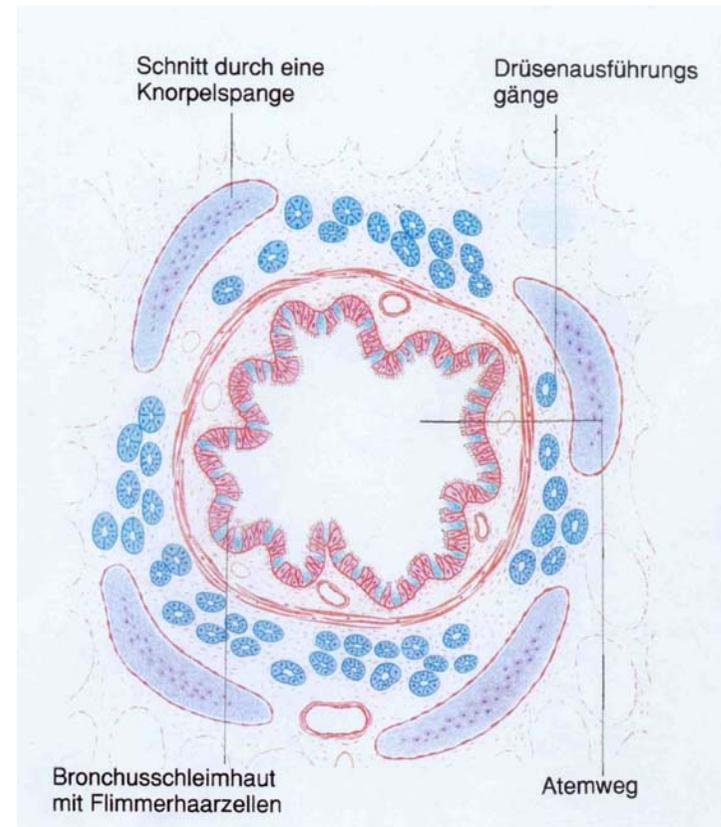
The diesel soot particles arrive, with the respiratory air, through nose or mouth. The flow passes the throat, the larynx and enters the trachea. At its lower end are the two main bronchia, which again branch into finer bronchiole. The repeated branching creates the bronchial tree structure.



The larynx, the trachea, the two main bronchia and the first bronchiole. The trachea and the upper bronchia have cartilaginous bands that assist in keeping the airways open.



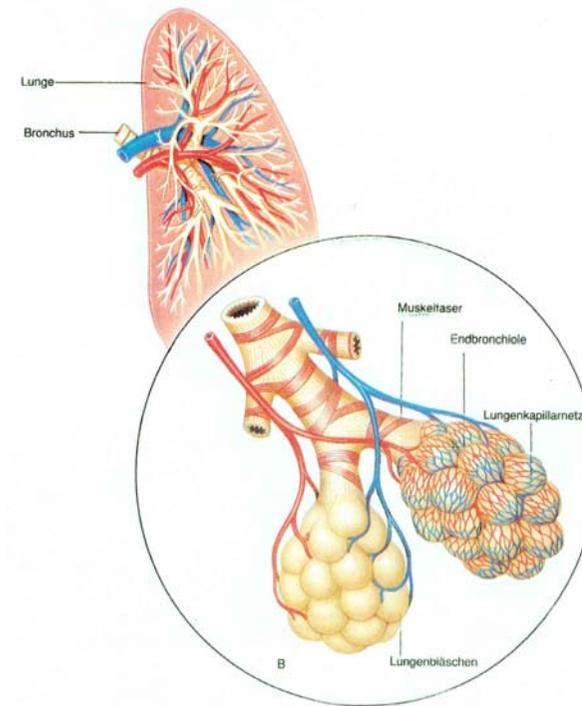
The lung tissue is exposed to reveal the tree-like structure of the airways (white) and the pulmonary blood vessels (red).



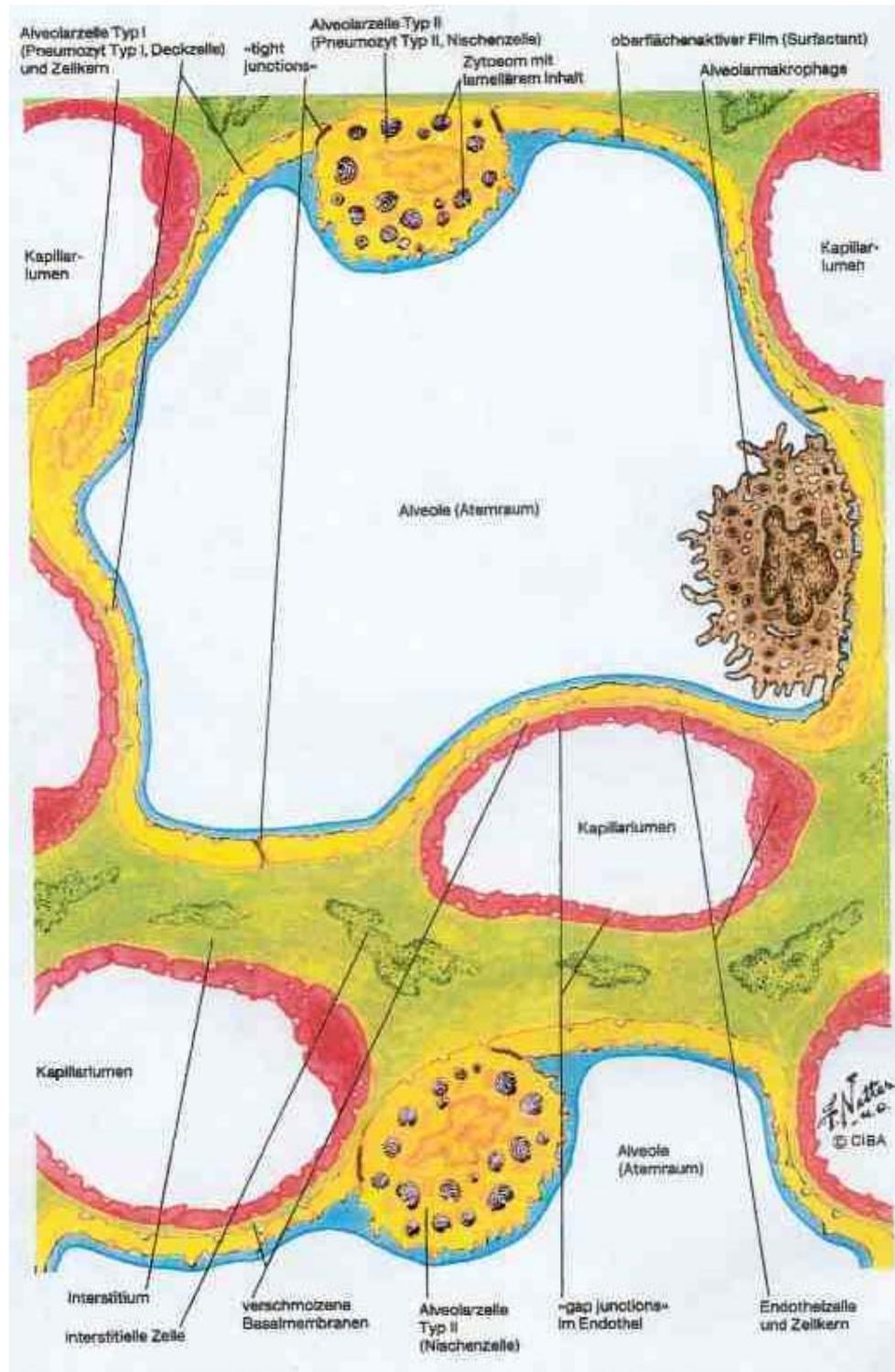
The inner surfaces of the bronchia are lined with a mucous membrane composed of ciliary and mucous secreting cells. These cells have an important role in clearing the respiratory path. Intruding particles, including diesel soot particles, are trapped in the sticky mucous film. The undulating cilia, function like a conveyor belt, and push the mucous-coated particles up into the throat.



Electron microscopy of the bronchial mucous membrane and its cilia. The cilia are destroyed in heavy smokers or chronic infections, and the mucous membrane partially depilated. Consequentially, the bronchial system can only intercept and expel intruding particles with difficulty, e.g. severe coughing.



The peripheral respiratory paths, the bronchioles, are very narrow. Each terminal bronchiole divides into a cluster of respiratory bronchioles from which the alveoli open. The alveolar cavity has a relatively large surface area. The outer alveolar surface is covered with capillaries, a net of very fine blood vessels. The alveolar wall is so thin that oxygen, from the respiratory air, rapidly diffuses into the blood. In the other direction, carbon dioxide diffuses from the blood into the alveolar cavity. Most diesel soot particles have a diameter 20 -200 nm. The inlets to the alveoli vary between 2 to 10  $\mu\text{m}$  during the respiratory cycle. Hence, the respiratory air can easily entrain the intruding particles into the alveoli.



A cross-section through the alveoli and its surrounding tissue, the interstitium and the capillaries. At the boundaries (so-called "tight junctions") of adjacent alveoli, the mobile leukocytes (white blood cells) specialized in alveolar scavenging migrate from the capillaries and interstitium into the alveoli. These "devouring" cells, one of which is illustrated, are named macrophages. The diesel exhaust ultrafine particles, too, can enter the "tight junctions". Subsequently, the particles invade the interstitium and are transported through the lymphatic to the lymph nodes.

#### 4. Cited publications

**Author(s)** Anderson PJ ; Wilson JD ; Hiller FC

**Address** Division of Pulmonary and Critical Care Medicine,  
University of Arkansas for Medical Sciences, Little Rock, USA

**Title** Respiratory tract deposition of ultrafine particles in subjects with obstructive or restrictive lung disease

**Published** Chest, 97(5):1115-20 1990 May

**Abstract** To evaluate the effects of lung disease on deposition of inhaled ultrafine particles (less than 0.1 micron diameter), we measured total respiratory tract deposition of non-hygroscopic particles of 0.02 to 0.24 micron in five subjects with obstructive lung disease and three subjects with restrictive lung disease and compared it with that in ten normal subjects. Deposition was measured as concentration difference of five size fractions in inhaled and exhaled air using an electrical aerosol analyzer. The data showed that deposition of these ultrafine particles was increased in subjects with obstructive lung disease when compared with normal subjects, while it was unchanged in subjects with restrictive lung disease. The increase in deposition in the subjects with obstructive lung disease was significant for particle sizes 0.04 to 0.24 micron. Possible mechanisms for increased deposition in airway obstruction include increased transit time of particles, abnormal expiratory collapse of airways due to flow limitation, and flow perturbations resulting from decreased airway caliber.

**Author(s)** Bhatia R ; Lopipero P ; Smith AH

**Address** Department of Medicine, University of California, San Francisco, USA

**Title** Diesel exhaust exposure and lung cancer

**Published** Epidemiology, 9(1):84-91 1998 Jan

**Abstract** We evaluated the relation between occupational exposure to diesel exhaust and cancer of the lung in a meta-analysis of 29 published cohort and case-control studies. Twenty-one of the 23 studies meeting the inclusion criteria had observed relative risk estimates greater than one. Pooled effect measures weighted by study precision indicated an increased relative risk (RR) for lung cancer from occupational exposure to diesel exhaust [RR = 1.33; 95% confidence interval (CI) = 1.24-1.44]. Subanalysis of case-control (RR = 1.33; 95% CI = 1.18-1.51) vs cohort studies (RR = 1.33; 95% CI = 1.21-1.47) and of studies that controlled for smoking (RR = 1.35; 95% CI = 1.20-1.52) vs those that did not (RR = 1.33; 95% CI = 1.20-1.47) produced results that did not differ from those of the overall analysis. On the other hand, cohort studies using internal comparisons (RR = 1.43; 95% CI = 1.29-1.58) showed higher relative risks than those using external comparisons (RR = 1.22; 95% CI = 1.04-1.44). Heterogeneity between studies was reduced when we stratified studies by the occupational setting in which exposure occurred. A positive duration-response relation was evident in those studies that were stratified by employment duration. This meta-analysis supports a causal association between increased risks for lung cancer and exposure to diesel exhaust.

**Author(s) Brändli O (1996)**

Address Zürcher Höhenklinik Wald, Faltigberg

Title Are inhaled dust particles harmful for our lungs?]

Published Schweiz Med Wochenschr, 126(50):2165-74 1996 Dec 14

Abstract Particles with diameters ranging from less than 0.02 to more than 100 microns and in concentration up to 120  $\mu\text{g}/\text{m}^3$  daily average TSP (total suspended particles) are measurable in the air of Swiss cities and responsible for the decrease of visibility on the Swiss Plateau and south of the Alps. The particle size shows a typical distribution: the coarse particles ( $> 2.5$  microns mass median diameter) are mostly of natural origin (plants, pollen, earth particles) and are deposited in the upper airways.

The fine particles ( $\text{PM}_{2.5} < 2.5$  microns) are predominantly deposited into the alveolar space. These fine and ultrafine particles ( $< 0.02$  microns) are produced by the burning of fossil fuels or by photochemical reactions. By bypassing the mucociliary and cellular defense mechanisms, fine particles can invade the lung parenchyma and cause an inflammatory response. The additional chemical layering of a carbon core by nitrates, sulfates and other organic materials and metals such as iron cause greater local oxidative and/or carcinogenic damage than in the vaporized state.

In comparing worldwide epidemiological studies, there seems to be a cohesive and consistent relationship between increases of particle concentration and the increase of mortality (mostly among patients over 65 with concomitant lung and heart diseases and among smokers) and morbidity (bronchitis, pneumonia, COPD, and, less convincingly, asthma). An increase in daily average  $\text{PM}_{10}$  (particles  $< 10$  microns) is correlated with an increase in mortality not related to accidents and suicides of 1.0% for the same and/or the following days. In Switzerland, mean annual concentrations of 14-53 micrograms/ $\text{m}^3$  TSP or 10-33  $\mu\text{g}/\text{m}^3$   $\text{PM}_{10}$ , well below the national standard (annual mean TSP 70  $\mu\text{g}/\text{m}^3$ ) have been measured in rural and urban areas. Even at these concentrations an increase in respiratory symptoms and a decrease in lung function, without evidence for a "safe" threshold, have been observed in the Swiss study of air pollution and lung diseases in adults (SAPALDIA). Although the noxious effects of the particles cannot be clearly separated from the effect of other pollutants (e.g.  $\text{NO}_x$ ,  $\text{SO}_2$ , ozone) in complex pollutant mixtures, the emission standards and national standards for ambient air should be revised, in particular by adding a standard for fine particles (e.g.  $\text{PM}_{10}$  or  $\text{PM}_{2.5}$ ).

**Author(s) Brüske-Hohlfeld I ; Möhner M ; Ahrens W ; Pohlabein H ; Heinrich J ; Kreuzer M ; Jöckel KH ; Wichmann HE**

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National Research Center for Environment and Health, Neuherberg.  
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Title Lung cancer risk in male workers occupationally exposed to diesel motor emissions in Germany

Published Am J Ind Med, 36(4):405-14 1999 Oct

Abstract **Background:** Although in several epidemiological studies exposure to diesel motor emissions (DME) shows an elevated lung cancer risk, it is still controversial whether DME is a human carcinogen.  
**Methods:** In a pooled analysis of two case-control studies on lung cancer in Germany a total of 3498 male cases with histologically or cytologically ascertained lung cancer and 3541 male population controls were included. Information about lifelong occupational

and smoking history was obtained by questionnaire. Drivers of lorries, buses, taxis, diesel locomotives and forklift trucks, bulldozers, graders, excavators, and tractors, were considered as exposed to DME and their cumulative exposure was estimated. All odds ratios were adjusted for smoking and asbestos exposure.

**Results:** The evaluation of lung cancer risk for all jobs with DME-exposure combined showed an odds ratio of OR=1.43 (95%-CI: 1.23-1.67). Most pronounced was the increase in lung cancer risk in heavy equipment operators (OR=2.31 95%-CI: 1.44-3.70). The risk of tractor drivers increased with length of employment and reached statistical significance for exposures longer than 30 years (OR=6.81, 95%-CI: 1.17-39.51). The group of professional drivers (e.g., trucks, buses, and taxis), showed an increased risk only in West Germany (OR=1.44, 95%-CI: 1.18-1.76), but not in East Germany (OR=0.83, 95%-CI: 0.60-1.14). DME-exposure in other traffic related jobs (e.g., diesel engine locomotive drivers, switchmen, forklift operators) was associated with an odds ratio of OR=1.53 (95%-CI: 1.04-2.24).

**Conclusions:** The study provides further evidence that occupational exposure to diesel motor emissions is associated with an increased lung cancer risk.

**Author(s)** Chambellan A ; Crestani B ; Soler P ; Moreau J ; Aubier M (2000)

Address Unité INSERM 408-CHU Bichat, Paris, France

Title Diesel particles and allergy: cellular mechanisms

Published Allerg Immunol (Paris), 32(2):43-8 2000 Feb

Abstract Urban air pollutants, particularly diesel exhaust particles are now known to contribute to the increased prevalence of asthma and allergic rhinitis. Diesel exhaust particles act as adjuvants in the immune response and may lead to the enhancement of allergic inflammation. This was first suggested by epidemiological studies and now largely confirmed by numerous experimental studies in animals and humans. We review the different mechanisms involved, including effects on cytokine and chemokine production, as well as activation of different immune cells. We also discuss the metabolic and cellular activation pathways used by polycyclic aromatic hydrocarbons, allergens and their interaction with diesel particles which act in synergy in this immune response toward IgE production and induction of allergic inflammation.

**Author(s)** Dasenbrock C ; Peters L ; Creutzenberg O ; Heinrich U (1996)

Address Fraunhofer Institute of Toxicology and Aerosol Research, Hannover, Germany

Title The carcinogenic potency of carbon particles with and without PAH after repeated intratracheal administration in the rat.

Published Toxicol Lett; VOL 88, ISS 1-3, 1996, P15-21

Abstract The role of carcinogenic PAH in soot- and carbon black-related lung tumor induction in rats was investigated after intratracheal administration of carbon blacks (CB) and two types of diesel soot (DS), either as original or as toluene extracted particles. The total particle dose per animal was 15 mg subdivided into 16-17 weekly applications. There was one vehicle control and two groups were treated with a total dose of either 30 or 15 mg pure BaP as positive control. The main tumor results were: (a) original DS induced a higher tumor rate than extracted DS; (b) the carcinogenic potency of extracted CB probably depends on the size of the primary carbon particles and on the specific surface area of the particles; (c) extracted DS covered with 11 micrograms BaP per mg carbon particles caused a lower lung tumor rate than original DS containing only 0.9 ng BaP per mg, but a variety of other PAH and NO<sub>2</sub>-PAH; (d) a total dose of 15 mg pure BaP caused a lung tumor rate very similar to that of 30 mg extracted DS, 15 mg original DS

or 15 mg Printex 90T CB extracted or covered with approximately 29.5 micrograms BaP per mg CB.

**Author(s) Donaldson Ken (1999)**

Address Biomedicine Research Group, Napier University, 10 Colinton Rd, Edinburgh and Respiratory Medicine Unit, Edinburgh Lung and the Environment Group Initiative, Colt Research Laboratories, Medical School, Teviot Place, Edinburgh, UK

Title The Role of Ultrafine Particles in the Toxic Effects of PM

Published <http://146.176.22.38/pm10/guest.htm#How>

Abstract No abstract. See synopsis at above internet site

**Author(s) Ferin J (1994)**

Address Department of Environmental Medicine, University of Rochester, School of Medicine and Dentistry, NY 14642, USA

Title Pulmonary retention and clearance of particles

Published Toxicol Lett; VOL 72, ISS 1-3, 1994, P121-5 (REF: 13)

Abstract Research in pulmonary retention and clearance of particles intensified in the fifties in connection with interests in pneumoconiosis and in inhalation of radioactive particles, and more recently with the increased interest in the effects of environmental particles. The studies enhanced our understanding of clearance mechanisms, the various clearance pathways, the different clearance capacities of various species and the importance of other factors affecting lung clearance. Based on research in recent years, the historical concept of inert and fibrogenic particles was abandoned. It seems that particles even at surprisingly low concentrations may have negative health effects and that ultrafine particles have higher than expected toxicity when compared to similar particles of a larger size.

**Author(s) Godleski JJ, Richard L Verrier, Petros Koutrakis, and Paul Catalano (2000)**

Address Harvard School of Public Health, Department of Environmental Health, Boston, Massachusetts 02115, USA

Title Mechanisms of Morbidity and Mortality from Exposure to Ambient Air Particles

Published HEI Research Report 91, February 2000

Abstract The studies reported here assessed pathophysiologic mechanisms that result from exposure to concentrated ambient particles (CAPs) in animals with and without cardiopulmonary compromise. These studies were carried out to determine the biologic plausibility of epidemiologic observations of increases in particulate air pollution associated with increases in human morbidity and mortality. Dogs were exposed two at a time to CAPs or filtered air via tracheostomy for six hours per day on three consecutive days. The electrocardiogram (ECG) and breathing pattern were recorded continuously, and indicators of inflammation were also assessed. In one experimental design, normal dogs were exposed in pairs to CAPs and subsequently to filtered air or to filtered air and subsequently CAPs (the double CAPs/double sham design). Comparisons were made between the CAPs measurements and each dog's own sham responses. In another design, one dog was exposed to CAPs while the chamber-mate received a sham exposure; these experiments were followed by crossover of the protocol the subsequent week (the crossover design). Comparisons were made between the CAPs

exposure and both the chamber-mate's sham and each dog's own sham responses. The crossover experiments were conducted in normal animals and in animals who had undergone balloon occlusion of the left anterior descending (LAD) coronary artery to induce myocardial compromise.

The effects of CAPs in animals with induced chronic bronchitis were part of the original specific aims; because these studies were not fully pursued, the results are presented only in Appendix A. In normal dogs, analyses of all double CAPs and crossover studies revealed low frequency (LF) and high frequency (HF) powers for heart rate variability (HRV) that were significantly higher for CAPs exposure compared to sham exposure. Variation in day-to-day exposure concentrations, aerosol composition, and pathophysiologic responses were also found.

The crossover design, continuous measures of aerosol mass, and biologic responses were incorporated in the development of a statistical model that allowed isolation of changes associated with CAPs from changes due to animal variations. Comparison of individual exposures with this model revealed a range from no response in any measured parameter to statistically significant changes in cardiac autonomic balance, pulmonary airflow, and breathing pattern. On days in which dogs showed statistically significant changes in responses, the findings were consistent in both cardiac and respiratory parameters. Days associated with significant increases in LF and HF HRV, LF/ HF HRV ratio, and heart rate standard deviation (HR SD) were also associated with decreases in average heart rate. These same days had decreases in respiratory frequency, tidal volume, minute volume, and peak flows with corresponding increases in respiratory cycle times and enhanced pause (Pauenh), a measure of broncho-constriction.

These cardiac and respiratory changes suggest an effect mediated via both the sympathetic nervous system and the vagus nerve. Alternatively, days associated with increased heart rate had decreases in the HR SD; decreases or no change in HF and LF HRV; increases in respiratory flows and volumes; and decreases in breathing cycle times, all suggesting only sympathetic nervous system mediation. When all data from the crossover design experiments were assessed with this model, the heart rate and respiratory rate were significantly decreased in relation to both cumulative and actual exposure and the LF HRV, LF/HF HRV ratio, HR SD, and all other respiratory parameters were significantly increased ( $p < 0.0001$  for all). When cardiac data were grouped by days in which the air mass trajectory came from the north or northwest (versus west, south, east, or northeast), significant increases in HR SD and HF HRV and significant decreases in average heart rate were associated with the northwest trajectory.

**Author(s)** Gradón L ; Orlicki D ; Podgórski A

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**Title** Deposition and retention of ultrafine aerosol particles in the human respiratory system. Normal and pathological cases

**Published** Int J Occup Saf Ergon, 6(2):189-207 2000

**Abstract** The particle number concentration in ambient air is dominated by nanometer-sized particles. Recent epidemiological studies report an association between the presence of nanoparticles in inhaled air at the workplace and acute morbidity and even mortality in the elderly. A theoretical model of deposition of 20 nm particles in the human alveolus was formulated. Gas flow structure and deposition rate were calculated for alveoli with different elastic properties of lung tissue. Data obtained in the paper show increased convective effects and diffusional rate of deposition of nanoparticles for alveoli with higher stiffness of the alveolar wall. The retention of deposited particles is also higher in

these pathological alveoli. Results of our calculations indicate a possibility of existence of a positive loop of coupling in deposition and retention of nanoparticles in the lung with pathological changes.

**Author(s) Gustavsson P ; Plato N ; Lidström EB ; Hogstedt C (1990)**

Address Department of Occupational Medicine, Karolinska Hospital, Stockholm, Sweden

Title Lung cancer and exposure to diesel exhaust among bus garage workers

Published Scand J Work Environ Health, 16(5):348-54 1990 Oct

Abstract Mortality and cancer incidence was investigated among the 695 bus garage workers employed as mechanics, servicemen, or hostlers for at least six months in five bus garages in Stockholm between 1945 and 1970. The exposure to diesel exhaust and asbestos was estimated by industrial hygienists. A small excess of lung cancer mortality was found in the cohort when occupationally active men in Stockholm were used as the reference group. A case-referent study was performed within the cohort, six referents being selected for each of the 20 lung cancer cases. The lung cancer risk increased with increasing cumulative exposure to diesel exhaust, but not with cumulative asbestos exposure. The relative risk for lung cancer among the highly exposed men was 2.4 (95% CI 1.3-4.5) as compared with those with low exposure. The study indicates that exposure to diesel exhaust increases the risk for lung cancer.

**Author(s) Heinrich U ; Peters L ; Funcke W ; Pott F ; Mohr U ; Stöber W (1982)**

Address Fraunhofer Institute for Toxicology and Aerosol Research, Hannover, Germany

Title Investigation of toxic and carcinogenic effects of diesel exhaust in long-term inhalation exposure of rodents

Published Dev Toxicol Environ Sci; VOL 10, 1982, P225-42

Abstract Syrian golden hamsters (480 males and 480 females) allocated into 24 groups were exposed 19 hours per day and 5 days per week for 6, 10.5, 15, or 18 months to total diesel exhaust, diesel exhaust without particles, a mixture of nitrogen dioxide (5 parts per million [ppm]<sup>2</sup>) and sulfur dioxide (10 ppm), or clean air. Two exposure groups from each test atmosphere were also treated by a single subcutaneous injection of either 3 mg or 6 mg of diethylnitrosamine/kg of body weight to evaluate an enhancing effect of diethylnitrosamine on exposure-related changes. Morphological evaluation was done by histopathology. Minor changes of the larynx and trachea were investigated by scanning electron microscopy, which showed a loss of ciliated cells in all exhaust-exposed groups. After exposure to diesel exhaust with or without particles, focal metaplasia and dysplasia of the respiratory epithelium were seen in the oldest animals by scanning electron microscopy. In the same specimens, attached mucous droplets indicated changes in mucous cells and mucous viscosity. Only the exposure to total diesel exhaust significantly increased the tumor rate in the upper respiratory tract of male hamsters treated with 6 mg of diethylnitrosamine per kg of body weight. At the lower diethylnitrosamine dose, no exposure-related effects on the tumor rates could be observed. The results from this study and from our other inhalation experiments appear to be insufficiently conclusive to demonstrate that diesel-engine exhaust should be classified as a cocarcinogen or enhancer for the test system used.

**Author(s)** Heinrich U ; Muhle H ; Hoymann HG ; Mermelstein R (1989)

Address Fraunhofer Institute of Toxicology and Aerosol Research, Hannover

Title Pulmonary function changes in rats after chronic and subchronic inhalation exposure to various particulate matter

Published Exp Pathol; VOL 37, ISS 1-4, 1989

Abstract

**Author(s)** Heiskel H ; Seidler A ; Bickeböller R ; Elsner G

Address Institut für Arbeitsmedizin, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany

Title Association between diesel exposure at work and prostate cancer

Published Soz Präventivmed, 43(6):282-92 1998

Abstract In a case-control study 192 patients with histologically confirmed prostate cancer were compared with 210 men in whom carcinoma of the prostate had been histologically excluded. Cases and controls were recruited from two urological practices in Hamburg and Frankfurt/M. and from the urologic polyclinic at the University of Frankfurt/M. The probands were questioned about smoking habits and alcohol consumption, about all occupational activities of least one years' duration, and about exposure to specific substances. Odds ratios (OR) were calculated using logistic regression analysis, adjusting for age, region and smoking. There were no differences between patients and controls in self-reported occupational exposures or the consumption of alcohol or smoking. There was a positive association between having worked in transportation/communication and having prostate cancer (p for trend = 0.006): ORs varied according to the number of years worked as follows: 1-10 years versus never, OR = 0.6 (95% CI: 0.3-1.2), 11-30 years, OR = 2.0 (95% CI: 0.8-4.8), > 30 years OR = 3.2 (95% CI: 1.3-7.5). Work in other occupational groups was not associated with an increased risk for prostate cancer. These results suggest that transport work may be associated with the development of prostate cancer.

**Author(s)** Knox RB, Suphioglu C, Taylor P, Desai R, Watson HC, Peng JL, Bursill LA (1997)

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Title Major grass pollen Lolpl binds to DEP's: Implications for asthma and air pollution

Published Clin Exp Allergy 1997; 27: 246-51

Abstract **Background:** Grass pollen allergens are known to be present in the atmosphere in a range of particle sizes from whole pollen grains (approx. 20 to 55 microns in diameter) to smaller size fractions < 2.5 microns (fine particles, PM<sub>2.5</sub>). These latter particles are within the respirable range and include allergen-containing starch granules released from within the grains into the atmosphere when grass pollen ruptures in rainfall and are associated with epidemics of thunderstorm asthma during the grass pollen season. The question arises whether grass pollen allergens can interact with other sources of fine particles, particularly those present during episodes of air pollution.  
**Objective:** We propose the hypothesis that free grass pollen allergen molecules, derived from dead or burst grains and dispersed in microdroplets of water in aerosols, can bind to fine particles in polluted air.

**Methods:** We used diesel exhaust carbon particles (DECP) derived from the exhaust of a stationary diesel engine, natural highly purified Lol p 1, immunogold labelling with specific monoclonal antibodies and a high voltage transmission electron-microscopic imaging technique.

**Results:** DECP are visualized as small carbon spheres, each 30-60 nm in diameter, forming fractal aggregates about 1-2 microns in diameter. Here we test our hypothesis and show by in vitro experiments that the major grass pollen allergen, Lol p 1, binds to one defined class of fine particles, DECP.

**Conclusion:** DECP are in the respirable size range, can bind to the major grass pollen allergen Lol p 1 under in vitro conditions and represent a possible mechanism by which allergens can become concentrated in polluted air and thus trigger attacks of asthma.

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**Title** Diesel exhaust particulates induce nasal mucosal hyper-responsiveness to inhaled histamine aerosol

**Published** Fund Appl Toxicol 1995; 27: 195-202

**Abstract** The prevalence of allergic rhinitis is increasing in many countries. It has been reported that the prevalence rate of allergic rhinitis caused by pollens in air-polluted areas are higher than in nonpolluted areas. Therefore, it is important to determine whether air pollutants are related to the increase in the prevalence rate of allergic rhinitis. In this respect, it is necessary to elucidate whether exposure to air pollutants affects the nasal mucosa and causes nasal mucosal hyper-responsiveness to chemical mediators released by antigen-antibody reactions.

In the present study using guinea pigs, we investigated effects of diesel exhaust particulates on (1) nasal airway resistance, (2) increases in nasal airway resistance and secretion induced by histamine aerosol, and (3) vascular permeability and the increase in vascular permeability is an important factor involved in increased nasal airway resistance and secretion. Intranasal pressure and nasal secretion from the nostril were measured as markers of nasal airway resistance and exocrine activity of the nasal mucosa, respectively. A 30-min administration of a suspension of diesel exhaust particulates into the nasal cavities caused a significant increase in intranasal pressure. The administration also augmented an increase in intranasal pressure and nasal secretion induced by histamine aerosol. In dorsal skin, diesel exhaust particulates increased vascular permeability. Diesel exhaust particulates also augmented vascular permeability are potent by histamine. These properties of diesel exhaust particulates are likely derived in part from the augmentation vascular permeability by these particulates.

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**Title** Pulmonary macrophages: Phenomena associated with the particle 'overload' condition

**Published** Govt Reports Announcements & Index (GRA&I), Issue 01, 1994

**Abstract** Numerous lines of evidence support the generalization that alveolar macrophage (AM)-mediated particle clearance, or the transport of particle-containing AM from the alveoli out of the lung via the mucociliary apparatus, is a prominent mechanism that determines the pulmonary retention characteristics of relatively insoluble particles. Studies have also shown that the alveolar deposition of excessive burdens of particles with even low intrinsic cytotoxicity can result in impairments of the AM-mediated particle clearance

mechanism and the development of pathologic disorders including pulmonary fibrosis and lung cancer, at least in the lungs of rats.

We briefly review evidence consistent with the idea that the high volumetric loads of particles contained in AM during particle overload conditions underlies their inability to translocate from the lung. Using a condition of particle overload brought about by subchronic exposure of rats to ultra-fine titanium dioxide as an experimental model, we have obtained ultrastructural and other evidence that indicates an association between particle overload and: The occurrence of aggregates of particle-containing AM in alveoli, Type II cell hyperplasia in alveoli that contain the AM aggregates, a loss in patent pores of Kohn in alveoli that contain the AM aggregates and show Type II cell hyperplasia, the interstitialization of particles at the sites where these phenomena collectively occur, and the development of fibrosis in alveolar regions where particle interstitialization occurs. The loss of pores of Kohn in the alveoli that contain aggregates of particle-laden AM suggests that these interalveolar pores normally serve as passageways through which AM may migrate to neighboring alveoli as they perform their function of phagocytizing particles that have deposited on the alveolar surface. The pores of Kohn also serve as short-cut pathways for AM to reach the mucociliary apparatus from more distal alveoli. International inhalation symposium on toxic and carcinogenic effects

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**Title** Occupational exposure to diesel exhaust and lung cancer: a meta-analysis

**Published** Am J Public Health, 89(7):1009-17 1999 Jul

**Abstract** **Objectives:** We undertook a meta-analysis of epidemiological studies investigating the relationship between occupational diesel exhaust exposure and lung cancer.  
**Methods:** Thirty of 47 studies initially identified as potentially relevant met specified inclusion criteria. We extracted or calculated 39 independent estimates of relative risk and derived pooled estimates of risk for all studies and for numerous study subsets by using a random-effects model. We also examined interstudy heterogeneity by using linear meta-regressions.  
**Results:** There was substantial heterogeneity in the pooled risk estimates for all studies combined and for most subsets. Several consistent with higher study quality, however, contributed to increased pooled estimates of risk and lower heterogeneity, including (1) adjustment for confounding by cigarette smoking and other covariates, (2) having a lower likelihood of selection bias, and (3) having increased study power.  
**Conclusion:** This analysis provides quantitative support for prior qualitative reviews that have ascribed an etiologic role to occupational diesel exhaust exposure in lung cancer induction. Among study populations most likely to have had substantial exposure to diesel exhaust, the pooled smoking-adjusted relative risk was 1.47 (95% confidence interval = 1.29, 1.67).

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Title How can ultrafine particles be responsible for increased mortality?

Published Monaldi Arch Chest Dis, 55(2):135-9 2000 Apr

Abstract The link between particulate air pollution at relatively low levels and adverse effects both in the lungs and of the cardiovascular system remains a puzzling event. The Author(s) have developed a hypothesis which suggests that ultrafine components of particulate air pollution may result in local and systemic oxidative stress, which produces lung inflammation, but also the systemic effects, resulting in mortality in susceptible individuals from cerebrovascular disease. Preliminary data in vitro and in vivo suggest that both local and systemic oxidative stress occur in response to ultrafine particles and that the effects of such oxidative stress on pro-inflammatory gene regulation and changes in blood coagulation may result in the adverse effects of particulate air pollution.

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Title Association of particulate air pollution and acute mortality: involvement of ultrafine particles

Published Inhal Toxicol 1995; 7: 111-24

Abstract

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Title Role of the alveolar macrophage in lung injury: studies with ultrafine particles.

Published Environ Health Perspect; VOL 97, 1992, P193-9

Abstract We conducted a series of experiments with ultrafine particles (approximately 20 nm) and larger particles (less than 200 nm) of "nuisance dusts to evaluate the involvement of alveolar macrophages (AM) in particle-induced lung injury and particle translocation in rats. After intratracheal instillation of both ultrafine particles and larger particles of TiO<sub>2</sub>, we found a highly increased interstitial access of the ultrafine particles combined with a large acute inflammatory reaction as determined by lung lavage parameters. An additional experiment revealed that intratracheal instillation of phagocytized ultrafine TiO<sub>2</sub> particles (inside AM) prevented both the pulmonary inflammatory reaction and the interstitial access of the ultrafine particles. Another experiment showed that the influx of polymorphonuclear cells (PMN) into the alveolar space unexpectedly decreased with higher doses of ultrafine particles, whereas alveolar epithelial permeability (protein leakage) increased.

The divergence between PMN influx into the alveolar space and changes in alveolar epithelial permeability implies that they are separate events. Pulmonary inflammatory parameters determined by lung lavage analysis correlated best with the surface area of the retained particles rather than with their mass, volume, or numbers. Because higher doses resulted in an increased interstitialized fraction of particles, we suggest that

inflammatory events induced by particles in the interstitial space can modify the inflammation in the alveolar space detectable by lung lavage. Our results demonstrate the dual role of AM for modifying particle-induced lung injury, i.e., both preventing such injury and contributing to it. We conclude that the increased pulmonary toxicity of ultrafine particles is related to their larger surface area and to their increased interstitial access.

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**Title** Respiratory effects are associated with the number of ultrafine particles  
**Published** Am J Respir Crit Care Med, 155(4):1376-83 1997 Apr  
**Abstract** 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 micron 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 micron in diameter), whereas most of the mass (82%) was attributable to particles in the size range of 0.1 to 0.5 micron. 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 micron (PM<sub>10</sub>). Therefore, the present study suggests that the size distribution of ambient particles helps to elucidate the properties of ambient aerosols responsible for health effects.

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**Title** Diesel exhaust and lung cancer mortality in potash mining  
**Published** Am J Ind Med, 36(4):415-22 1999 Oct  
**Abstract** **Background:** Findings from experimental studies on rodents and from epidemiological studies suggest that diesel exhaust may cause lung cancer. There is evidence that in several occupations, e.g., truck drivers and railway workers, the risk of lung cancer increases with duration of employment, and exposure to diesel exhaust provides the most likely explanation for these elevations of risk.  
**Methods:** We investigated the association between lung cancer mortality and exposure to diesel exhaust in a cohort study. The cohort comprised 5, 536 male potash miners who were followed from 1970 to 1994. Exposure was assessed from concentration measurements of the total carbon (i. e., elemental and organic carbon in total) in personal dust samples. The concentration values were multiplied by years of exposure to give a quantitative exposure measure. The concentration levels ranged from 0.12 to 0.39 mg/m<sup>3</sup> total carbon in fine dust. Work histories and smoking habit data were obtained from medical company records. Causes of death were ascertained from death certificates.  
**Results:** During the follow-up period, 424 deaths were recorded, including 133 of cancer, 38 of lung cancer. The relative risk of lung cancer between two groups with high and low exposure was 2.2 (95% confidence interval 0.8-6.0). With Cox regression, we

found a lung cancer relative risk 1.7 (0.5-5.8) after twenty years of exposure. Extensive scrutiny proved smoking not to be a confounder in this study.

**Conclusions:** The principal finding of the study is a doubling of relative lung cancer risk after twenty years of exposure in the workplaces with highest exposure. However, the observed elevation is nonsignificant even at a 90% level. Further follow-up is intended to enhance the study power.

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**Title** Predicted lung cancer risk among miners exposed to diesel exhaust particles

**Published** Am J Ind Med, 34(3):207-19 1998 Sep

**Abstract** Several quantitative risk assessment models have been published for occupational and environmental exposures to diesel exhaust particles (DEP). These risk assessment models are reviewed and applied to predict lung cancer for miners exposed to DEP. The toxicologically based unit risk estimates varied widely (from 2 to 220 x 10<sup>-6</sup> per micrograms/m<sup>3</sup>). The epidemiologically based unit risk estimates were less variable and suggest higher risks (from 100 to 920 x 10<sup>-6</sup> per micrograms/m<sup>3</sup>). The wide range of risk estimates derived from these analyses reflects the strong assumptions and large uncertainties underlying these models. All of the models suggest relatively high risks (i.e., > 1/1,000) for miners with long-term exposures greater than 1,000 micrograms/m<sup>3</sup>. This is not surprising, given the fact that miners may be exposed to DEP concentrations similar to those that induced lung cancer in rats and mice, and substantially higher than the exposure concentrations in the positive epidemiologic studies.

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**Title** Pulmonary function in workers exposed to diesel exhausts: The effect of control measures

**Published** American Journal of Industrial Medicine March 1991, Vol.19, No.3, p.283-289.

**Abstract** To assess the protective effect of exhaust pipe filters or respirators on pulmonary function, 15 workers in a tunnel construction site were studied. The total and respirable dust, combustible matter in respirable dust, carbon monoxide, nitrogen monoxide and nitrogen dioxide were measured for each subject during entire work shifts. The effect of the exposure on the lung function variables was measured by dynamic spirometry, carbon monoxide single breath technique, and nitrogen single breath washout. The exhaust pipe filtering had a protective effect, directly discernible in the drivers on vital capacity and FEV<sub>1</sub> and for the whole group on FEV<sub>1</sub>% and transfer factor. The dust respirators had no effect, probably because of the difficulties in correctly using personal protection under the circumstances in the tunnel. In the absence of a true exposure assessment, control measures for diesel exhaust can be tested by medical effect studies. Catalytic particle filters of diesel exhausts are one method of rendering the emissions less irritant, although they will not remove irritant gases. An indicator of diesel exhaust exposure should include the particle fraction of the diesel exhausts, but a discrimination between different sources of organic dust must be possible.

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**Title** Increased risk of obstructive pulmonary disease in tunnel workers  
**Published** Thorax, 55(4):277-82 2000 Apr  
**Abstract** **Background:** Tunnel workers are exposed to gases and particles from blasting and diesel exhausts. The aim of this study was to assess the occurrence of respiratory symptoms and airflow limitation in tunnel workers and to relate these findings to years of exposure.  
**Methods:** Two hundred and twelve tunnel workers and a reference group of 205 other heavy construction workers participated in a cross sectional investigation. Exposure measurements were carried out to demonstrate the difference in exposure between the two occupational groups. Spirometric tests and a questionnaire on respiratory symptoms and smoking habits were applied. Atopy was determined by a multiple radioallergosorbent test (RAST). Radiological signs of silicosis were evaluated. Respiratory symptoms and lung function were studied in relation to years of exposure and adjusted for smoking habits and atopy.  
**Results:** Compared with the reference subjects, the tunnel workers had a significant decrease in forced vital capacity (FVC) % predicted and forced expiratory volume in one second (FEV(1)) % predicted when related to years of exposure. Adjusted FEV(1) decreased by 17 ml for each year of tunnel work exposure compared with 0.5 ml in outdoor heavy construction workers. The tunnel workers also reported significantly higher occurrence of respiratory symptoms. The prevalence of chronic obstructive pulmonary disease (COPD) was 14% in the tunnel workers compared with 8% in the reference subjects.  
**Conclusion:** Exposure to dust and gases from diesel exhaust, blasting, drilling and rock transport in tunnel work enhances the risk for accelerated decline in FEV(1), respiratory symptoms, and COPD in tunnel workers compared with other heavy construction workers.