Berufsgenossenschaftliches
Institut für Arbeitsschutz – BIA

BIA-Report 7/2003e

BIA-Workshop "Ultrafine aerosols at workplaces"

Held on 21 and 22 August 2002
at the BG Institute for Occupational Safety and Health – BIA, Sankt Augustin, Germany

HVBG
Hauptverband der gewerblichen Berufsgenossenschaften

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Sankt Augustin

Published by: Hauptverband der gewerblichen Berufsgenossenschaften (HVBG)
Berufsgenossenschaftliches Institut für Arbeitsschutz – BIA
Alte Heerstr. 111, D-53754 Sankt Augustin
Telefon: +49 / 02241 / 231 – 01
Telefax: +49 / 02241 / 231 – 1333
Internet: www.hvbg.de
– October 2004 –

ISBN: 3-88383-676-1

ISSN: 0173-0387

BIA-Workshop „Ultrafine aerosols at the workplace“

Abstract

Ultrafine aerosols are aerosols made up of particles smaller than 100 nm. In comparison with their source materials, such nanoparticles have different optical, electrical, mechanical, and chemical properties. This is often quite useful in nanotechnology for creating nanostructured materials and even components and functional units. Ultrafine particles are not only unique to this field of hi-tech; they are present in our everyday lives and at various conventional workplaces. Experiments on animals in particular have indicated that the inhalation of poorly soluble ultrafine material particles can cause inflammatory reactions in the lungs and even lung tumours. Although there are hypotheses on the mechanics of ultrafine particles, no clear findings are as yet available. In August 2002, experts from Germany, Finland, Austria, Switzerland, and the USA presented their research results and findings on the topic of ultrafine particles at an interdisciplinary workshop held by the Berufsgenossenschaftliches Institut für Arbeitsschutz – BIA (BG-Institute for occupational safety and health). The following topics were handled at the workshop: medical aspects, toxicology of ultrafine particles/epidemiology, physics of ultrafine particles/measurement technology, ultrafine aerosols at industrial workplaces, and discussions on whether exposure limit values should be introduced. This report relates the presentations and excerpts of the results of the discussion on each topic.

BIA-Workshop „Ultrafeine Aerosole an Arbeitsplätzen“

Kurzfassung

Ultrafeine Aerosole sind Aerosole, deren Teilchen kleiner als 100 nm sind. Im Vergleich zum Material, aus dem sie entstanden sind, haben solche Nanopartikeln veränderte optische, elektrische, mechanische und chemische Eigenschaften. Dies macht man sich in der Nanotechnologie zunutze, um nanostrukturierte Materialien und sogar Bauelemente und Funktionseinheiten zu erzeugen. Ultrafeine Partikeln kommen aber nicht nur in diesem Hochtechnologiebereich vor, vielmehr sind sie auch im Alltagsleben und an verschiedenen konventionellen Arbeitsplätzen vorhanden. Insbesondere tierexperimentelle Studien weisen darauf hin, dass die Inhalation schwer löslicher ultrafeiner Partikeln aus Materialien Entzündungsreaktionen der Lunge und Lungentumoren hervorrufen kann. Über die Wirkungsmechanismen ultrafeiner Partikeln gibt es zwar Hypothesen, gesicherte Erkenntnisse liegen bis jetzt jedoch nicht vor. In einem vom Berufsgenossenschaftlichen Institut für Arbeitsschutz – BIA im August 2002 veranstalteten interdisziplinären Workshop stellten Fachleute aus Deutschland, Finnland, Österreich, der Schweiz und den USA Forschungsergebnisse und Erkenntnisse zum Thema ultrafeine Teilchen vor. In dem Workshop wurden folgende Themenkomplexe behandelt: Medizinische Aspekte, Toxikologie ultrafeiner Partikeln/Epidemiologie, Physik ultrafeiner Partikeln/Messtechnik, ultrafeine Aerosole an industriellen Arbeitsplätzen und Überlegungen zur Einführung von Expositions-grenzwerten. Die Beiträge sowie die auszugsweisen Ergebnisse der Diskussionen zu jedem Themenkomplex sind in diesem Report wiedergegeben.

Atelier BIA « Aérosols de particules ultrafines au poste de travail »

Résumé

Un aérosol est défini comme „ultrafin" lorsque les particules le constituant sont de taille inférieure à 100 nm (nanoparticules). Les nanoparticules ont des propriétés optiques, électriques, mécaniques et chimiques différentes de celles du matériau dont elles proviennent. Les nanotechnologies mettent ces différences à profit pour produire des matériaux et même des composants et des unités fonctionnelles à base de nanostructures. Toutefois, les particules ultrafines se rencontrent non seulement dans ce secteur technique de pointe mais davantage encore dans la vie quotidienne et à divers postes de travail traditionnels. Il faut noter en particulier que les études sur l'animal indiquent la possibilité de réactions d'irritation et d'action tumorigène au niveau du poumon en cas d'inhalation de particules ultrafines peu solubles. Sur les mécanismes d'action de ces particules, nous avons des hypothèses mais pas encore de connaissances validées. En août 2002, dans le cadre d'un atelier interdisciplinaire organisé par le Berufsgenossenschaftliches Institut für Arbeitsschutz – BIA (l'Institut pour la sécurité et la santé au travail des BGs), des experts venus d'Allemagne, de Finlande, d'Autriche, de Suisse et des Etats-Unis ont présenté les résultats de recherche et l'état de la connaissance dans le domaine des particules ultrafines. Cet atelier a abordé les grands thèmes suivants : aspects médicaux, toxicologie des particules ultrafines/épidémiologie, physique des particules ultrafines/métrologie, aérosols de particules ultrafines aux postes de travail de l'industrie, considérations sur l'introduction de valeurs limites d'exposition. Dans ce rapport sont présentées les communications des participants, ainsi que des extraits des discussions auxquelles ces différents thèmes ont donné lieu.

Seminario BIA „Aerosoles ultra finos en lugares de trabajo“

Resumen

Aerosoles con partículas de un tamaño inferior a 100 nm vienen definidos como aerosoles ultra finos. Estas nanopartículas disponen de propiedades ópticas, eléctricas, mecánicas y químicas modificadas, comparadas con el material del cual se originan. La nanotecnología saca provecho de ello para fabricar materiales nanoestructurados e incluso elementos constructivos y unidades funcionales. Pero, partículas ultra finas no existen solamente en semejantes ámbitos de la alta tecnología, ellas están presentes también en la vida cotidiana y en diferentes lugares de trabajo convencionales. Estudios experimentales con animales indican que la inhalación de partículas ultra finas difícilmente solubles puede provocar inflamaciones pulmonares y tumores de pulmón. Actualmente, todavía no se dispone de conocimientos asegurados sobre los mecanismos de acción de partículas ultra finas, solamente existen algunas hipótesis. En un seminario interdisciplinario, organizado por el Instituto para la Seguridad Laboral de los BGs (BIA, en sus siglas alemanas), en agosto de 2002, expertos procedentes de Alemania, Finlandia, Austria, Suiza y los EEUU expusieron resultados de estudios y conocimientos relativos al ámbito de las partículas ultra finas. En el seminario se abordaron las siguientes temáticas: aspectos sanitarios, toxicología de las partículas ultra finas / epidemiología, física de las partículas ultra finas / métodos de medición, aerosoles ultra finos en lugares de trabajo industriales, así como discusiones relativas a la introducción de valores límite de exposición. El presente Report recopila las ponencias y presenta, a manera de resumen, los resultados de los debates relativos a cada área temática.

Contents

Foreword

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Studies based on animal experiments in particular have found that inhaling poorly soluble ultrafine particles of several hundred nanometres in size can cause inflammation reactions in and tumours of the lungs. Although there are hypotheses on the effect mechanisms in ultrafine particles, knowledge on the topic is as yet inconclusive. Because little is known on this topic, a number of questions remains unanswered:

- What measurement data should be gathered at the workplace?
- Which has the greatest effects? Particle concentration, surface concentration, or – less likely – the "mass concentration"?
- What particle size should define the starting limit for measurement? 10 nm, 3 nm, or even less than 1 nm?
- How should aggregates, agglomerations, and the primary particles they are comprised of be dealt with?
- Beyond this, there are more questions about the chemical composition and solubility of the particles.

For assessing workplaces, having this information on the ultrafine aerosols present at workplaces would be quite welcome. The efforts involved in answering all the open questions can be made neither right now nor in the future. Thus, there will continue to be a great need for research in the field of ultrafine aerosols at workplaces.

It was the aim of the BIA workshop “Ultrafine aerosols at workplaces” held in August of 2002 to bring together the different scientific disciplines needed to discuss the diverse questions, to provide approaches for solutions, to discuss conventions, and to formulate open questions. This report serves to document the current state of the knowledge and to provide suggestions for future development.

Introduction

G. Riediger,
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Ultrafine aerosols are aerosols with particles < 100 nm. In comparison to the materials they are generated from, such nanoparticles have different optical, electrical, mechanical, and chemical properties. These differences are used in the field of nanotechnology to produce nanostructured materials and even components and functional units. Yet this does not mean that ultrafine particles only occur in this high technology field; even more, they are present in everyday life and at different conventional workplaces, e. g. in diesel engine emissions, in welding and soldering fumes, in material processing using lasers, in foundries and metal plants, in flame cutting, in plastic injection moulding, and even in grinding and polishing, just to name but a handful of their potential sources.

Studies based on animal experiments in particular indicate that inhaling poorly soluble ultrafine particles from materials whose particles appear otherwise inert, if inhaled in sizes of several 100 nm, can cause inflammation reactions in and tumours of the lungs. Although there are hypotheses on the mechanism behind ultrafine particles, knowledge is as yet inconclusive.

In a workshop held by the Berufsgenossenschaftliches Institut für Arbeitsschutz – BIA (BG Institute for occupational safety and health) from 21 to 22 August 2002, more than 30 experts – physicians, toxicologists, epidemiologists, physicists, and experts in occupational safety and health – from Germany, Finland, Austria, Switzerland, and the USA were invited to present the results of their research and other findings on the topic of ultrafine particles. The initial impetus for holding such a workshop can be traced to the international ISSA colloquium "Dust, smoke, and mist at the workplace: risks and prevention" at Toulouse from 11 to 13 June 2001, where one morning was dedicated to the topic "Ultrafine particles and specific dusts". Discussions around this colloquium

indicated an interest in an additional event to provide the opportunity for an open interdisciplinary exchange of opinion.

The presentations are compiled in this report. With a few exceptions, these are the presentations as they were recorded during the event and edited by the authors for publication. A discussion period was provided for each block of topics, and excerpts of the results are printed here.

Deposition, retention, and clearance of ultrafine particles [1]

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The term ultrafine particles is used to refer to particles < 100 nm in size. They originate mostly from the combustion processes and from photochemical reactions with heterogeneous and homogenous nucleation. Ultrafine aerosols make up a dynamic system that change over time. The particles grow through coagulation and condensation, and they can be reduced by evaporation such that both their concentration and their size distribution constantly change depending on the thermodynamic conditions.

As a rule, ultrafine particles are non-homogeneous formations. They are mostly composed of metals and carbonaceous inorganic and organic compounds. They generally have a shell that is created and modified by condensation and evaporation during thermal processes.

Their structures can often be complex: right after combustion, there are fragile aggregates (Figure 1, see page 16) that change over time (aging). Ultrafine aerosols are polydisperse.

Figure 2 (see page 16) shows the comparison of $PM_{2.5}$ (this is the particlulate matter comprising particles with an aerodynamic diameter of < 2.5 μm) on the left side and $PM_{0.1}$ on the right side, depending on the different sources (Airborne Particles Expert Group in the UK, 1999). As shown road traffic plays the dominant role in the mass of the ultrafine particles.

Figure 3 (see page 17) shows a size comparison between a 20 nm particle (top left), a 500 nm particle, a particle of 2.5 μm in size, and an alveolar macrophage.

[1] Produced on the basis of the oral presentation; reviewed and authorized by the author.

Figure 1:
Creation and properties of ultrafine particles

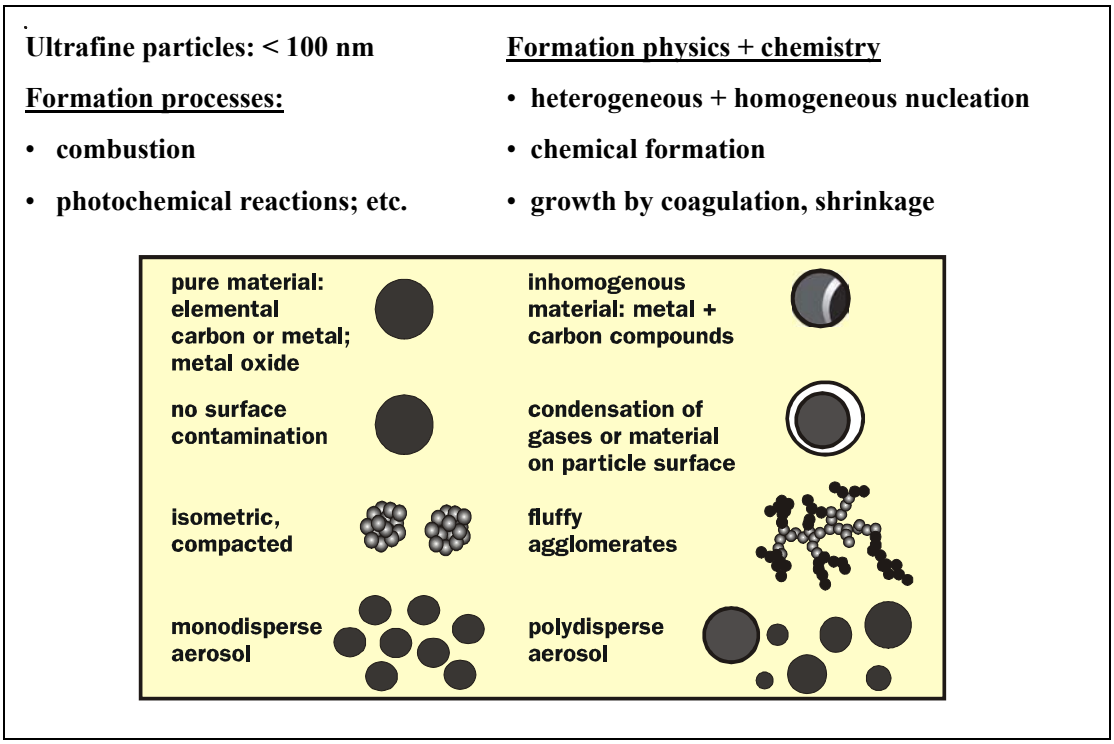


Figure 2:
Comparison of $PM_{2,5}$ and $PM_{0,1}$ from different sources in Great Britain

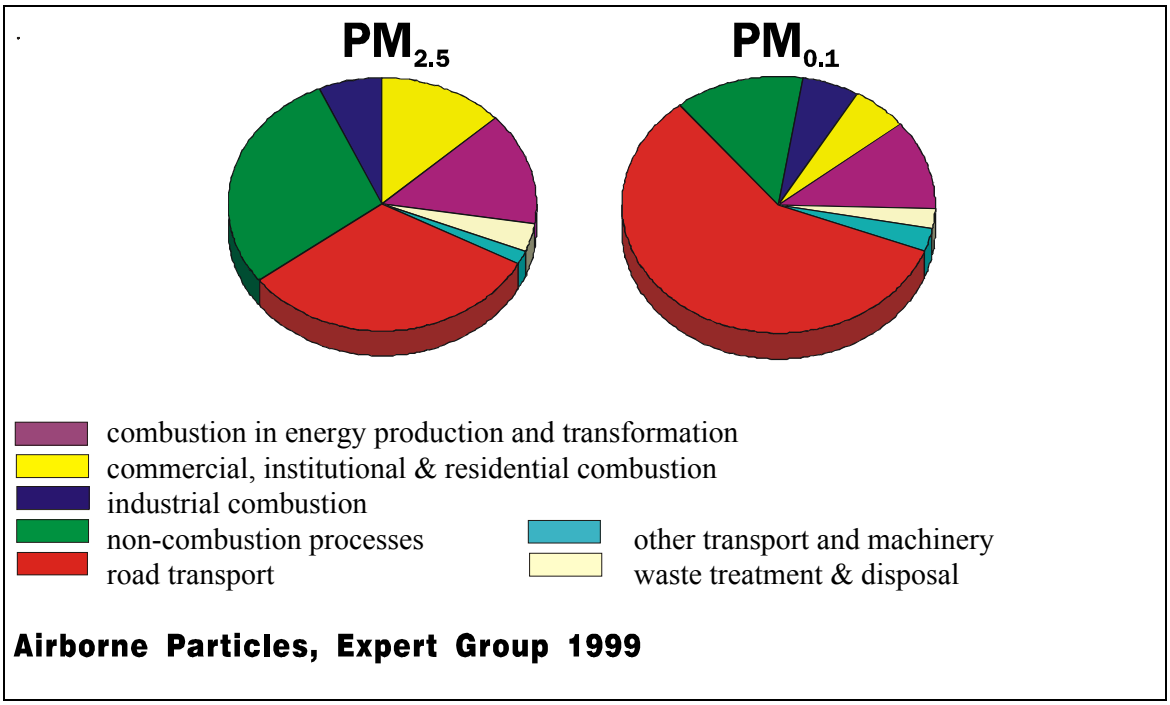
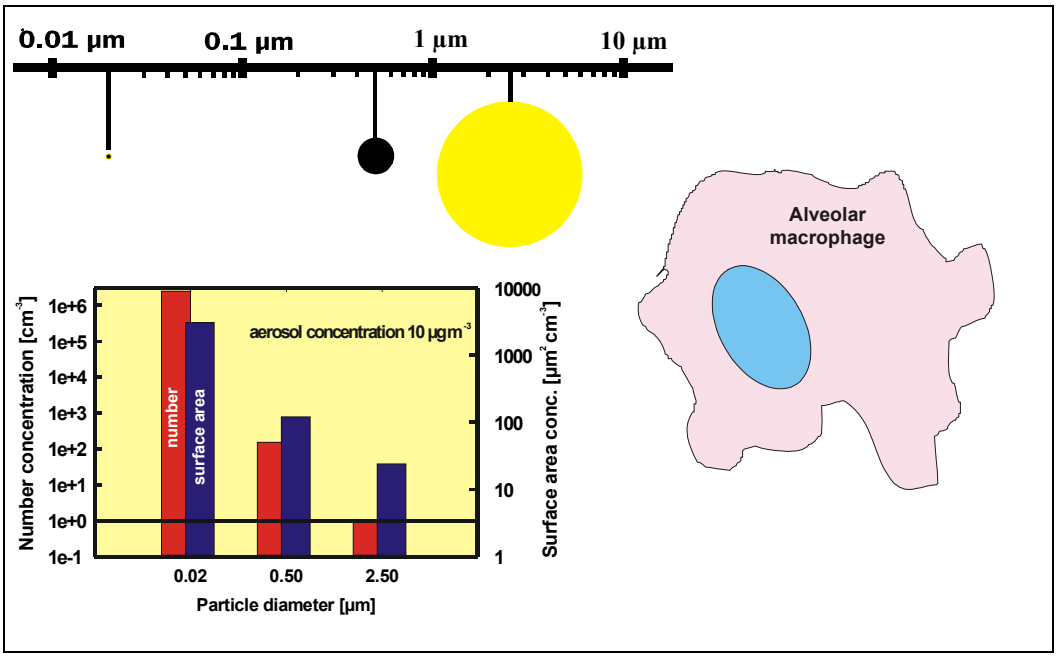


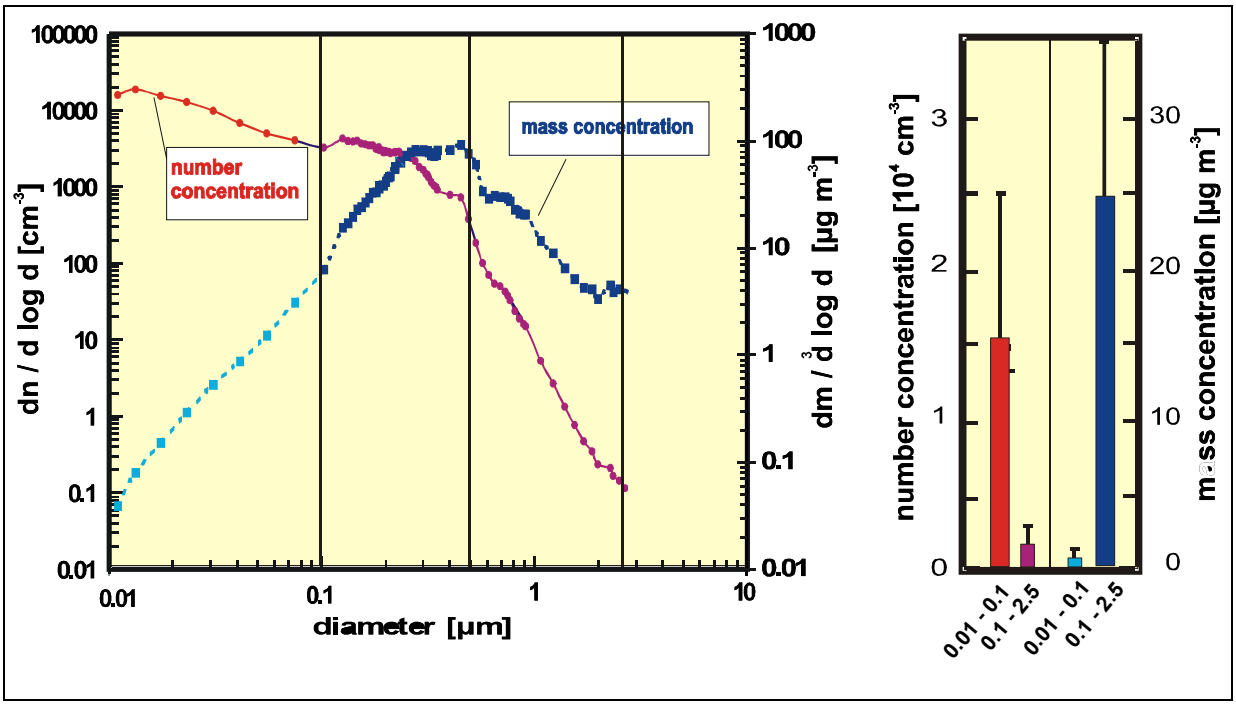
Figure 3:
Comparison of particle sizes for 20 nm,
500 nm und 2,5 µm with an alveolar macrophage



Assuming there is an aerosol with a mass concentration of 10 $\mu g/m^3$ composed of monodisperse spheres of uniform density, then it contains only one particle of 2.5 μm per cm^3 in size but as much as two million particles per cm^3 at 20 nm in size – the difference between the two is six orders of magnitude. Similar, but not quite so dramatic, is the difference of the surface areas: the 2.5 μm particles would have a surface concentration of around 20 $\mu m^2/cm^3$, whereas the 20 nm particles show 2,500 $\mu m^2/cm^3$ – a factor of around two orders of magnitude.

Figure 4 (see page 18) shows the comparison between the number distribution and the mass distribution using the example of an environmental aerosol as it was recorded in Erfurt, Germany, in the spring of 1996. The mass concentration of the particles with a size < 100 nm is negligible but the ultrafine particle fraction dominates the number concentration. In urban aerosols, the mass proportion of ultrafine particles ranges from only about 2 % to a maximum of 5 %.

Figure 4:
Comparison of the number and mass distribution using the example of an environmental aerosol in Erfurt in the spring of 1996



Now let us consider the deposition behaviour of ultrafine particles. Here there are three fields of properties that play a substantial role (Figure 5, see page 19): the dynamics of the particles, the geometry of the respiratory tract with its passages branching down to the alveoli, and the air flow dynamics in the respiratory tract.

Figure 6 (see page 19) shows deposition data based primarily on the table of the International Commission on Radiological Protection (ICRP). The upper curve presents the total deposition probability related to the particle diameter. The deposition probability in the whole respiratory tract is high for large particles and for ultrafine particles with a minimum of around 0.5 μm. The other curves show deposition probabilities in the different regions: first of all the large particles deposit in the upper respiratory tract. This is generally also true for the regions of the larger bronchi. In the area of the smaller bronchioles and, particularly, in the alveoli, the ultrafine particles show a high deposition probability. These observations hold for healthy adults. We still lack data on individuals with lung disease. Yet there are sporadic indications that the particle deposition behaviour is considerably different in lung disease patients.

Figure 5:
Fields of properties influencing the deposition behaviour of ultrafine particles

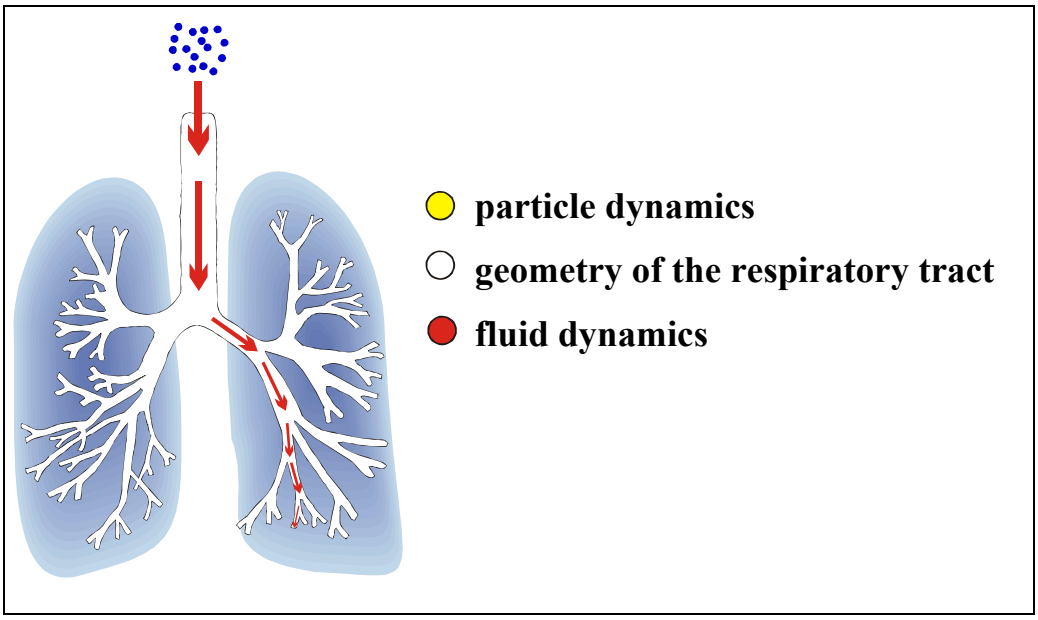
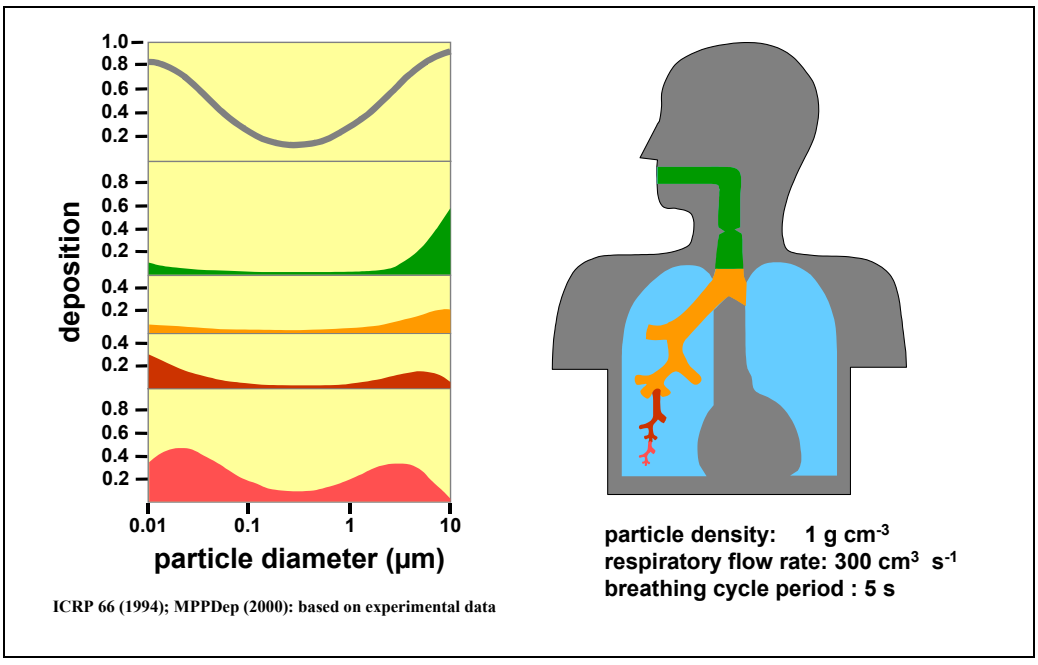
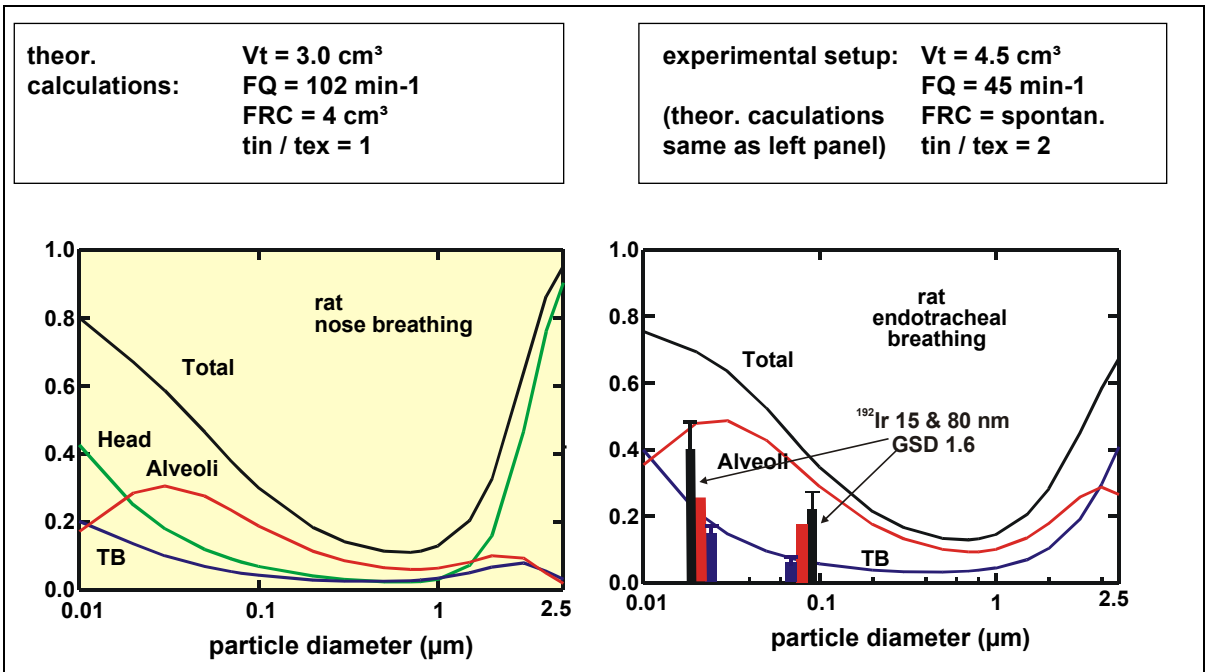


Figure 6:
Particle deposition in healthy individuals
(from top to bottom: total, extrathoracic, bronchi, bronchioli, alveoli)



The deposition curves for aerosols in rats shown in Figure 7 are predominantly on the basis of theoretical calculations: on the left for inhalation through the nose and on the right for ventilation through an endotracheal catheter; in addition experimental data from our own lab also are given here. Rats inherently breathe through the nose. The nose is an effective pre-filter, which is why the deposition probability for particle sizes above 1 μm rises quickly in the head region, but deposition probability in the alveoli rises also for decreasing particle sizes below 100 nm. The experiments produce somewhat different results, but they generally confirm the theoretically calculated trend.

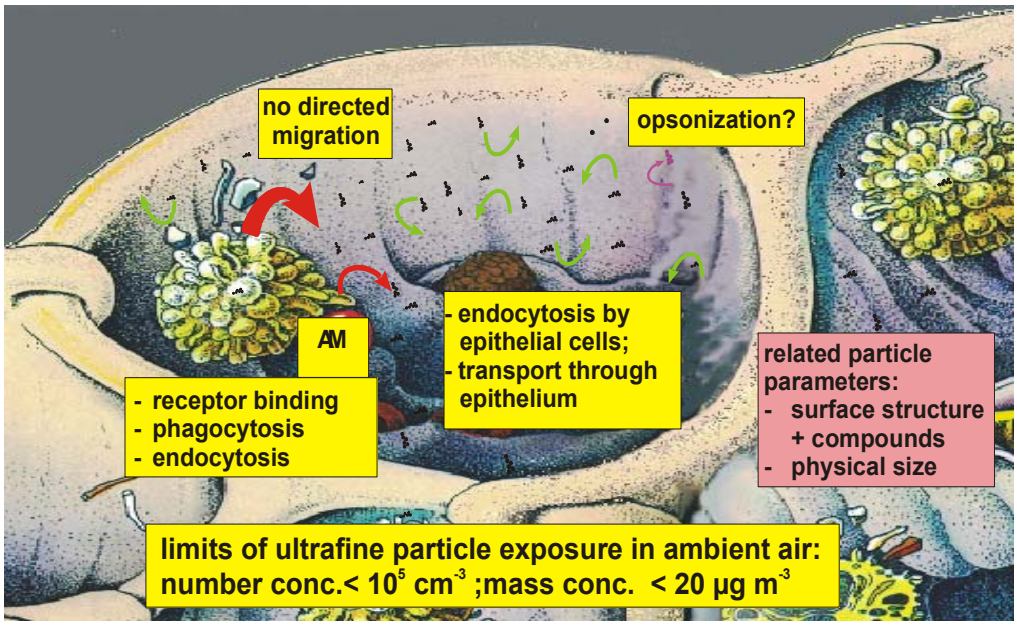
Figure 7:
Deposition curves in rats



What happens next to the deposited particles (Figure 8, see page 21)? As there are much more ultrafine particles than there are fine particles, the distribution of ultrafine particles on the alveolar epithelium is considerably greater in terms of numbers and rather even because they are deposited by diffusion. In the healthy human lungs of a non-smoker, there are roughly ten macrophages per alveolus, and these

macrophages are overwhelmed with recognition and picking up all these ultrafine particles. Although macrophages do pick up particles in their direct vicinity, the probability that alveolar macrophages (AM) pick up particles more distant decreases rapidly with distance. Here, the particles are retained on the epithelium longer where they are subject to endocytosis of the epithelial cells and transport through the epithelium. The relevant parameters here would be the structure and chemical composition of the surface as well as the size of the particles.

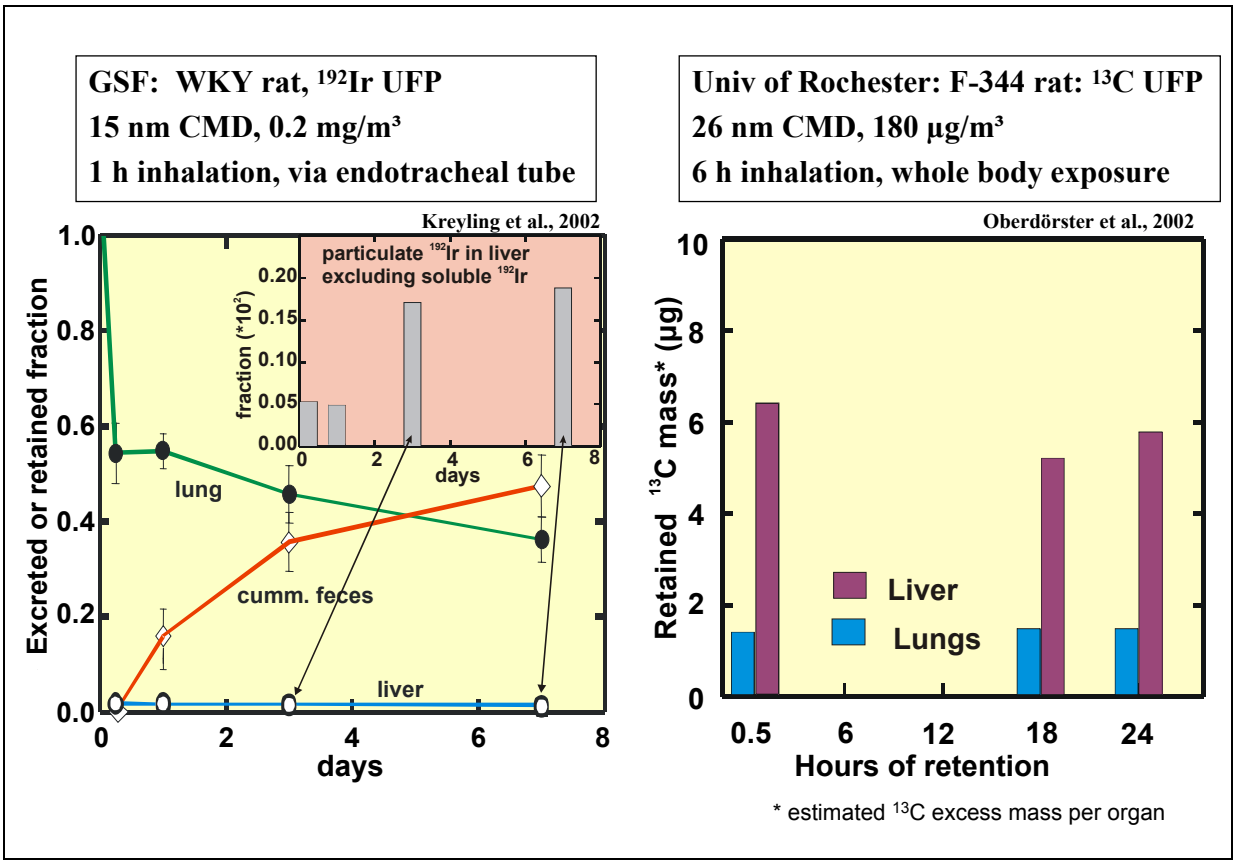
Figure 8:
Recognition, endocytosis, and phagocytosis of ultrafine particles



There is a hypothesis on the association between the exposure to ultrafine particles and health effects on the cardiovascular system. How can we explain this? One possibility is that the particles have direct effects and that they enter the bloodstream directly, thereby gaining easy access to secondary target organs such as the liver, the heart, and possibly the brain. How would the biokinetics look like (Figure 9, see page 22)?

Oberdörster et al. (right side of Figure 9) conducted studies on rats by exposing them to an aerosol with ^{13}C labelled carbonaceous particles of a median diameter of 26 nm and at a concentration of 180 $\mu g/m^3$ for six hours. After just 0.5 h – and also after 18 and 24 h – a substantial portion of the ^{13}C had translocated into the liver. The ultrafine particles thus have very rapid access to this extrapulmonary organ. The left side of Figure 9 shows the results of our studies with ^{192}Ir labelled iridium particles (15 nm median diameter, 0.2 mg/m^3, 1 h inhalation). The pattern looks quite different for the liver: only at a very low level (approximately 1 to 2‰) we found the poorly soluble ^{192}Ir particles. We found similar data for the brain and the heart.

Figure 9:
Biokinetic of ^{13}C- und ^{192}Ir-marked particles in the lung



Explanations for the discrepancy could in part be found in the particle materials that were used and that are actually measured. If the marker is not clearly defined and

securely attached to the particles, this may result in artefacts in the technical measurements. On the other hand, it could be that the different particles behave differently. We thus formulated a hypothesis that ultrafine particles could form complexes with proteins, since the particles are of a similar size as large proteins of the lungs. The biokinetics would then be determined either by the protein or by the particle. It appears plausible that different particles form different complexes with different proteins such that ^{192}Ir particles may bind to different proteins when compared to ^{13}C particles (Figure 10).

Figure 10:
Hypotheses on the biokinetics of ultrafine particles

Hypotheses:

- **Since UFP are similar sized as large proteins, they form complexes with proteins which determine their biokinetic fate**
- **Depending on particle surface properties, biokinetics of UFP-protein complexes may differ leading to different systemic translocation and accumulation patterns in secondary organs**

Preliminary in vitro studies on native rat BAL fluid and different ultrafine particles (Ir, elemental carbon, TiO_2) show:

- **all particles form protein complexes**
- **protein patterns are different between the particles used**

This led us to initiate in vitro studies with native lung lavage fluids in rats and different ultrafine particles (Ir, elementary carbon, TiO_2). These studies indicated that all particles form protein complexes, and that the protein patterns are different for the different particle types.

There are still a lot of questions that need to be answered. The processes seem to be more complicated than to allow us to speak too generally about ultrafine particles.

We can conclude by stating that what is currently known about the deposition of ultrafine particles is primarily based on theoretical calculations and unfortunately on too little experimental data (Figure 11). Ultrafine particles are deposited rather evenly in the respiratory tract. The surface, structure, and composition of the particles all play a role in the effects of insoluble ultrafine particles on biological systems. Their mass appears to be of rather little importance. But there are certainly also specific bio-available compounds that may play a role, such as hydrocarbons and other biologically reactive organic compounds – particularly those produced in combustion processes.

Figure 11:
Current state of knowledge on the deposition and effects of ultrafine particles

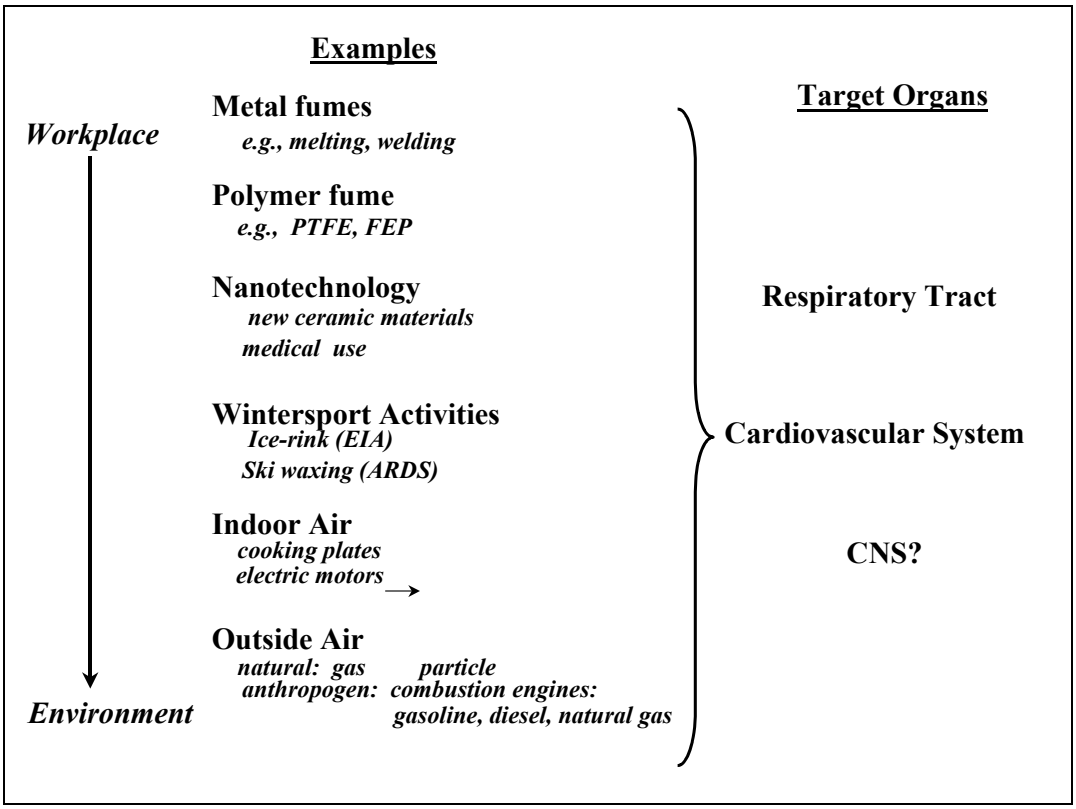
- **UFP deposition is prominently based on theoretical calculations, more experimental data are required**
- **UFP interactions are different from those of fine particles**
  - **Uniform UFP deposition throughout the respiratory epithelium**
  - **surface area of UFP is the interface**
  - **physical + chemical properties of the surface determine the interaction**
  - **UFP mass of minor importance**
  - **bioavailable compounds only important, if specific for UFP**
  - **UFP react at different sites compared to fine particles**

Distribution of ultrafine aerosols in the organism [1]

G. Oberdörster,
Department of Environmental Medicine, University of Rochester, USA

To begin, here are several examples of the sources of ultrafine particles at the workplace and in the environment (Figure 1): metal fumes (e. g. from welding, molten metals), polymer fumes (polytetrafluoroethylene – PTFE, fluoroethylene propylene – FEP), nanotechnology (new ceramic products, also in the field of medicine), winter sports (ice skating, ski waxing), indoor air (e. g. heating elements, electric motors), and outdoor air (natural and man-made aerosols).

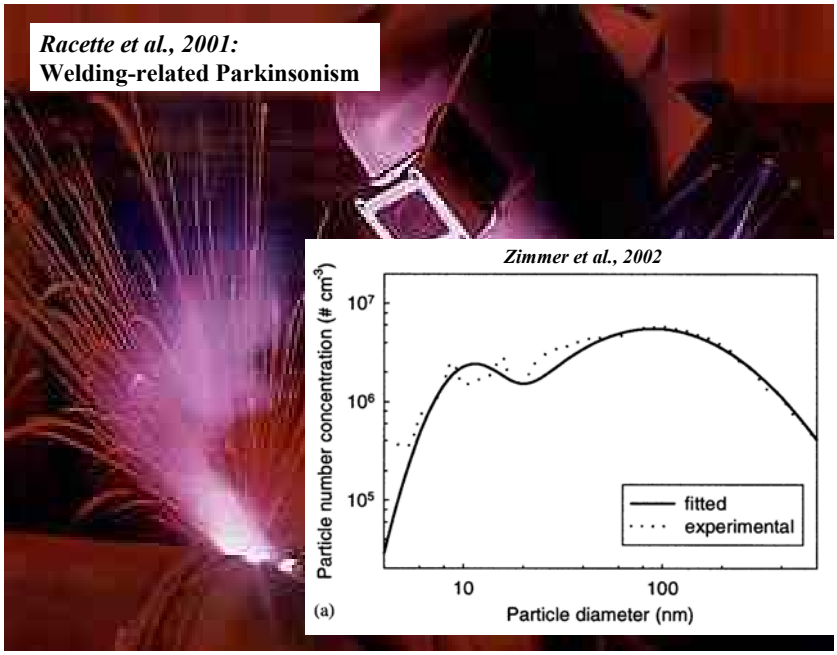
Figure 1:
Examples of sources of ultrafine particles at the workplace and in the environment



[1] Transcription on the basis of the oral presentation; reviewed and authorized by the author.

Figure 2 shows an example of the particle size distribution in welding fumes. *Racette* et al. noted in 2001 [1] that individuals exposed to welding fumes could develop Parkinson's disease 20 years earlier than was the case in the rest of the population. The question remains as to how great the role of ultrafine particles is in this.

Figure 2:
Particle size distribution in welding fumes

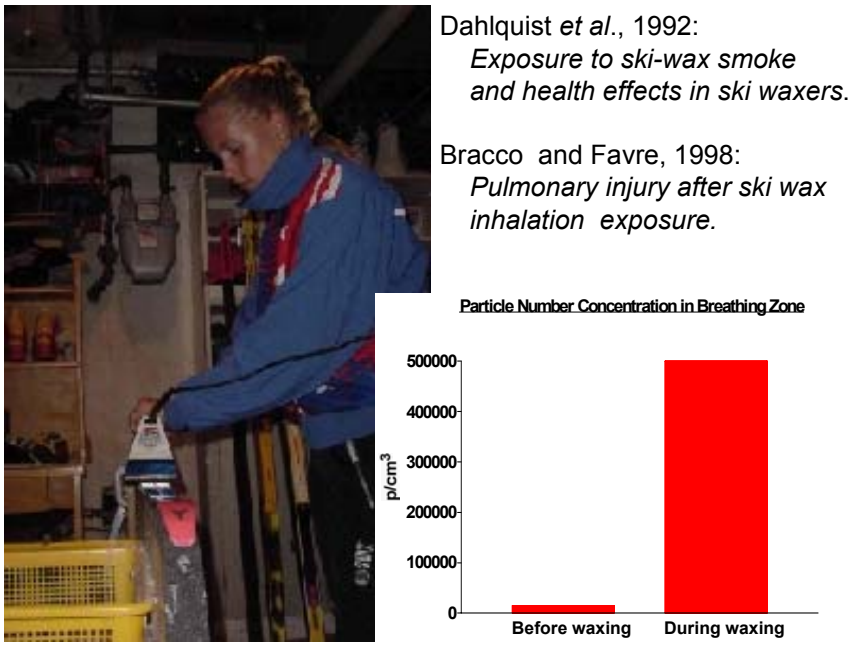


Another example pertains to an incident during the flight of a passenger plane. Passengers and members of the airline crew exhibited the typical symptoms of metal or polymer fume fever. Investigations into the cause of these symptoms later indicated that pyrolysis by-products from the Teflon-impregnated asbestos wrapping around the exhaust manifold of the on-board generator had caused the toxic reactions. Another case of polymer fume fever that was traced to the pyrolysis by-products from PTFE described in the literature was induced by smoking PTFE-contaminated cigarettes.

An example from winter sports (Figure 3, see page 27) has to do with using heat to apply wax to skis. Several measurements showed that the concentration of particles rises up to 500,000/cm³ during this activity. There are publications, such as *Dahlquist*

et al. (1992) [2] or *Bracco* and *Favre* (1998) [3], saying that the effects of ski wax fumes can result in acute diseases of the lower respiratory tract.

Figure 3:
Particle concentrations during the application of ski wax

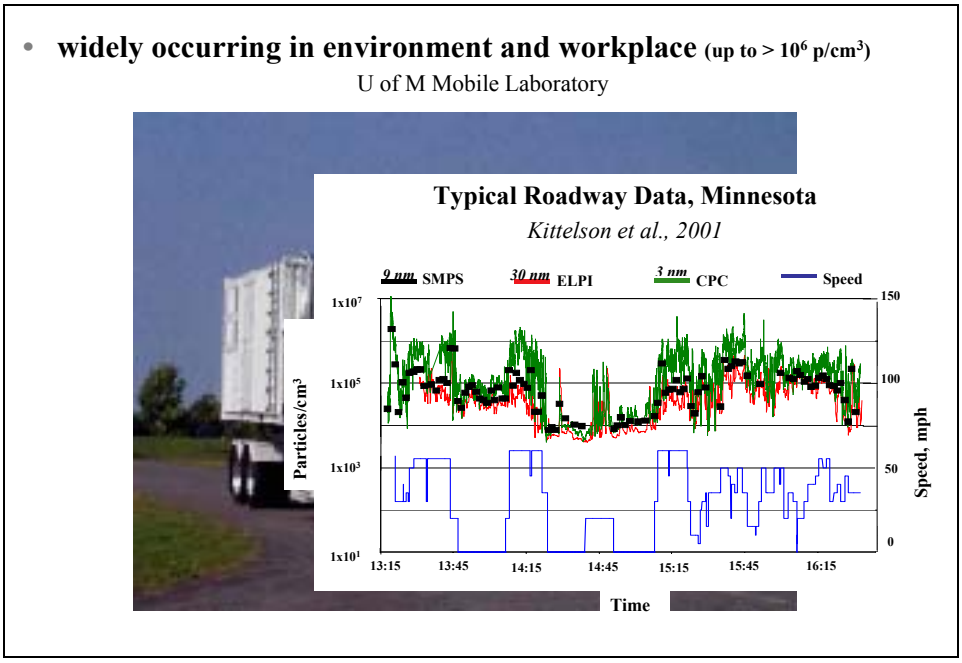


A vehicle at the University of Minnesota was packed with various devices to measure the aerosols and gases along main traffic routes. Some of the results of the aerosol measurements are presented in Figure 4 (see page 28). The small black boxes stand for SMPS results (Scanning Mobility Particle Sizer, for particles > 9 nm) and the adjacent curves stand for measurements obtained using ELPI (Electrical Low Pressure Impactor, for particles > 30 nm) and using CPC (Condensation Particle Counter, for particles > 3 nm). It is quite obvious that more than a million particles can be present per cm^3 in the air in road traffic, depending on vehicle speeds (lower curve with the right-hand scale) [4].

Figure 5 (see page 28) shows a typical environmental aerosol in terms of particle distribution, number, surface area, and mass. Whereas the numerical concentration

of ultrafine particles is quite high, the mass concentration is very low (several $\mu g/m^3$); the surface concentration is somewhere in-between.

Figure 4:
Measurements of ultrafine particles in road traffic



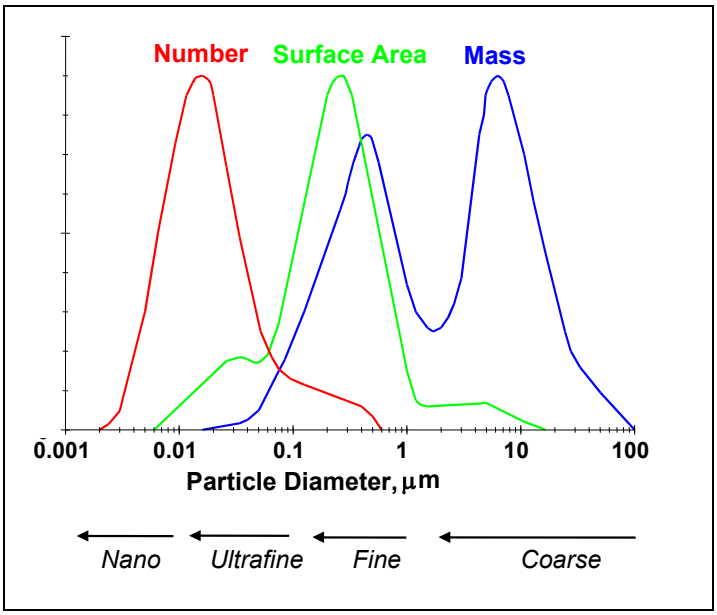


Figure 5:
Particle size distribution in terms of number, surface area, and mass [5]

Now for some results from dosimetry we conducted using TiO_2 particles of around 20 nm and around 250 nm in size: Figure 6 shows the percentage proportion of PMN (polymorphic core neutrophilic leukocytes) in BAL (bronchoalveolar lavage) 24 h after instillation of the TiO_2 particles in rats applied as it was related to the mass. Remarkable here is how the dose-effect curve is considerably steeper for the 20 nm particles in contrast to the 250 nm particles. Figure 7 (see page 30) shows the dose-effect relationship as a function of the particle surface area for the same test series. Here the ultrafine and fine particles can no longer be distinguished from one another. This means that the surface area plays a large role and is a better dose parameter than is the mass or the number of particles when dealing with poorly soluble ultrafine particles made of materials with a relatively low cell toxicity. For other ultrafine particles, the surface chemistry and reactivity of course also play an important role.

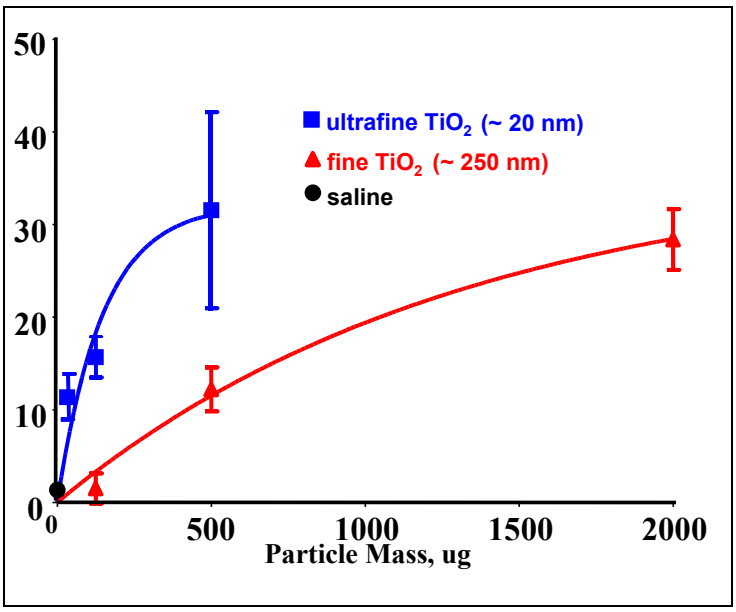


Figure 6:
Percentage of PMN in BAL 24 h after instillation of TiO_2 in rats presented as a function of particle mass

Figures 8 and 9 (see page 30) illustrate the deposition of PTFE particles in various regions of the respiratory tract of rats four hours after the exposure. The arrows point to ultrafine particles with fluorine used as a marker.

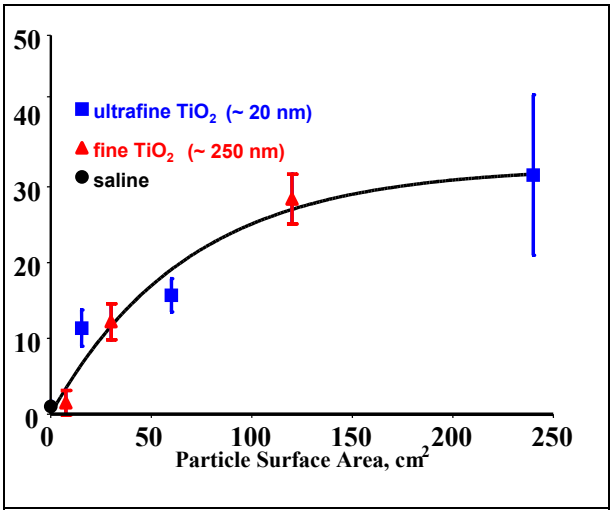


Figure 7:
Percentage of PMN in BAL 24 h after instillation of TiO_2 in rats as a function of the particle surface area

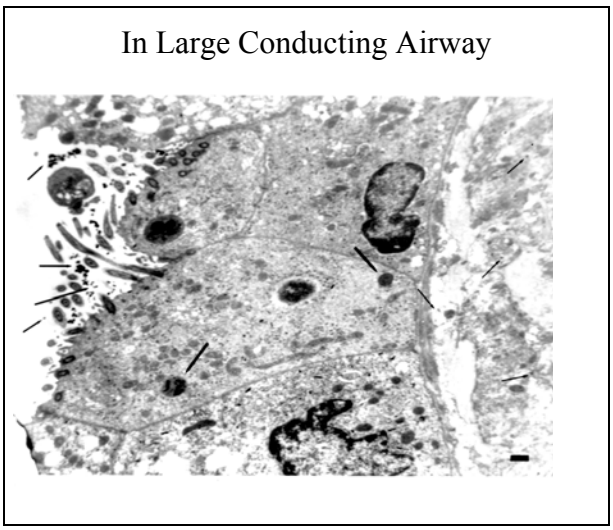


Figure 8:
Distribution of PTFE-particles in the large conducting airways of rats four hours after exposure [6]

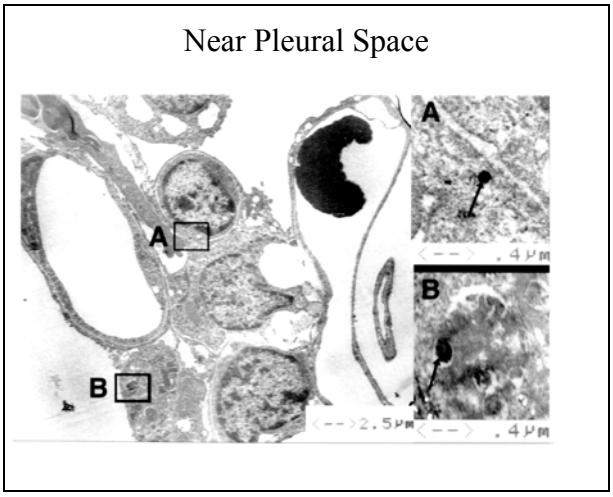


Figure 9:
Distribution of PTFE-particles in the near pleural space in rats four hours after exposure [6]

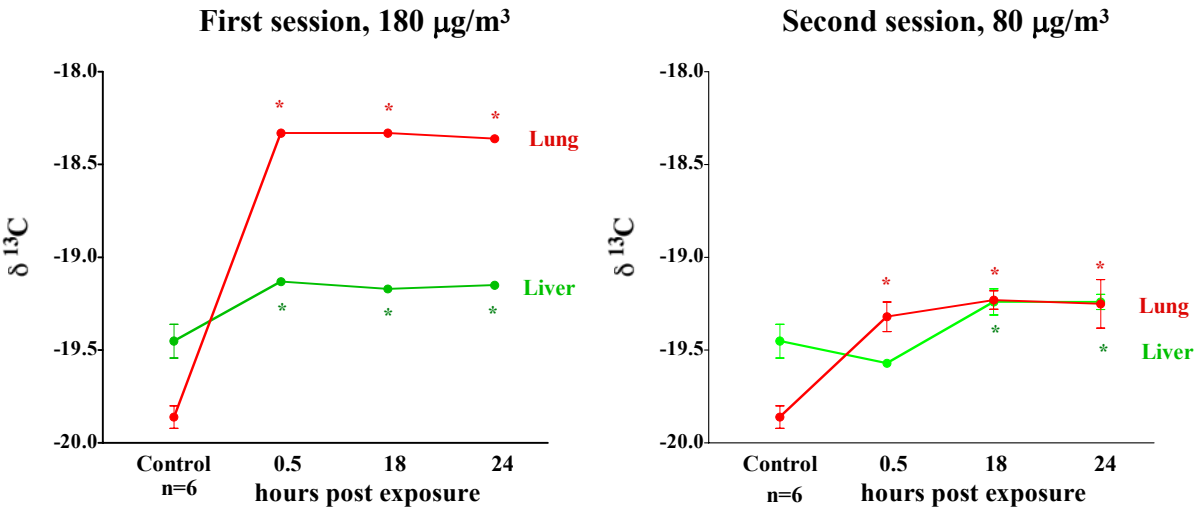
To investigate the question as to what extent inhaled ultrafine particles penetrate the circulatory system and other organs, we produced ^{13}C-containing particles of an average diameter of 20 to 30 nm with a geometric standard deviation of ≈ 1.6 by using ^{13}C rods in a spark discharge generator. For the analysis, the ^{13}C was determined using mass spectrometry, and the difference between the values for the tissue and those for a standard reference was calculated in ‰ (defined as $\delta^{13}C$). Since the tissue contains less ^{13}C than the standard, the difference is negative (Figure 10).

Figure 10:
Producing ^{13}C-containing particles

^{13}C:	***1.1% natural abundance***
^{13}C rods:	***slurry of ^{13}C powder + ^{13}C glucose*** ***extrusion through syringe ⟶ 3.5 mm diameter cylinders*** ***baking (~200°C) and graphitizing (~2400°C) in argon***
Uf particles:	***Use ^{13}C rods in electric spark discharge generator*** *(PALAS)* ***CMD = 20-30 nm; GSD ~1.6***
^{13}C analysis:	***Isotope ratio MS, $^{13}C/^{12}C$*** ***Compare tissue ^{13}C to reference (Standard) sample*** ***Result is expressed as difference: $\delta^{13}C$ in ‰*** ***(tissue has less ^{13}C than reference ⟶ $\delta^{13}C$ is negative)*** ***Detection limit: 0.2‰ (~2 ppm of added ^{13}C)***

Figure 11 (see page 32) shows the results for the liver (lower curves) and for the lungs (upper curves) in rats in two trials with different exposure concentrations 0.5, 18, and 24 hours after a six-hour inhalation period. The double variance analysis shows that the values for $\delta^{13}C$ marked with an asterisk (*) are significantly higher than for those in the control group (*Oberdörster*, et al., 2002 [7]).

Figure 11:
Results for the lungs and livers of rats in two trials with different exposure concentrations after six hours of inhaling ^{13}C particles



Once the results of both trials are standardised by spreading the determined mass of the ^{13}C per gram of the respective organ and per $\mu g/m^3$ of the exposure concentration over the period after the exposure (Figure 12, see page 33), it becomes obvious that the quantity of ultrafine ^{13}C particles deposited in the lungs does not change over a 24-hour period after exposure. An increase of ^{13}C particles in the liver can be measured only 0.5 hours after exposure, but the increase only becomes significant 18 and 24 hours after exposure [7].

The results obtained by a Belgian group (*Nemmar*, et al., [8 to 10]) are summarised in Figure 13 (see page 33). Colloidal albumin particles less than 80 nm in size marked with ^{99m}Tc were instilled in the trachea of hamsters, and the ^{99m}TC was detected in the blood within five minutes [8]. Even in human test subjects who had inhaled Technegas (particle size < 100 nm), the markers were found in the blood and in the liver only a short time after the exposure. Despite studies on the stability of the ^{99m}Tc markers using thin-layer chromatography, there are still concerns about the marker stability of the albumin and carbon particles, which perhaps went into solution or were otherwise deposited [9].

Figure 12:
Normalised ^{13}C excess concentration after exposure in rats compared to ^{13}C-marked ultrafine particles (n = 3)

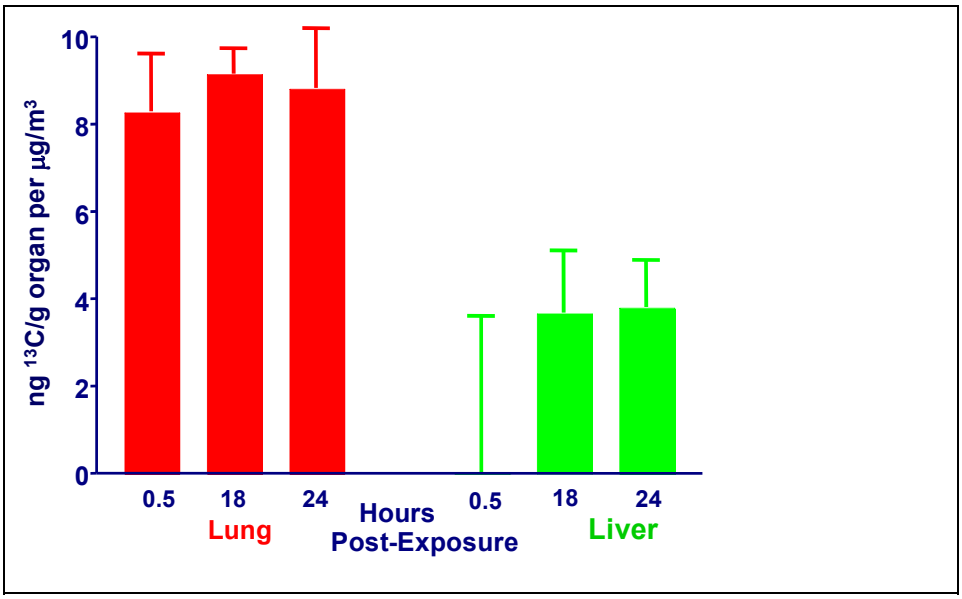


Figure 13:
Systemic transport of ultrafine particles from the respiratory tract

Nemmar *et al.*, (2001; 2002):

- **ultrafine ^{99m}Tc-albumin colloid particles (< *80 nm*)**
  hamster i.t. instillation, rapid diffusion (< 5 min.) into blood
- **ultrafine ^{99m}Tc-carbon (Technegas, < *100 nm*)**
  human subjects, inhalation, label in blood and liver shortly post-exposure

potential problems: stability of label?

- **ultrafine polystyrene particles (*60 nm*) and Rose Bengal thrombus model:**
  hamster i.t. instillation: positively charged (amine) increased thrombus,
  negatively charged (carboxylate) did not

effect of particle charge on cellular functions?

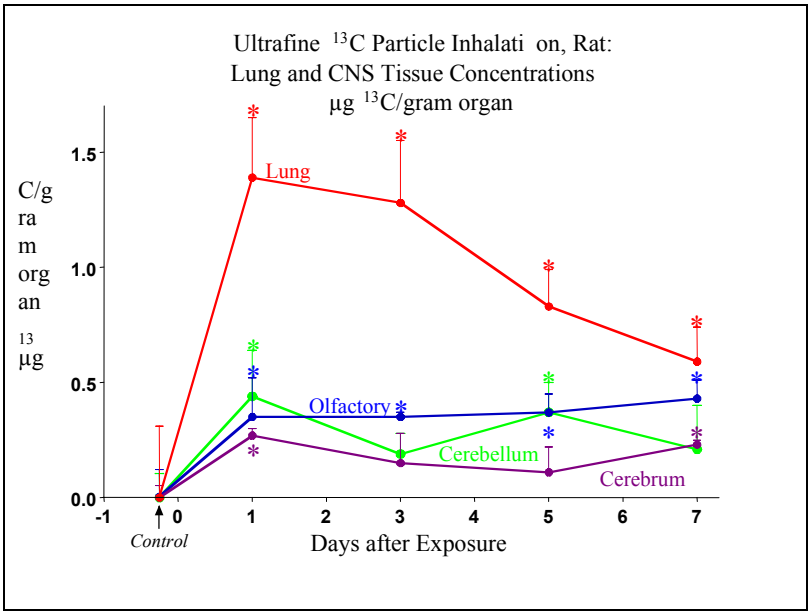
In other studies, the intratracheal instillation of ultrafine polystyrene particles (60 nm in size) showed charge-dependent effects in hamsters. Positively charged particles exhibited an increased thrombus in the femoral vein, but this was not true for the negatively

charged particles. This then raises the question of to what extent particle charges affect cell functions [10].

We conducted additional inhalation experiments with ultrafine ^{13}C particles on rats and, in Figure 14, expressed the measured amount of ^{13}C particles in μg per gram of organ tissue of the lungs and of the CNS in relation to the time after exposure. It is interesting to note that the ^{13}C particles made it not only into the olfactory centres of the brain, but also into the cerebellum and cerebrum.

Figure 15 (see page 35) provides a summary of various experiments showing that translocation of ultrafine particles does occur along the nerves, in particular along the olfactory nerve to the olfactory centre, at the astonishingly high speed of 2.5 mm/h.

Figure 14:
Organ deposition of inhaled ^{13}C-marked ultrafine particles in rats



The olfactory mucous membrane comprises around 50 % of the nasal mucous membrane in rats; in humans the figure is around 5 %, which could mean that neuronal transport plays a smaller role in humans (Figure 16, see page 35). Nonetheless, the rest of the nasal mucous membrane also contains sensory nerves to the trigeminal

nerve. *Lewis*, et al., [14] showed that manganese instilled intranasally can be transported along the trigeminal nerve into the brain.

Figure 15:
Summary of research on neuronal transport of ultrafine particles

Studies of Neuronal Translocation of UFP from Respiratory Tract

1941: *Bodian and Howe*: Olfactory axonal transport of Polio-virus (30 nm) after intranasal instillation in chimpanzee. [11]
Transport velocity: 2.4 mm/h

1970: *de Lorenzo*: Olfactory axonal transport of 50 nm colloidal gold after intranasal instillation in squirrel monkey. [12]
Transport velocity: 2.5 mm/h

1998: *Hunter et al.*: Rhodamine-labelled 40 nm microspheres translocation via sensory nerves of TB region to ganglion nodosum in hamster after intratracheal instillation. [13]

2002: *Oberdörster et al.*: ^{13}C particles (CMD ~ 25 nm) in olfactory bulb after whole-body inhalation exposure in rats. [7]

Figure 16:
Neuronal transport of ultrafine particles (rat/human comparison)

Significance of Olfactory UFP Transport in Rats vs. Humans

Area of olfactory mucosa:

Rats: **~ 50 % of nasal mucosa**

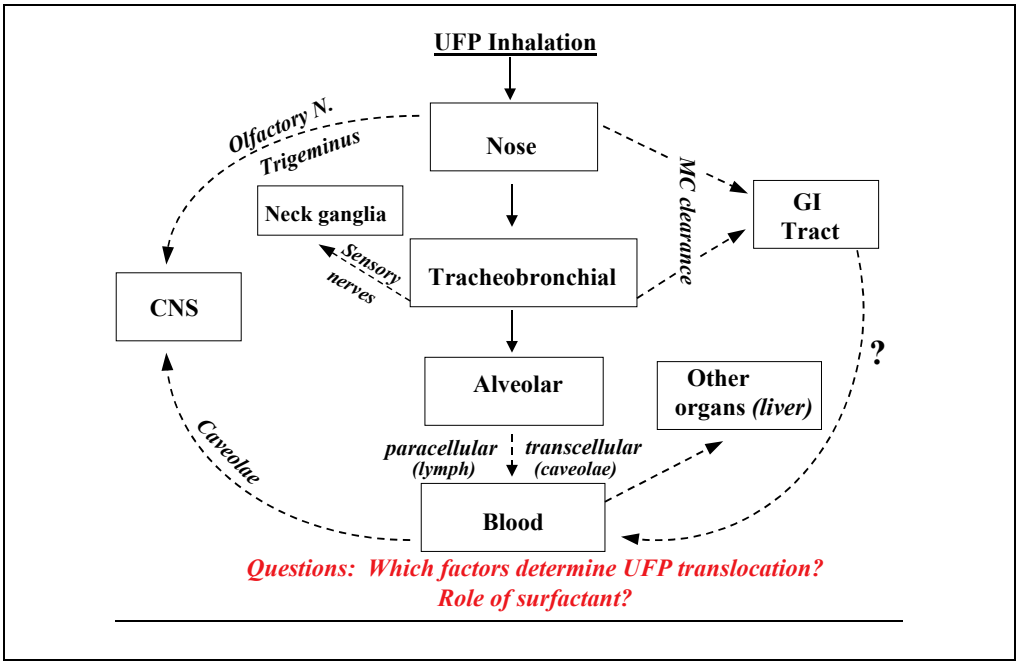
Humans: **~ 5 % of nasal mucosa**

But:

- **Presence of sensory nerves to Trigeminus throughout nasal mucosa**
- **Translocation of intranasally instilled Mn in rats along Trigeminus to CNS has been shown** (*Lewis* et al., 2002)

Figure 17 provides a general overview of the hypotheses on how ultrafine particles can be transported after they are deposited in the nasal, tracheobronchial, and alveolar regions. From the nasal area, transport is possible along the olfactory nerve and along the trigeminal nerve to the central nervous system, and along the mucociliary clearance to the gastrointestinal tract – the latter also from the tracheobronchial area. From the alveolar region, and perhaps also from the gastrointestinal tract, ultrafine particles can enter the bloodstream, thereby entering the central nervous system and other organs such as the liver. Perhaps transport to the bloodstream via caveolae from the alveolar region plays a role here. Other questions remain about which factors determine the transport and about what role surfactants (surface area-active substances) play in the lung.

Figure 17:
Overview of hypotheses on the transport of ultrafine particles



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Discussion

Question: What could explain the difference between the experiments in Neuherberg and in Rochester? The question of whether or not ultrafine particles enter the blood-stream is after all relevant to the cardiovascular effects.

Answer: The difference in the way the experiments were conducted was that the Ir experiments were conducted using intratracheal instillation with anaesthetised animals, whereas the ^{13}C experiments were done using whole-body exposure on a non-anaesthetised animal. Also experiments with C-coated Ir particles indicated that the Ir cores were mostly to be found in the lungs, and that translocation was only very low. The disadvantage of using ^{13}C lies in the fact that ^{13}C is already present in every biological tissue at around 1 % within a range of individual variability. So the experiments should be repeated using ^{14}C. Yet it is certain that translocation of particles from the respiratory tract into the circulatory system can occur. The first interaction that the particles have after they are inhaled into the lungs is the interaction with the lung surfactant. Up to a certain amount of exposure, the surfactant is able to buffer the dust exposure; the system breaks down beyond this exposure threshold. The dose dependency of this breakdown – which itself depends on the particle surface area, and even on the structure and chemical composition of the particles – is a critical question.

Toxicology of ultrafine particles [1]

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1 Introduction

Nanotechnology is expected to bring a fundamental change in manufacturing in the next few years and will have an enormous impact on Life Sciences, including drug delivery, diagnostics, nutraceuticals, and production of biomaterials. Engineered nanoparticles (< 100 nm) are an important tool to realize a number of these applications. The reason why these nanoparticles (NP) are attractive for such purposes based on their important and unique features, such as their surface to mass ratio which is much larger than that of other particles, their quantum properties, and their ability to adsorb and carry other compounds. NP on one hand have a large (functional) surface which is able to bind, adsorb and carry other compounds such as drugs, probes, and proteins. On the other hand, NP have a surface that might be chemically more reactive as compared to their fine (> 100 nm) analogues. Many of these special purpose engineered NP are produced in small quantities. In 2003, single-walled and multi-walled nanotubes had a worldwide production of 2,954 kg. However, the Carbon Nanotechnology Research Institute (Japan) plans on expanding their production from ~1,000 kg in 2003 to 120,000 kg/year within the next five years. Although current production of engineered nanomaterials is small, it is evident that production rates will accelerate exponentially in the next few years.

In addition to these specifically engineered nanomaterials, nano-sized particles are also being produced non-intentionally in diesel exhaust and other combustion processes. It is estimated that 50,000 kg/year of nano-sized materials are being produced

[1] Updated version of the workshop presentation as announced in the course of the workshop due to current findings; Sept. 2004

through these unintended anthropogenic sources. These combustion NP are included in particulate matter (PM) which is measured by mass and related to adverse effects in patients with lung and cardiovascular disease. Combustion NP have also been denominated as ultrafine particles, and are primary particles or agglomerates with a diameter < 100 nm. These ultrafine particles are a small mass fraction of total anthropogenic particulate emissions, described with total suspended particles (TSP), particulate matter (PM) or PM beyond a specific size in micrometers (PM_{10}, $PM_{2.5}$, PM_1). It is estimated that 50,000 kg/year of nano-sized materials are being produced through these unintended anthropogenic sources. The first publication on this topic was the so-called Six Cities study [1] that described an association between mortality in six US cities and the annual mean of particulate mass sampled by convention with a 50 % cut-off at 2.5 μm ($PM_{2.5}$). From this and later studies it is estimated that per 10 µg/m³ increase in the concentration of $PM_{2.5}$, overall mortality increases by 0.9 %, while deaths from specific respiratory diseases can increase by as much as 2.7 %. There is ample evidence that a small proportion of the mass but a large proportion of the number of the particles in ambient air are ultrafine in size. Numerous toxicological studies have now forwarded these ultrafine particles to be responsible for adverse effects, but so far few human studies have been able to investigate this.

Interestingly most of the toxicological work on NP has been generated with a small set of bulk NP, that have been around in industry for some decades and are produced in quantities that currently exceed many tons per year (Table 1, see page 43). According to the National Nanotechnology Initiative (USA), the largest production volume in 2004 was for colloidal silica, titanium dioxide, and various iron-oxides (Table 1). All these bulk NP were considered to be so-called nuisance dusts until it was observed that upon prolonged exposure in rats inflammation and lung tumours can occur [2 to 4]. A schematic summary of key studies on toxicological effects of NP is given in Table 2 (see page 44), and this is considered as both direct and indirect evidence that NP are important components in the adverse effects of PM_{10}. The question now is whether in this triangle of different applications and sources of NP (Figure 1, see

page 43) the different pieces of toxicological evidence can be mutually used or whether a more sophisticated approach is necessary.

Table 1:
Different sources and applications of nanoparticles

Source of NP	Examples	Application/use
Combustion NP	Diesel exhaust particles Fly-ashes	Environmental exposure
Bulk synthetic NP	Titanium dioxide (TiO_2) Carbon blacks Amorphous silica Iron oxides	Cosmetics Pigments, tires, toner Paints, fillers
Engineered NP	**Organic** Liposomes Polycyanoacrylates **Inorganic** Gold Dendrimers Zeolites Silver	 Drug delivery Drug delivery Quantum dots (imaging) diagnostics

Figure 1:
Schematic illustration of the different sources and applications of nanoparticles (NP) and the evidence for their relation with adverse effects in humans or animals. Epidemiology and toxicology have demonstrated acute effects of combustion NP in humans, as well as chronic effects of NP in animals. It remains an open issue whether the hazards and risks found with those types of NP can be extrapolated to engineered NP, which is illustrated by the question marks.

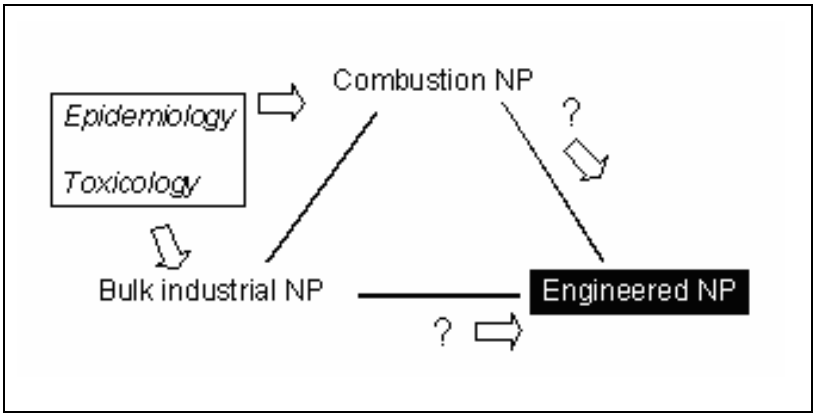


Table 2:
Important findings on the biological activity and key-publications in the toxicity of combustion and bulk nanoparticles (NP) between 1990 and now

Description of finding	References
NP TiO_2 causes pulmonary inflammation. Later studies show that inflammation is mediated by surface area dose.	*Ferin* et al, 1992; *Tran* et al, 2000 [5; 6]
NP cause more lung tumours than fine particles in rat chronic studies. Effect is surface area mediated.	*Driscoll* et al, 1996; *Borm* et al, 2004 [4; 7]
NP inhibit macrophage phagocytosis, mobility and killing.	*Renwick* et al, 2001 [8]
NP affect immune response to common allergens.	*Granum* & *Lovik*, 2002 [9]
NP are related to lung function decline in asthmatics.	*Peters* et al, 1997 [10]
NP cause oxidative stress in vivo and in vitro, by inflammatory action and generation of surface radicals.	*Donaldson* et al, 2002; *Dick* et al, 2003 [2; 11]
NP exposure adversely affects cardiac function and vascular homeostasis.	*Stone & Godleski* et al, 1999; *Brook* et al, 2002 [12; 13]
NP have access to systemic circulation upon inhalation and instillation.	*Nemmar* et al, 2002; *Kreyling* et al, 2002 [14; 15]
NP can affect blood coagulation in human and animal models.	*Nemmar* et al, 2003 [16]
NP interfere with Ca-transport and cause increased binding of pro-inflammatory transcription factor NF-kB.	*Stone* et al, 2000 [17]
NP can affect mitochondrial function.	*Li* et al, 2003 [18]
NP can translocate to the brain from the nose.	*Oberdörster* et al, 2004 [19]
NP do affect rolling in hepatic tissue.	*Khandooga* et al, 2004 [20]

2 Effects of inhaled nanoparticles

2.1 General paradigms in particle toxicology

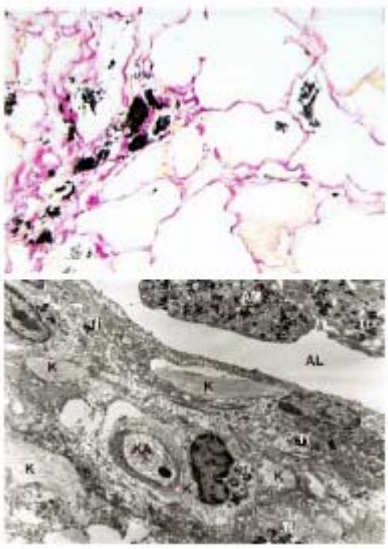
For the interpretation of inhaled particle effects, five D's have to be taken into account, i. e. Dose, Deposition, Dimension, Durability, and Defence. First of all the dose at a specific site (in the lungs) determines the potential toxicity. This deposited dose is of course dependent on the concentration and the dimensions of the particle. Interestingly, the deposition probability of NP increases steeply in the respiratory tract the smaller the particles are. Moreover, a major fraction will be deposited on the fragile epithelial structures of the terminal airways and gas exchange region. If a particle is neither soluble nor degradable in the lung it has a high durability and there will be rapid local accumulation upon sustained exposure. The lung, however, has extensive defence systems such as mucociliary clearance (upper airways) and macrophage clearance (lower airways, alveoli) to remove deposited particles. Although the above concept is simple, most of these parameters are interrelated and dimension – as in the case of fibres or nanotubes – may have profound effects on defense and thereby chronic dose. Long (> 20 μm) fibres are not taken up by alveolar macrophages, and therefore have a longer half-life in the lung when compared to the same material with shorter fibres and, consequently, have a higher toxic potency. In addition, particle transport by macrophages from the alveolar region towards the larynx is slow in man even under normal conditions, thus, eliminating only about a third of the deposited particles in the lung periphery; i. e. the other two thirds accumulate in the lungs without clearance unless they are biodegradable and cleared by other mechanisms. If particles are reactive or present at sufficient dose, macrophages and epithelial cells can be activated or damaged leading to inflammation which drives most pathogenic effects of particles.

2.2 Pulmonary deposition and translocation of nanoparticles

Although the deposition of inhaled NP in the respiratory tract follows largely the same distribution as fine particles, the underlying mechanisms are different. NP (< 100 nm)

have a size dimension that makes them less subject to gravity and turbidometric forces and therefore their deposition occurs mostly by diffusion. In addition their size makes them to interact with other potential targets than conventional fine particles. As a result of their small size, defence is less efficient since recognition by macrophages is suggested to be impaired or less effective. In addition for drug delivery, particle surfaces have been treated to behave as "stealth" particles and remain unrecognised by phagocytosing cells. Because of their low uptake by macrophages and their diffusion behaviour, NP are suggested to be taken up by endothelial cells and they have access to cells in the epithelium, the interstitium, and the vascular walls. However, after instillation of massive doses of NP into the lungs of experimental animals, most particles are located in the interstitium and do not reach the blood stream (Figure 2).

Figure 2:
A. Interstitial localisation of ultrafine TiO_2 particles 2 years after intratracheal instillation of a high dose (30 mg) of TiO_2 (20 nm, $P_{2.5}$) in female Wistar rats. The black particle agglomerates are located either in the interstitium or the alveolar lumen. The Sirius red staining indicates areas with collagen formation. B: Cellular and subcellular distribution of ultrafine TiO_2 (20 nm) two years after in vivo pre-treatment (as in panel A). The TEM picture shows TiO_2 particles (Ti) in an epithelial cell adjacent to an alveolar macrophage (AM). Magnification of the lower panel is 12,800. Images are courtesy of dr *Doris Höhr* (lower panel) and *Welf Mahlke* (upper panel).



It is only after increasing endothelial or epithelial permeability that particles do translocate to the blood. This may be achieved by mediators released during an inflammatory response such as hydrogen peroxide or histamine [16]. Wherever they deposit or translocate to, NP have properties such as a large surface that can carry and absorb many endogenous substances such as proteins. It has been shown that particle recognition and distribution can be dramatically affected upon coating with plasma proteins such as ceruloplasmin [21] or cations such as aluminium [22].

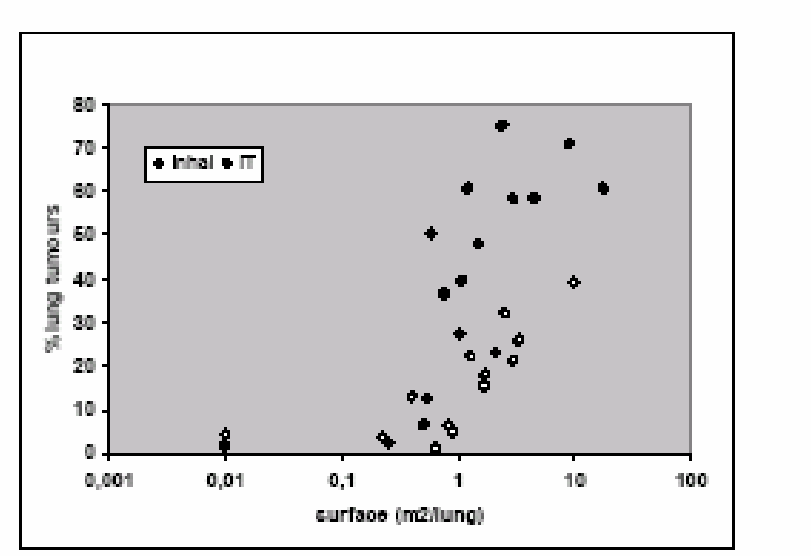
2.3 Pulmonary inflammation and immune defense

The toxicological profile of (bulk and combustion) NP has only emerged during the past decade. An early key study demonstrated that ultrafine TiO_2 (20 nm) caused more inflammation in rat lungs than exposure to the same airborne mass concentration of fine TiO_2 (250 nm) [5]. Until then TiO_2 had been considered a non-toxic dust and indeed had served as an inert control dust in many studies on the toxicology of particles. Therefore, this report was highly influential in highlighting that a material that was low in toxicity in the form of fine particles but could be toxic in the form of ultrafine particles. Later studies have demonstrated that the pulmonary inflammation, usually measured as the number of neutrophilic granulocytes (PMN) in bronchoalveloar lavage (BAL), is related to the instilled or inhaled surface area of particles although at similar surface some ultrafines seem to be more inflammatory than others [11]. Among mechanisms by which NP could cause an enhanced inflammatory response, direct effects have been reported on alveolar macrophages such as inward leaching of Ca^{2+} , impairment of phagocytosis and cytoskeletal changes [4]. Epithelial and nerve cells may also contribute to airway inflammation by producing pro-inflammatory cytokines such as interleukin-8 [23] or pharmacologically active compounds such as capsacein. In this neurogenic inflammation, stimulation of sensory nerve endings releases neurotransmitters which may affect many types of white blood cells in the lung, as well as epithelial and smooth muscle cells. Another potential consequence of exposure to NP may be their effect on the capacity to defend against micro-organisms or, in contradiction, an augmentation of allergic immune response to common allergens [9].

2.4 Pulmonary carcinogenicity

Poorly soluble particles (PSP) without specific toxicity such as carbon black and titanium dioxide (TiO_2) are known to cause fibrosis, neoplastic lesions, and lung tumours in the rat [4]. NP (TiO_2, carbon black) can induce lung tumours in rats at considerably lower gravimetric lung burdens than their larger sized analogues and actually the retained particle surface metric has been used to describe the lung tumour rate in chronic inhalation studies. It is now generally accepted that the continued presence of high levels of particle surface leads to impairment of alveolar macrophage clearance, culminating in rapid buildup of particles, chronic inflammatory response, fibrosis, and tumorigenesis, known as the so-called rat lung overload. The overall pattern is one of chronic inflammation that occurs upon saturation of lung clearance by overloading of macrophages at which point particle accumulation starts and inflammatory cell influx increases sharply. The inflammatory cell influx is held responsible for the lung tumours after chronic particle exposure to PSP due to their mutagenic activity and actions on cell proliferation. The importance of particle surface is illustrated by a graph that summarizes findings on lung tumours in chronic animal studies using poorly-soluble particles, including NP (Figure 3, see page 49). The graph shows that both inhalation and instillation of particles cause induction of tumours that is related to the deposited particle surface. Since NP have a larger specific surface area, at similar gravimetric dose, they cause higher tumour doses at similar mass dose. Still this surface dose concept is probably an oversimplification for several reasons. First, ultrafine particles at similar surface area appear to exhibit significant differences in inflammatory activity. Secondly, it is unclear whether ultrafine particles following inhalation have a different lung distribution between alveolar spaces, macrophages and interstitium and how relevant this is for tumour formation. Thirdly, at high local concentrations of NP, these particles should be considered to penetrate target cells and enter the mitochondria [18] and the nucleus exerting direct effects to DNA.

Figure 3:
Association between lung tumour response and the particle surface area for various poorly-soluble low toxicity particles (PSP) gathered from different rat studies. The open circles represent different inhalation studies done over the past 15 years. The closed circles are taken from a study where fine and ultrafine particles were administered by intratracheal instillation in rats and lung tumours were evaluated by histopathology score after 129 weeks. In both cases a straight line is obtained with a threshold between 0.2 and 0.3 m^2 surface dose per rat lung, which suggests a no-effect level.



2.5 Importance of surface modification and coatings.

Whatever test will be used or developed, it needs to be considered that most suppliers apply post synthetic strategies to modify NP to prevent aggregation or stimulate dis-aggregation. In summary, post synthetic routes open a variety of possible surface modifications which can be adjusted to any application, using chemicals such as 4-dimethylaminopyridine, various thiols, fluoroalkanes, alkoxysilanes, and phospho-rous containing substances. Particle coating with polyethylene glycol is a common treatment in drug delivery to prevent recognition by the reticulo-endothelial system and increase the half-life of the particle conjugated drugs. Work-related examples are given by data on respirable, non-ultrafine quartz samples. Coating with aluminium lactate or the polymer poly-(2-vinyl-pyridine N-oxide), PVNO has a dramatic beneficial impact on the various adverse effects of the native quartz, including phagocytosis/

endocytosis, oxidative DNA damage and inflammation upon intratracheal instillation in rat lung [22; 24].

In sunscreens NP are often used as "nanomirrors" on the skin and partly reflect the sunlight. Because of their scattering properties, they increase the optical pathway of UV photons entering the upper part of the horny layer. In this way, more photons are absorbed by the stratum corneum and by the applied organic filter substances. Coated titanium dioxide NP are commonly used as UV filter substances in commercial sunscreen products. Concern has been raised about a possible photo-catalytic activity of titanium dioxide on living tissues and to reduce potential adverse effects, the titanium dioxide used in cosmetic preparations is often coated. Surface modified TiO_2 has been the subject of considerable toxicological investigation and has shown that the hydrophobic coatings usually tend to lower the inflammatory response after inhalation or instillation (e. g. [25]). However, one study reported a very high acute toxicity after instillation of doses around 1 mg per rat [26]. With this regard it is crucial to know how the surface modification has been achieved and if this can be released from the NP in biological media (low pH in macrophages). In the case of sunscreen-grade coated titanium NP the stability of the coating was investigated by laser induced plasma spectroscopy. No changes in the mechanical stability of the coated micro-particles could be detected during the manufacturing and penetration of the sun-screen.

Other studies have indicated that blood coagulation by latex particles, when infused into the jugular vein of hamsters [16] was dependent on the surface charge. Studies on nasal translocation showed that surface charge and chemistry affected the rate of translocation to the blood. Uptake of lipid particles through the blood brain barrier was only achieved successfully when using a specific (Tween-80) surface coating, which mediates its binding to the apo-E receptor. Most likely, but unknown, surface chemistry also plays a role in the uptake of NP through the olfactory epithelium into the brain. Therefore, it is recommended that for testing an NP formulation, the surface modification procedure and its effects on typical surface properties as zeta potential and surface reactivity should be known [27].

2.6 Nanoparticles: explaining epidemiological findings with particulate matter?

Studies with inhaled NP have forwarded several major mechanisms by which the ultrafine component of PM may cause responses that explain the mortality in those with existing pulmonary and cardiovascular diseases [1; 28]. Mechanisms to explain for these effects can be discriminated into direct and indirect pathways, as effects by particles themselves or processes induced by particles (mainly in the lung). As a mechanism for direct effects of NP a series of studies have addressed the issue whether NP can translocate from the lung to the circulation, and exert their effects when being in the systemic circulation. However, quantitative estimates of translocation range between 50 % of ^{13}C NP (26 nm size) within 24 hours in a rat model to less than 1 % using 18 nm Iridium particles in vivo or in isolated perfused. This wide variation shows that apart from particle size, particle surface chemistry and maybe particle charge may be important parameters determining the translocation of NP from the lung. Apart from particle characteristics, also epithelial and endothelial permeability are considered to play a role. Recently, carbonaceous NP were shown to translocate from the nasal cavity along the same pathway to the central nervous system (CNS), based on their presence in the olfactory bulb of rats after inhalation [19]. Such a mechanism was first reported for polio virus (30 nm) in monkeys and was later described for nasally deposited colloidal gold particles (50 nm) moving into the olfactory bulb of squirrel monkeys. Among indirect effects inflammation has been considered to affect target organs by lung mediators that become systemically available. However, inhalation studies with NP at particles numbers found in the general environment did not demonstrate pulmonary inflammation as described at higher doses. Two mechanisms have been supposed that could be considered as indirect mechanisms:

- *Seaton* et al suggested that in susceptible individuals, exposure to NP will invoke alveolar inflammation, and that the release of inflammatory mediators can trigger systemic hypercoagulability of the blood thereby increasing the risk for cardiovascular events [29].

- A second mechanism is the progression and destabilisation of atheromatous plaques by inhalation of PM [30]. Although this mechanism remains to be investigated using NP, NP properties should be able to invoke the same destabilisation mechanisms (inflammation, LDL oxidation, lipid peroxidation) as the PM used in earlier studies.

A large series of molecular epidemiological studies have supported aspects of the plausibility of the above mechanisms. A large multinational trial on cardiovascular risks (MONICA) performed between 1984 and 1988, reported a higher blood viscosity and C-reactive protein [10; 31; 32] during an air pollution episode that coincided with the survey in 1985. Recent studies from the same research group in Erfurt (Germany) have identified combustion NP as an important variable explaining cardiac deaths due to increased ambient particle exposure. In fact, the association increased the smaller were the particles and individuals with cardio-vascular diseases were more likely to die than others. Clearly further research is needed, but the research reported to date has direct relevance to public-health policy, since both coal-burning and traffic emissions continue to be major sources of NP exposure worldwide. Recent cohort and intervention studies in the Netherlands and Ireland have demonstrated the importance of regulation combustion derived particle emissions [33; 34].

3 Conclusions and recommendations

As discussed earlier on, one of the crucial questions is whether the hazards and risks of inhaled bulk and combustion NP can be extrapolated to engineered NP as used in their widely different productions and applications in nanomaterials. Concern, however, is at place and illustrated by a recent example from drug delivery [35]. In the latter publication NP are being advocated by the National, Heart, Lung and Blood Institute (NHLBI) for exploration in atherosclerosis, inflammatory lung diseases, diabetes, and hemorrhagic disorders. When knowing the effects of inhaled combustion NP or PM_{10} in these patient groups, a striking discrepancy emerges between the anticipated therapy and the observation that these patients are the primary targets at air pollution episodes. Secondly, since the epidemiology of combustion NP (PM) has

identified those with chronic obstructive pulmonary disease (COPD), asthma and cardiovascular disease as the risk groups, it needs careful consideration whether animal models for these diseases should be used and developed to test hazards of engineered NP.

Communication and open minds are needed for exchange of know-how and testing methods between inhalation toxicologists and those active in nanomaterials. Interactions between both areas of research need to be established. This exchange will have to lead to common know-how that can be used to develop both safe and sustainable nanomaterials.

Acknowledgements

The authors are indebted to many collaborators in the development of their know-how in this area. In particular, collaboration with *Ken Donaldson* (ELEGI, Edinburgh), *Wolfgang Kreyling* (GSF, Munich), *Roel Schins* (IUF, Dusseldorf), *Germ Visser* (DSM research, Heerlen) and *Detleff Müller-Schulte* (Magnamedics GmbH) has generated a lot of the thinking that is included in this chapter. In addition, *Catrin Albrecht*, *Doris Hoehr* and *Welf Mahlke* are acknowledged for the use of their work on lung microscopy.

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Epidemiology of ultrafine particles [1]

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1 Abstract

Research into ambient particle pollution as it affects human health has gone on for several decades now. Thanks to the improvements in the reduction of particle emissions, the significance of this topic has seemed to decline. However, over the last several years, it has become obvious that the reduction in ambient particle concentration has largely been the result of a reduction in larger (coarse) particles. With regard to respirable fine and ultrafine particles (aerodynamic diameters < 2.5 and $0.1\ \mu$m), this reduction is now proving to have been much less substantial. Even more, for many years there has been an increase in the concentration of ultrafine particles in the air we breathe.

After improvements in atmospheric measurement methods it was possible to study the effects of fine and ultrafine particles on human health. The international literature has consistently shown that current ambient concentrations of fine particles have led to an observable short-term impact on daily mortality – especially on cardiovascular and respiratory causes – as well as on the number of hospital admissions for these diseases, on worsening symptoms among asthmatics and among patients with chronic respiratory diseases, and on increases in medication use of these patients. A small number of studies on ultrafine particles also show that the effects of these are independently relevant, in addition to those of fine particles. Long-term studies additionally show that exposure to higher concentrations of fine particles can lead to a reduction in life expectancy by about one to two years.

[1] This manuscript is a largely identical translation of the article
Wichmann, H. E.: Epidemiologische Erfahrungen zur Wirkung von Fein- und Ultrafeinstäuben. In: *Mücke, W.* (ed.): Wirkung und Erfassung von Fein- und Ultrafeinstäuben, Tagung 14.2.2002. Munich. Altendorf: Gräbner 2002

Due to these findings, important international organisations have named particle contaminations as the most important problem in the hygiene of respiratory air.

2 Introduction

The following definitions are used when referring to particles or aerosols:

- Total Suspended Particulates (TSP) includes particles of < 15 µm in diameter measured using the current technique of β absorption. Older gravimetric measurements included particles of up to 35 µm.
- Inhalable suspended particulates include particles < 10 µm (PM_{10}).
- Respirable suspended particulates include particles < 2.5 µm ($PM_{2.5}$). This is also called fine particulates (FP). Sulphate can also be used as a marker for fine particels.
- Ultrafine particles (UP) include particles < 0.1 µm.

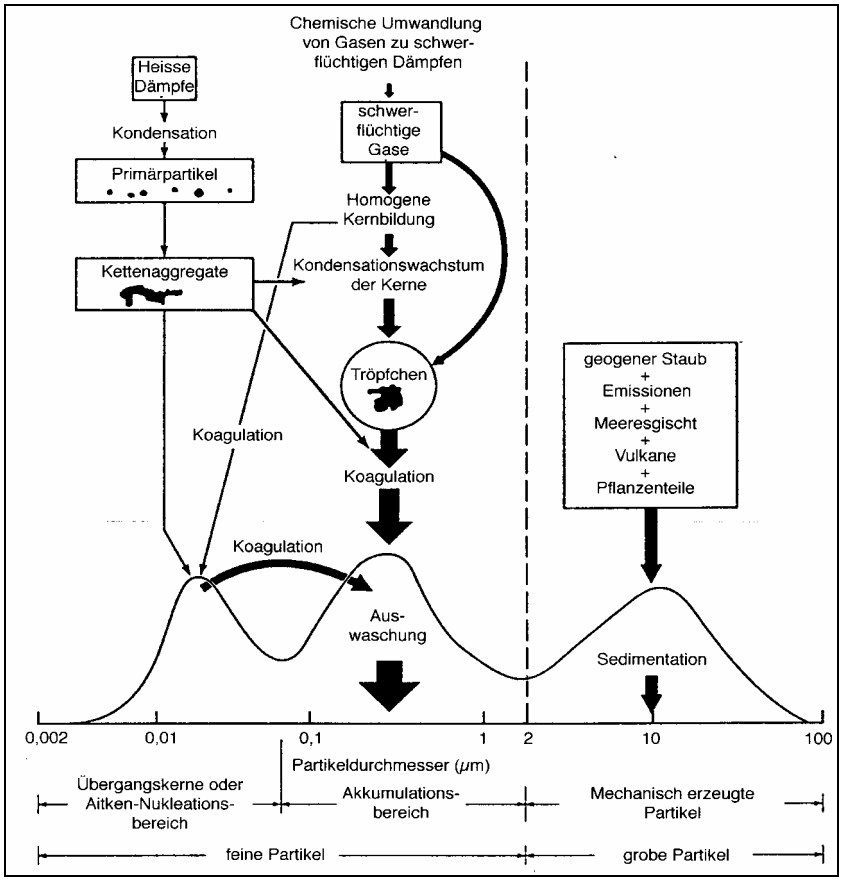
Aerosols are spread in the air in a dispersion. Solid aerosols are generally called particles, but also gases and liquids can coagulate to form aerosols in the atmosphere. Particles originale both from natural sources (marine aerosols, geological mineral dusts, and bioaerosols) and from a number of human-based sources.

These particles or aerosols by no means form static systems, but instead form systems undergoing constant change. Ultrafine particles can coagulate due to their highly diffusive intrinsic mobility, leading to the formation of larger particles (Figure 1, see page 61).

The life cycle of ultrafine particles can range from fractions of a second up to several hours, depending on the aerosol concentration and the thermodynamic conditions. Once the particles have exceeded a diameter of 0.1 µm, their diffusion speed decreases to the point that their life cycle in the airborne state extends up to several weeks. This range of relatively stable particles with diameters from 0.1 to 1 µm is called the

accumulation mode. This means that these fine particles can be transported over long distances (up to several 1,000 km). Cloud formation and rainfall are the reasons that mainly cause the particles to be washed out of the atmosphere. They can also be deposited dry.

Figure 1:
Schematic presentation of the coagulation processes in suspended particulates (from *Spengler*, et al. [1])



Heisse Dämpfe = hot vapours, Kondensation = condensation, Kettenaggregate = chain aggregates, Koagulation = coagulation, chemische Umwandlung von Gasen zu schwer flüchtigen Dämpfen = chemical transformation of gases to low volatile vapours, schwer flüchtige Gase = low volatile gases, homogene Kernbildung = homogeneous core formation, Kondensationswachstum der Kerne = condensational growth of the cores, Tröpfchen = droplets, Auswaschung = washing out, grober Staub = coarse dust, Emissionen = emissions, Meeresgischt = sea spray, Vulkane = volcanoes, Pflanzenteile = plant matter, Sedimentation = sedimentation, Übergangskerne oder Aitken-Nukleationsbereich = transitional cores or Aitken nucleation range, Partikeldurchmesser (µm) = particle diameter (µm), Akkumulationsbereich = accumulation range, Mechanisch erzeugte Partikel = mechanically produced particles, feine Partikel = fine particles, grobe Partikel = coarse particles

Ultrafine particles are captured in the presence of fine and large particles (scavenging effect). Overall, the reduction of larger particles with increasing air cleaning measures in the past may have led to a decrease in the effectiveness of the scavenging effect today. This explains why the ultrafine particle concentration in the environment may have risen, even if fewer ultrafine particles are currently emitted (see below).

Depending on the fuel and technology used, all combustion processes release larger or smaller quantities of particulate emissions (primary particles). The particles differ in their chemical compositions, their surface structures, and their diameters. The physico-chemical properties thus affect both their transmission and their ambient concentrations. They thereby influence the transport of particles, the length of time they stay in the atmosphere, and their deposition in the environment, or inhalation into the lungs.

Currently, only estimates from Great Britain are available as to the sources of ultrafine particles (Figure 2, see page 63, Airborne Particle Expert Group – APEG [2], *Harrison*, et al. [3]). More than 60 % of the ultrafine dusts there came from road traffic, and the proportion with traffic as a source was even higher in London.

In Germany, the size distribution of particles has been measured in Erfurt since 1991. The measurements have covered the size range of 0.01 to 2.5 µm. A typical distribution of the particle number and the particle mass is presented in Figure 3 (see page 63). In the period between September 1995 and December 1998, 58 % of the number concentration (NC) was of particles between 0.01 and 0.03 µm, and 88 % was of ultrafine particles. In contrast to this, only 3 % of the mass was found under 0.1 µm, 78 % between 0.1 and 0.5 µm, and 95 % under 1 µm. $PM_{2.5}$ was 83 % of PM_{10} and 66 % of TSP. The following average immission concentrations were measured: 16,000 ultrafine particles/cm³, 26 µg $PM_{2.5}$/m³, 38 µg PM_{10}/m³, 49 µg TSP/m³ (*Wichmann*, et al. [4]).

Figure 2:
Sources of PM_{10}, $PM_{2.5}$, $PM_{0.1}$ (ultrafine particles) in Great Britain 1996 (APEG [2])

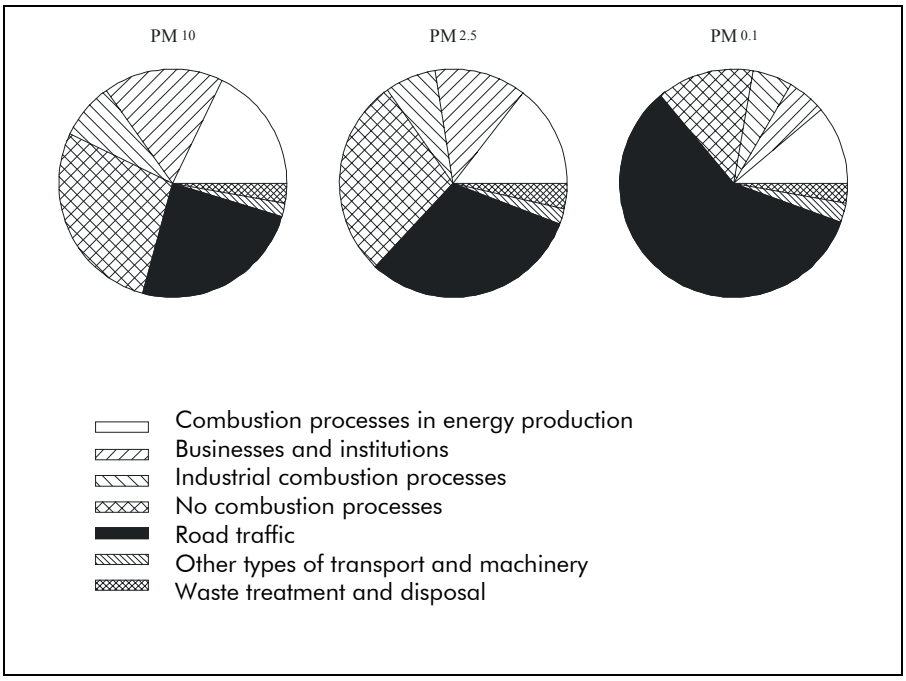
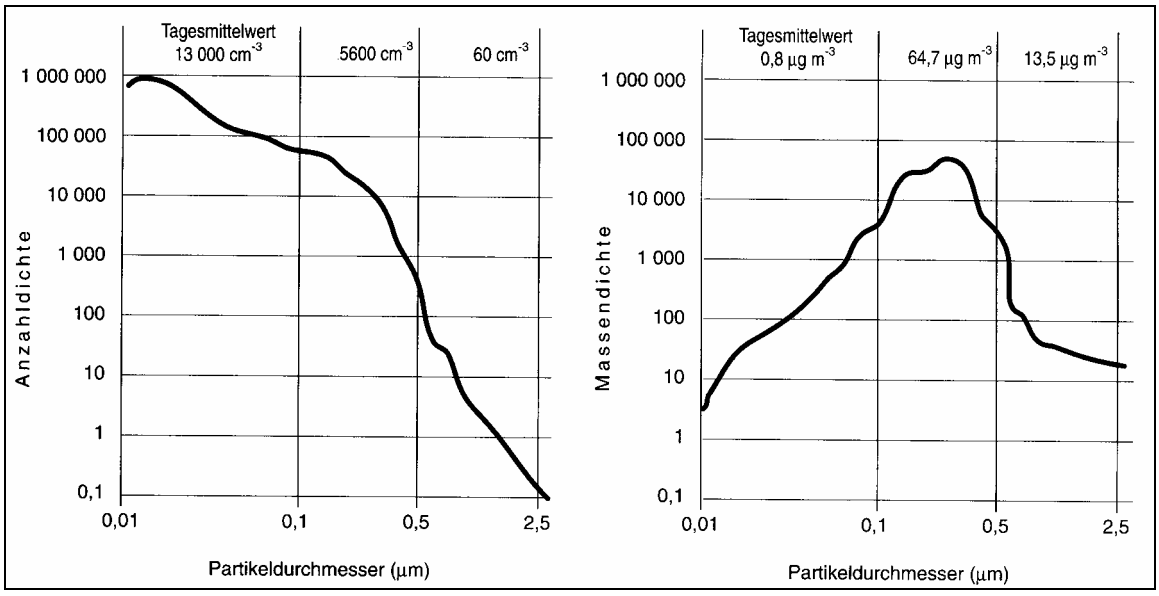


Figure 3:
Distribution of the numbers and the mass of particles with diameters between 0.01 and 2.5 µm, measured in Erfurt in the winter of 91/92, from *Peters*, et al. [5]



Tagesmittelwert = daily average, Anzahldichte = number density,
Massendichte = mass density, Partikeldurchmesser = particle diameter

The chronological trend of the number and mass concentration is presented in Figures 4 and 5 (see page 65). After a marked rise, the total particle count (0.01 to 2.5 μm) has been relatively stable since 1995/96. This also holds true for ultrafine particles (0.01 to 0.1 μm. The smallest fraction (0.01 to 0.03 μm) of nucleation particles rose in comparison, especially in terms of their proportion as a percentage (Figure 4). In contrast to this, $PM_{2.5}$ decreased considerably during the observed period (Figure 5). The measurements of particles in outdoor air showed the greatest seasonal variation, with the highest concentrations in winter. The concentration of ultrafine particles had a marked weekday effect, with 40 % lower concentrations on the weekend in comparison to the concentrations during the week. This and a clear increase during the hours with the most traffic indicate that motorcars were a significant source of ultrafine particles.

Figure 4:
Seven-year trend of relative number concentrations (NC in percentages) for different particle size classes (0.01 to 0.03, 0.03 to 0.05, 0.05 to 0.1, 0.1 to 0.5 μm diameter; columns from left to right) in Erfurt, Winter 1991/92 to 1998/99. The proportion in the smallest size class increases continuously (from *Wichmann*, et al. [4]).

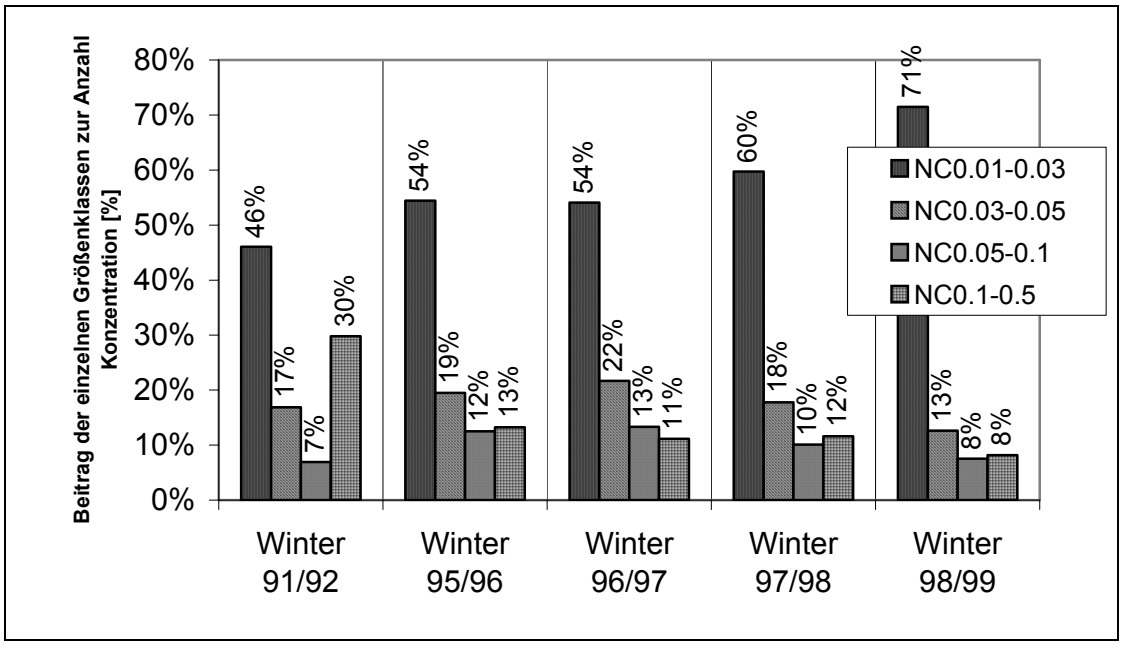
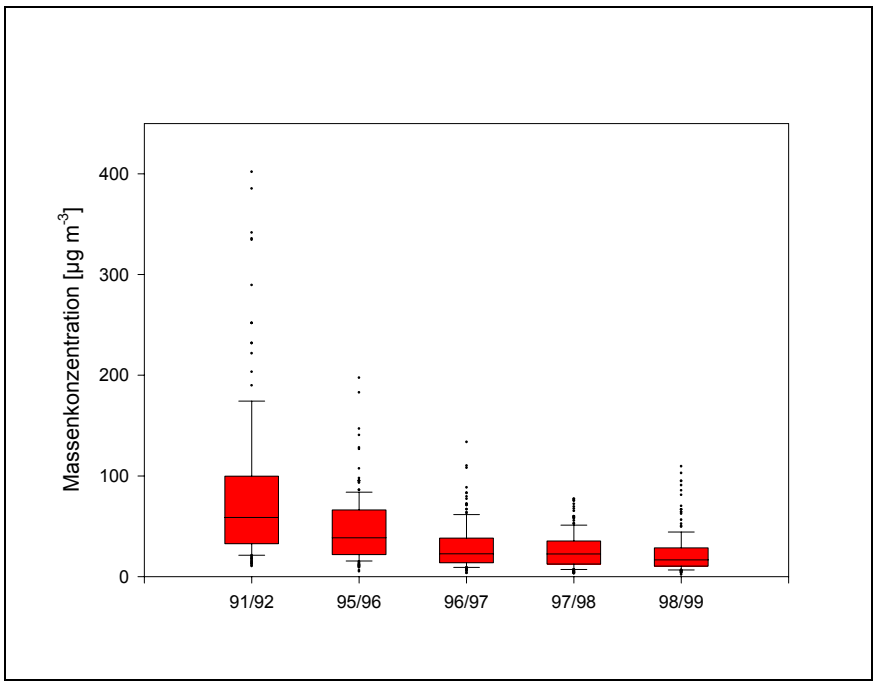


Figure 5:
Seven-year trend of mass concentration of fine particles ($PM_{2.5}$) in Erfurt, Winter 1991/92 to 1998/99 (from *Wichmann*, et al. [4])



Massenkonzentration = mass concentration

Ultrafine particles have since been measured in Finland, the Netherlands, and Germany (*Kreyling*, et al. [6], *Ruuskanen*, et al. [7]). The concentrations were between 15,000 and 20,000 particles/cm³ on average per year.

3 Exposure of humans

The individual exposure to suspended particulates is the sum of the ambient exposure the contribution of indoor sources, and the contribution of personal activities. A large number of studies tried to determine personal exposure (*Ott*, et al. [8], US EPA [9], *Jantunen*, et al. [10], WHO [11]) or to model it (*Samet*, et al. [12], *Wilson*, et al. [13]). In summary, the most important sources of particulate mass concentration indoors are the soil brought in from the outside, resuspended soil, and particles from personal activities, as well as pollutants from motor vehicles, industrial sources, secondary sulphates, and ocean salt, which all come from outdoor air. The smaller the particles are, the larger is their penetration from outdoors to indoors. Overall, there is a low

correlation between outdoor air concentrations and measured concentrations indoors and in personal monitoring. This is apparently due to the wide variation from person to person in the exposure to non-outdoor air sources. This helps explain the apparent paradoxon that statistical interrelationships have been found between health effects and ambient concentrations (see below), even though people spend their time primarily indoors: particles from outdoor air and from indoor air can be considered as being independent pollutants whose effects must be separately considered.

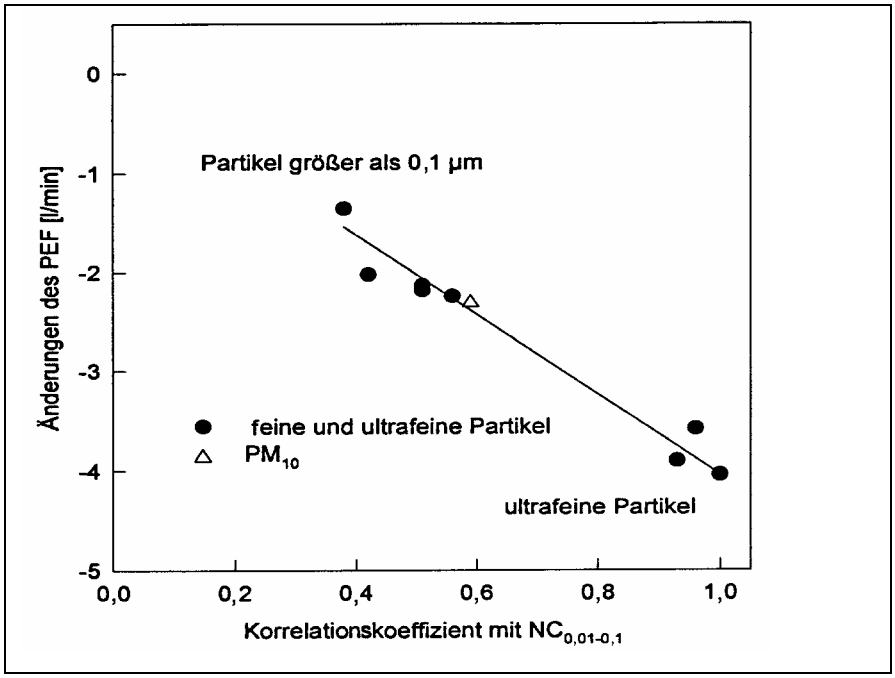
4 Epidemiological studies on short-term effects

By far the largest number of epidemiological studies on the suspended particulate problem were conducted on short-term effects where the objective was to determine whether an increase in morbidity or mortality in the general population or in selected test subjects or patients was measured after these had experienced high particle concentrations with effects occurring on the same day, or only after several days' delay. The findings are summarised and evaluated by US EPA [9, 14], WHO [11; 15; 16], and *Wichmann*, et al. [17]. Older studies rely on measurements of TSP and PM_{10}; newer studies increasingly use $PM_{2.5}$ and individual ultrafine particles. The following sections present studies primarily conducted in Germany, thus allowing us to draw more precise conclusions on the situation here.

4.1 Lung function and respiratory symptoms

Symptoms of the upper and the lower airways, as well as cough, increase with rising particle concentrations; lung functioning, measured as PEF, FEV1, or FVC, decreases. Many of these studies were conducted on asthmatics, in whom the use of medication also increased with higher exposure. In Germany, diary studies in adults with asthma showed reactions to fine and ultrafine particles, whereby the effects of ultrafine particles were somewhat greater (Figure 6, see page 67, *Peters*, et al. [18]). Studies in Finland resulted in similar findings (overview in *Wichmann*, Peters [19]).

Figure 6:
Changes in lung function in asthmatics depending on ambient particles (for the inter-quartile range). The ultrafine particles are associated with a more pronounced decreasein lung function more than is the case with fine particles or with PM_{10} (according to *Peters*, et al. [18])



Korrelationskoeffizient = coefficient of correlation
Änderungen des PEF = change of PEF
feine und ultrafeine Partikel = fine and ultrafine particles
Partikel größer als … = particles larger than …

4.2 Cardiovascular endpoints

Germany experienced an episode of pollution with a high particle concentration in January 1985. During this episode, patients with cardiovascular disease in the Rhine-Ruhr region saw an increase in hospital admissions (+ 19 %) and ambulance transports (+ 25 %). The increases of hospital admissions due to coronary heart insufficiency (+ 30 %), arrhythmia (+ 49 %), and cerebral circulatory problems (+ 57 %) were particularly notable (*Wichmann*, et al. [20]).

The pollutant concentrations also increased in Augsburg during this episode, but without reaching levels that would cause the German directive on smog to come into effect. At that time, only total suspended particulates were measured, but one may assume that these included a considerable proportion of fine particles that were transported to

Augsburg by eastern wind (*de Leeuw*, et al. [21]). The data on blood plasma viscosity in Augsburg that were available from this episode and from other periods were assessed to test the hypothesis of *Seaton*, et al. [22], that blood flow could be slowed by particles. A two- to three-fold increase plasma viscosity was observed above the 95th percentile, which can be considered as a risk for myocardial infarction (*Peters*, et al. [23]; *Koenig*, et al. [24]). The increase in plasma viscosity is probably caused by the particles deposited in the lungs initiating an inflammatory reaction that influences blood clotting via an acute phase reaction. As the C reactive protein (CRP) is a sensitive parameter for inflammation, tissue damage, infection, and a risk factor for heart attacks, the corresponding Augsburg data were further analysed. This analysis showed that the effects of the particles and the episode on CRP were even more pronounced than were their effects on plasma viscosity (*Peters*, et al. [25]; *Koenig*, et al. [26]). Heart rate is to be considered an independent marker for the autonomous control of the heart. Its influence could also be studied using the Augsburg data. The heart rate increased in the 1985 smog episode, where the strongest connection was made to suspended particulate concentrations (*Peters*, et al. [27]). The observed effect was also particularly pronounced among individuals who also had elevated plasma viscosity (*Peters*, et al. [28]). The analyses of the effects of airborne pollutants on blood pressure provided more evidence that the cardiovascular risk profile can worsen depending on particle exposure. Individuals who also showed elevated plasma viscosity and a faster heart rate were particularly affected (*Ibald-Mulli*, et al. [29], Table 1, see page 69).

Other studies indicated comparable effects on the fibrinogen concentration, as in a study in London and in a national study in the USA as well as in animal experiments (overview in *Wichmann*, et al. [17]). An increase in heart rates depending on particle concentration was also observed in a study on senior citizens in the US. Other studies there on the effects of airborne pollutants on heart-rate variability also supported a possible influence of particles on autonomic control of the heart (*Liao*, et al. [31], *Pope*, et al. [32; 33], *Gold*, et al. [34]). The question of whether particles show evidence of influencing manifest clinical symptoms was investigated in Boston. Patients with implanted defibrillators suffering from coronary heart disease were studied to find out if there was a connection between airborne pollutant concentrations and therapeutic

discharge of the devices due to tachyarrhythmias or ventricular fibrillation. The frequency of therapeutic discharge rose depending on the particle concentration and NO_2 (as a marker for road traffic) (*Peters*, et al. [35]). Further North American studies showed that hospital admissions for cardiovascular diseases rose on days with elevated particle concentrations (overview in US EPA [9], *Wichmann*, et al. [17]). The presence of a cardiopulmonary disease appears to make individuals more susceptible to the effects of pollutants (*Peters*, et al. [28], *Zanobetti*, et al. [36]).

Table 1:
Summary of the changes in cardiovascular parameters in the framework of the MONICA cohort in Augsburg as related to airborne pollutants [18; 27; 29; 30]

		Men		**Women**	
		OR	**(95% CI) ***	**OR**	**(95% CI)**
Plasma viscosity above 95th percentile (*Peters* et al. [18])					
Episode		3.62	(1.61; 8.13)	2.26	(0.97; 5.26)
SO_2	100 µg/m³	1.54	(0.90; 2.61)	2.03	(1.17; 3.53)
TSP	100 µg/m³	1.75	(0.79; 3.89)	2.30	(0.92; 5.79)
CRP above 95th percentile (*Peters* et al. [30])					
Episode		24.5	(2.48; 242.1)		
SO_2	100 µg/m³	2.93	(1.19; 7.20)		
TSP	100 µg/m³	3.60	(1.46; 8.86)		
		Average change	(95% CI)	Average change	(95% CI)
Heart rate [beats per min.] (*Peters* et al. [27])					
Episode		1.38	(-0.08; 2.83)	2.29	(0.71; 3.88)
SO_2	100 µg/m³	1.28	(0.52; 2.04)	1.34	(0.51; 2.17)
TSP	100 µg/m³	1.79	(0.42; 3.16)	1.66	(0.29; 3.03)
Systolic blood pressure [mm Hg] (*Ibald-Mulli* et al. [29])					
Episode		0.20	(-1.83; 2.24)	0.61	(-1.73; 2.96)
SO_2	100 µg/m³	1.20	(0.09; 2.31)	1.20	(-0.58; 2.98)
TSP	100 µg/m³	1.37	(-0.34; 3.08)	2.48	(0.54; 4.41)

* CI = Confidence interval, OR = Odds Ratio

4.3 Visits to general practioners (GP) and hospital admissions

Studies on visits to general practitioners in Paris and London indicated that there were relationships between airborne pollution and asthma as well as other diseases of the respiratory tract and – somewhat weaker – cardiovascular disease. The significance of these studies, all of which are based on the information provided by independent practitioners, is that they show that suspended particulates can affect more individuals than the hospital admission rates alone seem to suggest, both in terms of the numbers of people affected and in terms of the strength of the effects themselves. In general, these studies show that only looking at hospital admission figures can lead to a marked underestimation of the number of severe respiratory problems in the population (US EPA [9]). The most important European study on hospital admissions was the APHEA study, which was conducted in 15 European cities (with German participation). Particles and sometimes other pollutants were found to influence admission rates due to respiratory diseases and especially due to COPD (chronic obstructive pulmonary disease) and asthma (*Anderson*, et al. [37], *Schouten*, et al. [38], *Spix*, et al. [39], *Sunver*, et al. [40]). Additional studies on hospital admissions in Paris and Birmingham supported these observations, as did countless studies from North America (*US EPA* [9]). The NMMAPS study (National Morbidity, Mortality, and Pollution Study) in particular merits mention, which was conducted in 14 cities and which indicated the highest particle effects on hospital admissions due to respiratory tract disease, followed by cardiovascular disease (*Samet*, et al. [41]).

4.4 Low birth weight

A few studies report that there is a relationship between particle concentrations and low birth weight, diminished birth rates, and the number of premature births, although these relationships cannot be considered as conclusive (overview in US EPA [9], *Wichmann*, et al. [17]).

4.5 Mortality

For some time now, a clear relationship has been observed between suspended particulates and daily mortality, supported above all by North American studies

(US EPA [14], WHO [15]). Further, more comprehensive studies are now available using $PM_{2.5}$ and in part UP alongside TSP and PM_{10} (Overview in US EPA [9]). The following description is restricted to larger international studies and studies from Europe and especially from Germany.

In the APHEA study, the influence of particles and other airborne pollutants on mortality was investigated in 15 European cities (*Katsouyanni*, et al. [42]). Greater effects were found in the Western European cities than in the Central and Eastern European cities. In addition, a tendency for greater effects of NO_2 was noted in cities with higher particle concentrations. The authors explored the idea that the short-term effects of NO_2 on mortality could be due to other motor vehicle components (*Touloumi*, et al. [43]). Studies on cause-specific mortality indicated greater effects for respiratory causes of death in comparison to cardiovascular causes of death (*Zmirou*, et al. [44]). The APHEA 2 study, which was expanded to cover 29 European cities, showed effects of particles comparable to those shown in APHEA. The effects were more intense for older individuals. The particle effects were also greater in cities (where NO_2 levels were also higher), in warm climates, and at lower base mortality. These specific characteristics of individual cities could explain the observed heterogeneity among those cities. In particular, the authors interpret the common effects of NO_2 and particles as an indication that the particles from motor vehicle exhaust are more toxic than are other particles (*Katsouyanni*, et al. [45]).

The NMMAPS study was conducted in the USA. This study investigated the effects of particles and other pollutants on mortality in the 20, and then 90, largest cities in the USA (*Samet*, et al. [41]). The study found a rise in overall mortality that is comparable to the results of the APHEA study and somewhat lower than the results of the summary estimates in [16]. The most intense particle effects were apparent in the north-eastern US, followed by the industrial Midwest and southern California. The increase in cardiovascular and respiratory mortality was somewhat higher. Importantly, an extensive analysis was conducted on the inclusion of other pollutants. The analysis showed that other pollutants had little influence on the estimates of the particle effects.

Extensive experience with the short-term effects of airborne pollutants is also available from Germany. In the Rhine-Ruhr region, several smog episodes in 1962, 1979, and 1985 showed an increase in mortality. Whenever a separate analysis was conducted, suspended particulates were found to have greater effects than did SO_2 (*Steiger* and *Brockhaus* [46]; *Steiger* [47]; *Wichmann*, et al. [20; 48 to 50]; Peters, et al. [23; 27; 28; 35]). Corresponding results came from the former GDR, where mortality was investigated in Erfurt from 1980 to 1989 and in Thuringia from 1985 to 1989 and from 1991 to 1995. These studies also showed that the particle-associated size had the greatest effects (*Spix*, et al. [51 to 53], *Wichmann*, et al. [54, 55]). A study on the influence of particle size on mortality was conducted in Erfurt from 1995 to 1998 (*Wichmann*, et al. [4]). Associations were found between mortality and particle number and particle mass concentration. Immediate effects (with manifestation in 0 to 1 day) and delayed effects (with manifestation 4 to 5 days after exposure to the pollutants) were observed. The immediate effects appeared to be more closely associated with mass concentration (i. e. with fine particles) than with number concentration (i. e. with ultrafine particles), and the reverse was found for delayed effects. There was also a tendency towards more immediate effects for respiratory causes of mortality and more delayed effects for cardiovascular causes of mortality.

4.6 Interpretation of studies on short-term effects

Substantial questions on the interpretation of studies on short-term effects are discussed in detail in *Wichmann*, et al. [17]:

- It should be assumed that "premature mortality" is a real phenomenon. Early mortality in older studies with high concentrations of classic pollutants was between one to two weeks. Newer studies showed, however, that these pollutants can result in a loss of months or even years of life. Yet studies of short-term effects are not suitable for predicting the long-term effects of particles.

- In most morbidity and mortality studies, the relationship to the suspended particulate mass appeared either without delay or after only one day. Studies on ultrafine particles indicated delays of several days, but these delays still need verification

from further studies. In general, considering several days' overages (e. g. the average over the past five days) often shows greater effects than considering individual days.

- The question of potential confounding by meteorology was comprehensively analysed in [14]. There is accordingly no suggestion that the pollutant effects can be mimicked by meteorological influences. Nonetheless, it is important to model the influences of temperature and humidity adequately in order to obtain a valid quantification. Here, it must be kept in mind that adverse health effects can arise at both high and low temperatures. In mortality studies, the role of influenza epidemics must also be considered, since this also has a strong influence on mortality.

- Due to the existing correlations between daily concentrations of suspended particulates and gaseous airborne pollutants – which can be caused by the weather or by the presence of a common source – localising the effects of different pollutants can, on the one hand, be difficult, while it is, on the other hand, of great practical significance. One suitable method is to compare the strength of the effects when considering individual pollutants as well as using models that take more than one pollutant into consideration. This method is at best exemplified in the NMMAPS study (*Samet*, et al. [12, 41]): The authors analysed health effects of the gases ozone, nitrogen dioxide, sulphur dioxide, and carbon monoxide alongside the particles (PM_{10}). Including these gases only changed the risk estimates for particles marginally in comparison to the single pollutant model. In particular, the estimate remained statistically significant increased. Conversely, the effect estimates for the gases that were increased in the single pollutant model decreased when the particles were taken into the model. Overall, confounding of the risk estimates for particles due to gaseous pollutants can be largely ruled out.

- For Germany, the question of health effects of sulphur dioxide in addition to effects of particles was investigated. The results of the studies on mortality in Erfurt provide a good basis for this question because they cover a long period of time during which dramatic changes occurred to the composition of the pollutants and to their concentrations. Whereas the effect estimates for 10 $\mu g/m^3$ total suspended

particulates remained practically unchanged from 1988 to 1998, the effect estimates for sulphur dioxide changed dramatically by a factor of 43 (*Wichmann*, et al. [4]). This suggests that sulphur dioxide was not the causal factor, but instead that it was an indicator for something else.

- Ultrafine particles, nitrogen dioxide, and carbon monoxide exhibited comparable patterns. The changes in their concentrations differ little between summer and winter, but there are pronounced fluctuations during the week, with much lower concentrations at the weekend. This suggests motor vehicle traffic is the common source. These pollutants all indicated an effect on mortality that was delayed by several days (*Wichmann*, et al. [4]).

- It is important to know whether the particles are natural (crustal particles) or of human origin. The distinction can be made by studying dust storms. When studying dust storms in the Midwestern US, *Schwartz*, et al. [56], found no increase in mortality even though the elevated particle exposure caused by these phenomena should have had considerable effects. The authors concluded that there was no indication that particles from dust storms had any influence on daily mortality. Studies in Utah (*Pope*, et al. [33]) produced similar conclusions. *Laden*, et al. [57], analysed the role of natural dust particles as a proportion of fine dust on daily morbidity on the basis of data on the elementary composition of the particles. In a regression analysis, they found the greatest increase for fine particles from mobile sources, followed by a weaker effect of particles from burning coal. Particles from crustal materials were not connected with any rise in mortality.

- The available comprehensive epidemiological data do not point to the existence of a threshold value for suspended particulates. The thorough analysis of this question in the NMMAPS study should be noted (*Samet*, et al. [12, 41], *Daniels*, et al. [58]). The existence of a threshold value was analysed on the basis of the data from the 20 largest cities in the US while using different models for the dose-effect relationship. It was found that the results fit best to a linear model without a threshold value for both total mortality and for cardiopulmonary mortality. It should also be noted that the finding that no threshold value can be found for the general population

does not contradict a threshold value at the individual level. *Schwartz*, et al. [59], thus discuss the fact that it is mathematically nearly impossible to find a threshold value for the overall population even if different threshold values exist for individuals. Also, the variability in personal exposure from person to person plays a statistical role in comparison to the concentrations recorded at measurement stations.

- What portion of the population is at-risk? The deterioration in the health of patients with cardiovascular disease is substantiated by both mortality and morbidity. The available studies also show physiological changes to the heart and to blood coagulation, in agreement with the findings of the animal experiment studies. Numerous short-term effects were also described in epidemiological studies on respiratory tract diseases. In most cases, this meant a deterioration in the existing disease, although acute respiratory infections can also be considered as the presence of a new disease. Numerous studies found acute respiratory symptoms in connection with suspended particulate pollution, while asthma patients were particularly sensitive. Some studies also found a reduction in lung function. The agreement between toxicology and epidemiology under identical conditions is quite remarkable. Thus, the study by *Pope*, et al. [60], during a strike at a steel mill in Utah Valley found a drop in hospital admissions due to respiratory disease in comparison to the years before and after the strike. An animal study conducted by the US EPA, where particles collected from Utah Valley were instilled in rats, indicated changes of several health-related parameters – but not for dusts collected during the year of the strike [9]. Age also proves to be an important factor in epidemiological studies. The increased susceptibility to suspended particulates among the very young and the very old is probably related to the fact that both groups are quite often affected by existing diseases.

- Most epidemiological studies on short-term effects of suspended particulates are from North America and Europe, but findings from other regions of the world are also increasingly available. Despite the very different conditions in these regions and nations, the findings are surprisingly similar both quantitatively and

qualitatively. This suggests there is a general transferability between different countries, although regional peculiarities do exist at a more detailed level.

4.7 Quantitative estimation of the short-term effects of particles

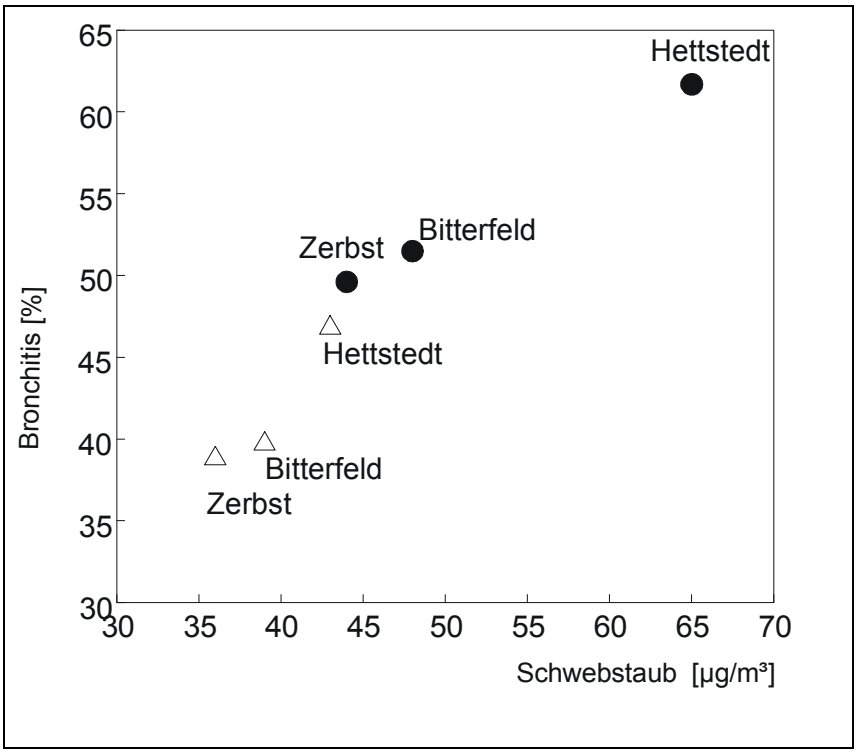
The best quantitative estimates of particle effects are currently possible on the basis of PM_{10} and $PM_{2.5}$. Although there are numerous studies available on the influence of total suspended particulate (TSP), this also includes that coarse particles are of lower relevance for the health effects. Ultrafine particles should be considered as potentially relevant, yet the few studies that are available do not allow precise quantitavies estimates that could serve as the basis for setting environmental standards.

5 Long-term effects

5.1 Cross-sectional studies on lung function and on respiratory tract symptoms

Respiratory health of school-age children was studied in 24 US and Canadian cities and in 12 cities in southern California. Researchers found connections with fine and inhalable particles that were only partially consistent for respiratory disease, especially bronchitis, as well as for lung function (*Dockery*, et al. [61], *Raizenne*, et al. [62], *Peters*, et al. [63, 64]). In ten and then in eight cities in Switzerland, similar studies were conducted on school-age children and adults. Whereas respiratory symptoms and bronchitis in children were associated with all pollutant parameters, an influence of PM_{10} was found in the lung functioning of adults (*Braun-Fahrländer*, et al. [65], *Ackermann-Liebrich*, et al. [66]). In Germany, a connection was found between diseases of the upper respiratory tract in children in Leipzig and their exposure to suspended particulates and other pollutants (*von Mutius*, et al. [67]). Studies were also conducted repeatedly on school-age children in three places in Saxony-Anhalt. The manifestation of bronchitis and infectious diseases (but not of asthma and allergies) decreased markedly as the air quality improved. The association with suspended particulates was the strongest (*Heinrich*, et al. [68], Figure 7, see page 77).

Figure 7:
The prevalence of bronchitis in 5- to 14-year-old children in Hettstedt, Bitterfeld, and Zerbst (Saxony-Anhalt) in the years 1992/93 (•) and 1995/96 (Δ) as related to suspended particulates (Schwebstaub) (*Heinrich*, et al. [68])



5.2 Prospective cohort studies

With respect to long-term effects the validity provided by cohort studies is greater than that of cross sectional studies. Only three cohort studies are available from the USA. The Harvard six cities study observed some 8,000 adults between 14 and 16 years of age in the Northeast and in the Midwest. Sulphate and $PM_{2.5}$ showed the greatest effects. The mortality in the city with the highest pollution of fine particles was 26 % higher than in the city with the lowest rate of pollution for such particles (*Dockery*, et al. [69]). The study conducted by the American Cancer Society observed some 550,000 adults in 154 cities over a period of seven years, finding a relationship between exposure to sulphate, which can be considered as proxy for fine particles. In places for which $PM_{2.5}$ measurements were available, this parameter showed the greatest effects. The difference between the cities with the highest and with the lowest pollution was 17 % in terms of the overall mortality. Cardiopulmonary mortality showed greater

differences (*Pope*, et al. [70]). In California, some 6,500 non-smoking Adventists over 15 years of age were studied. Relationships were found between total mortality – in particular, the mortality among individuals with respiratory diseases – and PM_{10} and sulphate (as a marker for fine particles). These relationships were more pronounced among males (especially those who spent a lot of time outdoors) and less pronounced among females. For lung cancer, elevated risks were found in connection with all the pollutants studied, but these were not always consistent (*Abbey*, et al. [71], US EPA [9]).

Table 2:
Comparison of the relative risks for total mortality as related to fine dusts in three prospective cohort studies (from US EPA [9])

PM Index	Study	Group	Relative Risk
PM_{10} (50 $\mu g/m^3$)	Six Cities	All	1.504[x] (1); 1.530[x] (2)
		Male non-smokers	1.280 (1)
	AHSMOG	Male non-smokers	1.242
$PM_{2.5}$ (25 $\mu g/m^3$)	Six cities	All	1.364[x] (1); 1.379[x] (2)
		Male non-smokers	1.207 (1)
	ACS (50 cities)	All	1.174[x]
		Male non-smokers	1.245[x]
SO_4^{2-} (15 $\mu g/m^3$)	Six cities	All	1.504[x] (1); 1.567[x] (2)
		Male non-smokers	1.359
	ACS (151 cities)	All	1.111[x]
		Male non-smokers	1.104
	AHSMOG	Male non-smokers	1.279
$PM_{10-2.5}$ (25 $\mu g/m^3$)	Six cities	All	1.814[x] (1); 1.560 (2)
		Male non-smokers	1.434 (1)

(1) Method 1 compares Portage vs. Steubenville (Table 3, *Dockery* et al. [69])
(2) Methode 2 is based on ecological regression models (Table 12 to 18, U.S.-EPA [14])
Six Cities: Harvard six-cities study (*Dockery* et al. [69])
ACS: Study of the American Cancer Society (*Pope* et al. [70])
AHSMOG: Adventist Health Study on Smog (*Abbey* et al. [71])
[x] $P < 0.05$

When the three studies are compared, only the relative risks for overall mortality are truly comparable. Individuals who have never smoked indicated the lowest risks,

followed by former smokers and then smokers. Prior damage to the respiratory tract caused by smoking is the most likely explanation for this. Although all three studies point to associations between total mortality and PM_{10}, $PM_{2.5}$, and/or sulphate, there are differences in the specific causes of death that need to be explained (Table 2, see page 78, and US EPA [9]).

5.3 Isolating the particle effects from the effects of other pollutants

The Harvard six-city study and the study of the American Cancer Society were reanalysed by *Krewski*, et al. [72]. The two studies indicated that the strongest effects were caused by $PM_{2.5}$ and sulphate. The only other pollutant in these studies that also showed a (somewhat weaker) significant effect was SO_2. Taking SO_2 and particles in multiple-pollutant models into account at the same time, the effect estimate for $PM_{2.5}$ and sulphate was markedly smaller. The spatial correlation for all three pollutants was so great that it was impossible to associate the effects unequivocally. Overall, isolating the effects of various pollutants in long-term effect studies is more difficult than in short-term effect studies due to the stronger correlations and the lower number of data points.

5.4 Considering individual confounders

In studies on long-term effects, it is important to take individual lifestyle variables into account. These variables include smoking, occupational exposures, etc., but also unspecific parameters, such as educational attainment or social status. These variables can cause confounding when comparing cities with different levels of pollution if they are not considered approxipriately. (This is different in the case of short-term effect studies, as the same population groups here are compared "to themselves" on different days so that these variables remain constant). In cohort studies, the relationship between the concentration of fine particles and mortality was greater for individuals with lower education. This could suggest a non-identified modifying socioeconomic influence that could lead to an overestimation of the particle effects (*Krewski*, et al. [72]).

5.5 Reduced life expectancy

On the basis of two older cohort studies, *Brunekreef* [73] analysed what influence there was of the connection between suspended particulate exposure and mortality on life expectancy in the Netherlands and in the USA. Using mortality tables for these countries, he found a difference of 1.1 or 1.3 years in the life expectancies of 25-year-olds when comparing regions with and without ambient particle pollution. This indicated that relatively small differences in long-term exposure to suspended particulates can have substantial effects on life expectancy. These calculations did not consider the influences on individuals under 25 years of age. Yet as was found in other studies, small children can be particularly sensitive to long-term exposure to suspended particulates. Increased mortality in children would thus reduce the life expectancy rates for the population well beyond the estimated amounts (*US EPA* [9]).

Künzli, et al. [74; 75], studied the health effects of air pollution caused by motor vehicle traffic in Switzerland and Austria using the above mentioned risk estimates for PM_{10} and epidemiological data countries as a basis. Traffic-induced air pollution resulted in some 3 % of the total mortality, or some 20,000 cases of mortality per year. More than 25,000 new cases of chronic bronchitis in adults, more than 29,000 bronchitis episodes among children, and more than 500,000 asthma attacks among children and adults, and more than 16 million person days with limited activity per year were attributed to these road traffic emissions. These figures were also used in estimating the economic consequences (*Sommer*, et al. [76]).

The same authors also looked into the question of whether the attributive risk of particles should be estimated on the basis of time-series analyses or of cohort studies. They came to the conclusion that the influence of particles on mortality in the general population should be quantified on the basis of the long-term effects, as these are found in cohort studies. Short-term studies (time-series analyses) result in an understatement of the risks involved (*Künzli*, et al. [77]).

6 Concluding remarks

The World Health Organisation [16], the EU Commission [78], the US-National Research Council (NRC) [79], and the US Environmental Protection Agency [9] all consider fine particles to be one of the key environmental health issues in Europe and the USA at present. For the US Congress, the NRC compiled a detailed research catalogue on the requirements for particulate research. In addition, the US Congress allocated research funding of 40 to 50 million dollars per year for particle research over a period of some 15 years. In contrast, the problems caused by particulate matter are receiving the attention only after some delay in Europe, and especially in Germany.

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Discussion

Are the observed effects associated with a specific group of people?

Those affected include the sick and people with prior injuries, especially asthmatics and people with obstructive lung disease, heart patients, and the elderly. School-age children and young adults have been affected less.

The observations in East Germany were especially interesting, as they showed the half-life for ultrafine particles remaining in the air had more than doubled within a period of five to seven years. This can be explained by increasingly cleaner air. The scavenging effect – that is, the capture of ultrafine particles by fine and larger particles in the air – decreased to the point that the ultrafine particles remain in the air longer.

How complete was the methylation of the surface of TiO_2 particles?

The efficiency of the coating is estimated to be around 60 %, although it is not known whether 60 % of the particle surface or 60 % of the particle number is coated.

The chemistry involved plays a large role, both that of the particle surface and that of the substances that settle on the particle surface. Examples include gas-form components or polycyclic aromatic compounds that settle on the particle surface, thus managing to get into places they would not ordinarily get to. This carrier function of ultrafine particles is important because of the penetration abilities and the time of stay associated with these particles. Due to the surface activity of ultrafine particles, newly created aerosols behave differently than do older aerosols.

Another aspect has to do with the solubility of the particles. The biologically relevant surface is the surface that remains after water- and lipid-soluble layers come off. Depending on the solubility rate, the bioaccessible surfaces thus change over time. On the other hand, the questions of how the water- and lipid-soluble components are metabolised and how this changes toxicity are also of great interest.

The dynamic behaviour of ultrafine aerosols [1]

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1 Mechanisms of formation of ultrafine particles

The ubiquitous way of ultrafine particle (UFP) formation is the gas to particle conversion route. This process is characterized by an initial nucleation step i. e. the formation of very small particle embryos from the molecular phase. These nuclei subsequently grow by coagulation and/or surface growth mechanisms (heterogeneous condensation, surface reaction). The details of the overall process depend very much on the amount of available condensible gaseous materials, their thermodynamic and chemical properties as well as on the process conditions. In some limiting cases, the size distribution of the resulting aerosol can be predicted from easily measurable process parameters.

Figure 1 (see page 94) gives a schematic overview of the various mechanisms potentially involved in the formation of UFP by gas to particle conversion.

The aerosol is formed from precursor materials which are either vapourized from a liquid or solid reservoir or are existent as intimately mixed reactive gases. The formation of condensible vapour is achieved by cooling and/or by chemical reaction of the precursor gases resulting in super-saturations high enough for homogeneous nucleation to occur.

At high nucleation rates where a high density cloud of embryos is being formed the particle growth will be predominantly controlled by coagulation. This is the case for example for silica and welding fumes formed in flame processes. The temperature history of the process as well as material parameters of the condensed aerosol matter

[1] Updated version of the workshop presentation as announced in the course of the workshop due to current findings.

such as viscosity, surface and volume diffusion are key parameters controlling the resulting particle morphology and internal structure. If the aerosol material is in the liquid state all the time, the particles remain spherical upon coagulation due to rapid coalescence of the colliding droplets. If the intraparticle material flux is quenched throughout the process due, for example, to a sharp temperature drop in the region of particle formation, coalescence is inhibited. Eventually necks between colliding particles will still be formed resulting in aggregates with strong internal sinter bonds. At the low temperature end of the process coagulation leads to agglomerates held together by week van der Waals or electrical forces.

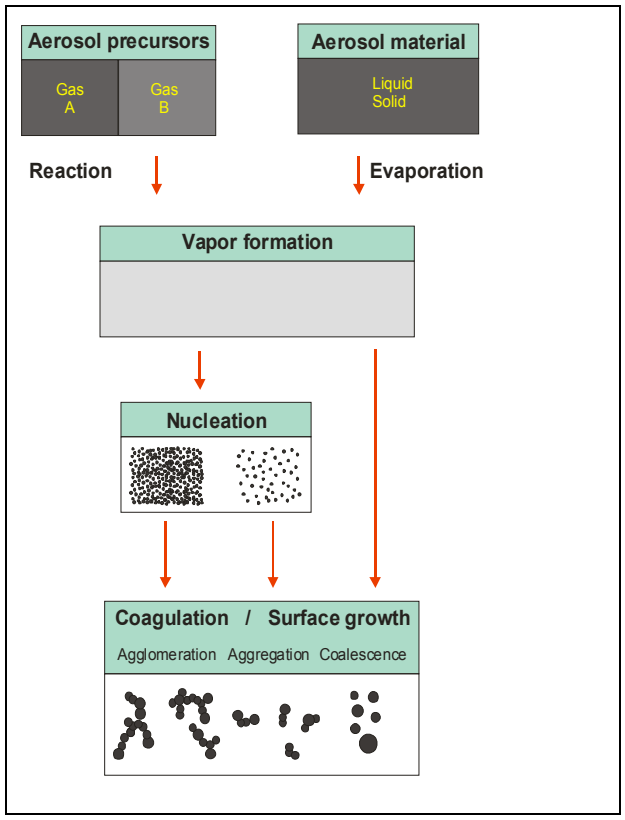


Figure 1:
The various facettes of particle formation and growth by the gas to particle conversion route

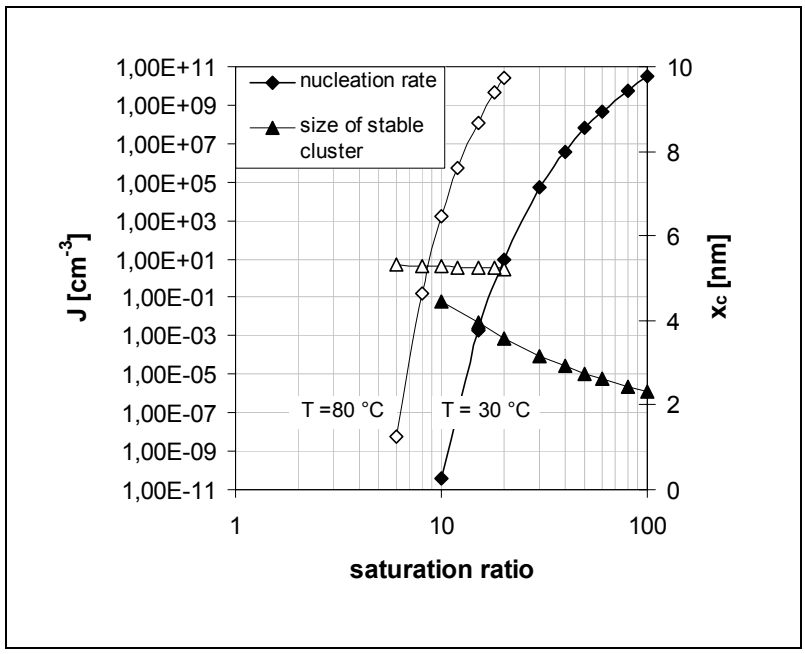
At low nucleation rates leading to small number concentrations of newly formed particles, direct heterogeneous condensation of the aerosol vapour on existing particle surfaces will control the dynamics of the aerosol size distribution. Examples are condensed organic vapours in fugitive emissions such as asphalt fumes. Condensational

growth can result in quite large particles with diameters outside the ultrafine size region even if the total mass concentration is small.

2 Nucleation and condensation

Homogeneous nucleation of a pure vapour phase into droplets of size, x_c,will occur when the energy gained due to the heat of condensation, $(\pi/6)x_c^3(RT/\bar{v})\ln(S)$, is larger than the energy consumed due to the formation of the liquid surface, $\pi x_c^2\sigma$. (Here, S, is the surface tension, R, the gas constant, T, the absolute temperature, $\bar{v}$, the volume of the vapour molecule, S the saturation ratio and σ the surface tension of the condensed liquid.) This is the case when molecular clusters formed randomly at supersaturated conditions have a critical size that allows them to grow by further condensation of vapour molecules. Smaller clusters will evaporate. Thus, the process is controlled by both, the collision kinetics between vapour molecules as well as the thermodynamic state of the vapour phase. It is characterized by the nucleation rate, the number of critical clusters formed in unit time per unit volume. It is usually measured in units of particles/cm³s. This quantity depends in a very sensitive manner on the super-saturation and on (macroscopic) material parameters, for example the surface tension of the condensed liquid. In general, an exact ab-initio prediction of the nucleation rate is very difficult, among others because the relevant material parameters are not readily available at temperatures of interest or which may even not be applicable to molecular clusters. However, the nucleation rate is a very steep function of the saturation ratio. It changes by orders of magnitude when the saturation ratio varies only slightly (Figure 2, see page 96). From the perspective of uncontrolled particle formation at workplaces it is often sufficient to consider homogeneous nucleation as an all-or-nothing effect taking place when the super-saturation reaches a critical value. This value is well above one, the saturation ratio necessary for heterogeneous condensation of vapour onto pre-existing surfaces. Estimates of the critical saturation ratio can be made sufficiently precisely. As a matter of fact it is the thermodynamic conditions i. e. the super-saturation that is not known in most cases of practical interest.

Figure 2:
Nucleation rate and diameter of critical clusters for triethylene glycol as a function of the saturation ratio of the vapour (Becker-Döhring theory of nucleation); a critical cluster size of 5 nm is made of more than 200 molecules

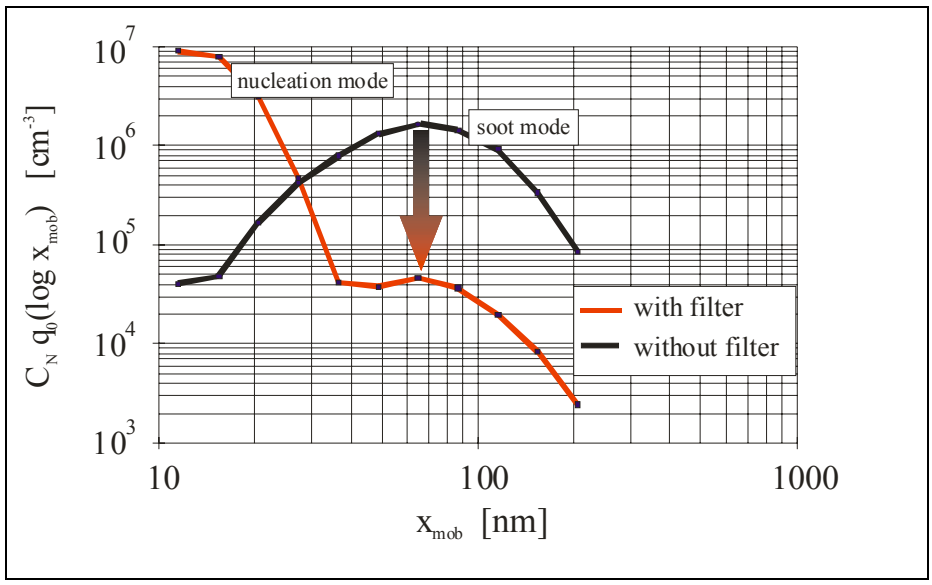


In many high temperature processes such as the flame production of commodities (for example titanium dioxide by the oxidation of titantium tetra chloride) the reaction of the gaseous precursors leads to new compounds the critical cluster size of which is extremely small, of the order of the molecular diameter. Here, nucleation is a pure kinetic process and the nucleation rate of the aerosol material is equal to the reaction rate of the gaseous precursors. Further particle growth is primarily by coagulation. The same situation holds for fume formation over hot liquid metals where the precursor is the metal vapour which nucleates either by cooling or by oxidation in the air. These are very important mechanisms for ultrafine particle formation.

When particles are already present in the air, heterogeneous condensation and nucleation are competing for the available condensible vapour. Heterogeneous condensation of condensible species will prevail when the surface area available is larger than the one expected to be formed by homogeneous nucleation at the specific thermodynamic conditions. In this case the formation of new (ultrafine) particles can be inhibited. Qualitatively this effect is nicely shown in Figure 3 (page 97) presenting

two particle size distributions measured in the cooled exhaust behind the tailpipe of a diesel engine. When the engine has no soot filter the size distribution is unimodal with a modal diameter around 100 nm, quite typical for soot agglomerates. These agglomerates are already being formed inside the cylinder. When the exhaust gas is cooled condensible non-elemental carbon material such as hydrocarbons, and sulfuric acid condenses onto the large surface area provided by the soot particles. When a soot filter is installed in the exhaust line close to the engine the number concentration of the solid elemental carbon fraction and hence its surface area is significantly depleted and the condensible species still in the gas phase at the location of the filter can form a new nucleation mode upon cooling, resulting in a very high number concentration of nanoparticles in the exhaust gas. Similar phenomena can occur at workplaces too. However, they are extremely difficult to predict in detail due to lack of information on the thermodynamic conditions and the chemical composition of the condensible vapour phase.

Figure 3:
Particle size distribution of a diesel engine exhaust. Engine operated with and without a soot trap.



The kinetics of heterogeneous condensation of vapour onto pre-existing particles leads to an increase of the amount of condensed vapour material per particle mass with

decreasing particle size (enrichment). Since the condensation rate of vapour molecules onto UFP is proportional to the surface area concentration, C_a the content of adsorbed toxic material in the ultrafine particle fraction is proportional to the specific surface area. This is of toxicological importance in view of, for example, polycyclic aromatic compounds (PAHs), heavy metals, and other condensible toxic substances being found in increased concentrations in the ultrafine particle mode thus serving as efficient transport vehicle for the respective substances.

3 Coagulation

In many relevant cases of high temperature formation of UFP, binary coagulation is the dominant growth process determining the final size distribution. Key parameters controlling coagulation are the relative motion between the particles, their size and number concentration as well as material properties determining the rearrangement of material inside the particles.

Solid UFP appear often as agglomerates composed of a large number of primary particles. Examples are diesel soot and welding fumes. The size of the primary particles is controlled by the temperature history of the growth process. In regions of high temperature, colliding particles will coalesce as long as the typical coalescence time between particles is small compared to the collision time and the residence time in the high temperature zone. For amorphous substances the typical coalescence time, τ_f, is given by

$$\tau_f = \frac{x_p \eta}{\sigma} \qquad (1)$$

where

x_p = diameter of the colliding particles

η = viscosity of the aerosol material

σ = surface tension of the aerosol material

The viscosity exhibits an extremely sensitive Arrhenius type temperature dependency. For 1 nm silica particles, for example, the fusion time varies from 0.0001 s at 2,300 °C to 0.01 s at 2,000 °C and 80 s at 1,670 °C. Thus, as soon as the system cools down, coalescence is quenched and the colliding particles retain their spherical shape and size, x_{pp}. Aggregates and agglomerates are being formed from these primary particles upon further particle collision. The structure of the growing agglomerates is characterized by the fractal Dimension, D_f, relating the agglomerate diameter, x_a, to the number of primary particles, N_{pp}: $x_a \propto N_{pp}^{1/D_f}$.

Since collision is a binary process, the typical collision time between particles depends on their number concentration. For approximately equal sized particles (particle volume v_p) the collision rate is given by

$$R_c = \beta(v_p, v'_p)\ C_N = \frac{\beta(v_p, v_p)}{\rho_p\ v_p} C_M \tag{2}$$

where

C_N, C_M = number, respectively mass concentration of the aerosol

ρ_P = material density

The quantity $\beta(v_p, v'_p)$ is the collision frequency function generally defined for collisions between particles of volume v_p and v'_p. This function specifies the physical collision mechanism. In the underlying context the dominating collision mechanism is due to the Brownian motion of the particles. For particles with diameters smaller than the mean free path of the gas, the so-called free molecular size range, the collision frequency function takes the form:

$$\beta(v_p, v'_p) = \left(\frac{3}{4\pi}\right)^{\mu} \left(\frac{6kT}{\rho_p}\right)^{1/2} \left(\frac{x_{pp}}{2}\right)^{2(1-3/D_f)} \left(\frac{1}{v_p} + \frac{1}{v'_p}\right)^{1/2} \left(v_p^{1/D_f} + v_p'^{1/D_f}\right)^2$$
$$\mu = \frac{2}{D_f} - \frac{1}{2} \tag{3}$$

where

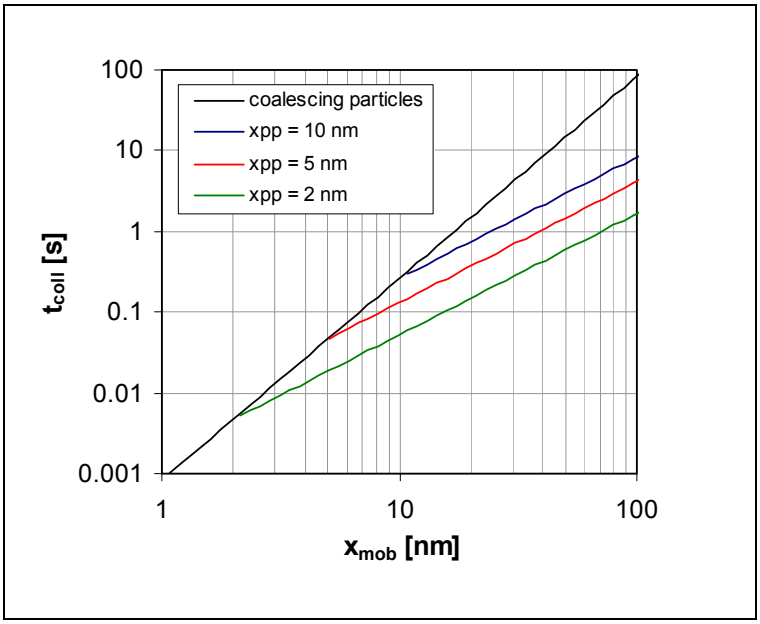
ρ_p = particle material density

D_f = fractal dimension

For instanteneously coalescing particles $D_f = 3$. For agglomerates the fractal dimension D_f takes a value of approximately 2.

Figure 4 shows the typical collision time, $1/R_c$, for unit density UFP at a mass concentration of 1 mg/m³. This graph may serve as a rule of thumb to judge the stability of the size distribution of the ultrafine particle mode under the specific workplace conditions.

Figure 4:
Time between particle collisions at a mass concentration of 1 mg/m³ assuming "free molecular" coagulation. Agglomerates grow significantly faster than instantaneously coalescing spheres. A fractal dimension of 2 was assumed, typical for diffusion controlled cluster agglomeration. For the seek of direct comparison we have chosen the mobility diameter as particle equivalent diameter.



At a concentration of 1 mg/m³ a unimodal coalescing aerosol with a modal diameter of 100 nm will change only little in time scales of the order of minutes, whereas for

agglomerates coagulation is still significant under the same conditions. The higher collision rate of open agglomerates compared to compact droplets is due to the larger capture radius of the agglomerates related to their open fractal structure. This effect increases with decreasing size of the primary particles since the exponent $2(1-3/D_f)$ in Equation 3 is negative.

Close to the respective sources for UFP, for example the evaporation zone of the welding process, the mass concentration of condensed material is much higher than 1 mg/m³. Particles arriving at the breathing zone of the worker have experienced many collision events and the coagulating aerosol size distribution has reached an asymptotic state. This state is characterized by a constant value of the geometric standard deviation and the fact that the average diameter of the distribution is independent of the initial values of the number concentration and the size of the condensed nuclei. In the free molecular regime the asymptotic particle growth follows a power law of the form

$$\begin{aligned} \bar{x}_p &= \frac{6}{\pi} x_{pp}^q \left(\frac{A}{\rho_p} C_m t \right)^z \\ z &= \frac{1}{D_f (1-\mu)} \\ q &= \frac{D_f - 3}{D_f - 4/3} \\ A &= 2^{6/D_f - 1/2} (1-\mu) \left(\frac{3}{4\pi} \right)^{\mu} \left(\frac{6kT}{\rho_p} \right)^{1/2} \end{aligned} \qquad (4)$$

with

$z = 2/5,\ \ q = 0,\ \ \mu = 1/6$ for coalescing spheres and

$z = 2/3,\ \ q = -1.5,\ \ \mu = 1/2$ for agglomerates with a fractal dimension of 2

Figure 5 (see page 102) shows the complete growth curves of a coagulating, coalescing aerosol ($D_f = 3$) with the initial particle diameter (at $t = 0$) as curve parameter. Asymptotically, all curves finally merge into one single curve. As an example,

the vertical line represents an aerosol with mass concentration of 1 mg/m³ aged for 10 s. It is seen that initial populations characterized by average diameters of 10, respectively, 1 nm have reached the same asymptotic state. If the initial aerosol particles were 100 nm in size, coagulation would have not affected the distribution during the same time period, consistent with Figure 4. Figure 5 together with the above equation (4) can be used to estimate the average size of a coagulating monomodal aerosol. If the average diameter is larger than about 50 nm, corrections to pure free molecular coagulation have to be made.

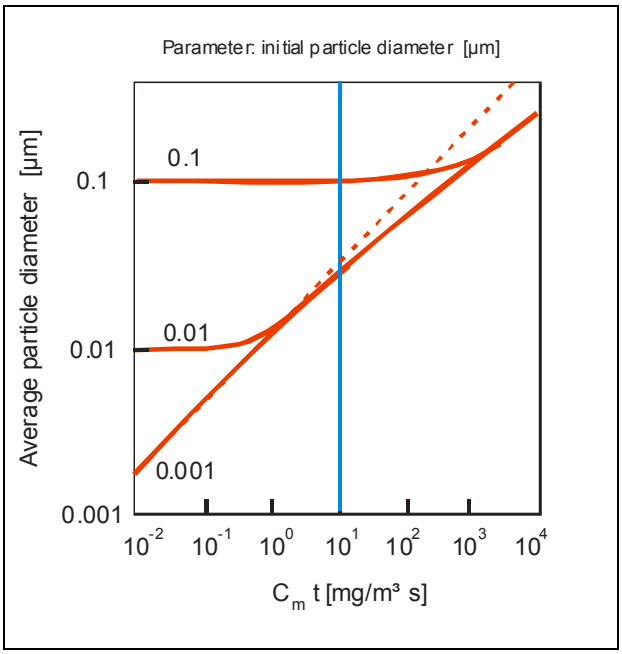


Figure 5:
Growth curves for a coagulating aerosol initially monodisperse however with different initial particle sizes. Dashed curve: theory of pure free molecular coagulation.

In the asymptotic state, the geometric standard deviation takes a value of approximately 1.35 which is reached earlier when the starting distribution is monodisperse as compared to when the initial distribution is wide (Figure 6, see page 103).

So far we have considered the coagulation of a unimodal aerosol of UFP (intramodal coagulation). Under realistic workplace conditions, background dust originating from other sources is generally also present onto which the UFP can deposit by diffusion (intermodal coagulation). Since the diffusion coefficient of the UFP is proportional to the inverse of the particle diameter squared, the strength of this loss mechanism decreases drastically with increasing particle diameter of the UFP resulting in much

longer scavenging times. Thus, scavenging by the coarse dust and intramodal growth are competing processes leading to different results as shown in Figure 7.

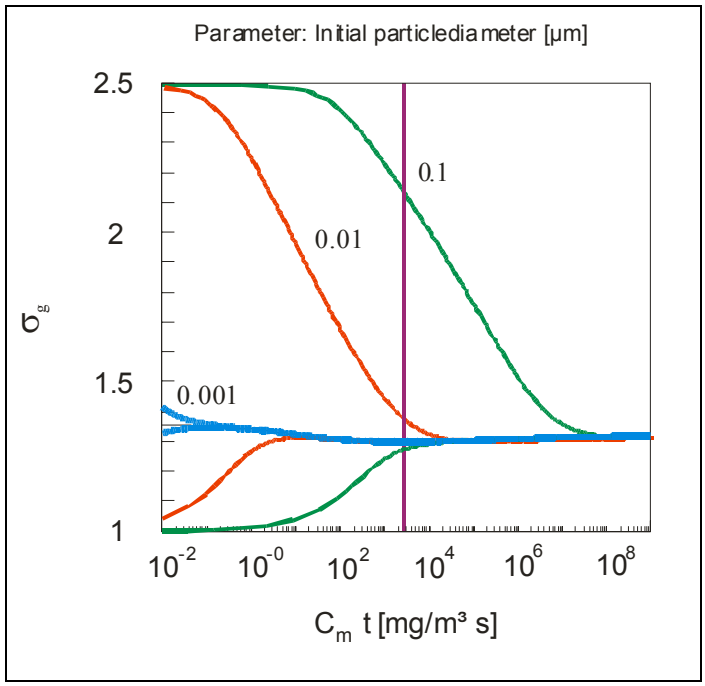


Figure 6:
The evolution of the geometric standard deviation of a coagulating aerosol

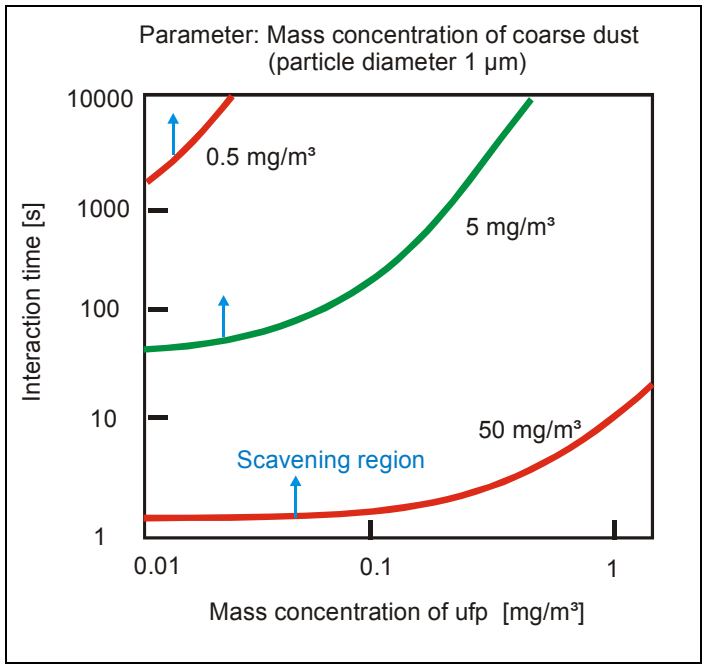


Figure 7:
Svavenging of UFP by coarse dust

The regions above the respective curves represent the situation where the UFP mode is scavenged by the coarse particles. When the parameter points fall below the curves the ultrafine particle mode will prevail. The interaction time necessary for scavenging increases with increasing mass concentration. This is due to intramodal coagulation of the ufp mode leading to particle growth and, thus, to a reduction in the mobility of the UFP. It is also seen that dust concentrations of more than 5 mg/m³ are necessary in order for the coarse mode to serve as an efficient scavenger for the ufp. The example is based on monodisperse 1 μm coarse particles. For larger particles even a higher mass concentration is required to provide the same sink strength for diffusional deposition of UFP. Thus, for typical residence times at workplaces and typical background dust concentrations, UFP generated locally are unlikely to be substantially scavenged by the background dust present in the air.

4 Transport

For air velocities prevailing at workplaces the UFP can be considered as particles having no inertia. Particle deposition on surfaces is mainly controlled by diffusion, turbulent diffusion, and thermophoresis. Deposition is quantified by the so-called deposition velocity, V_{dep}, relating the particle flux onto the surface to the particle concentration above the surface:

$$j = V_{dep} C_m \qquad (5)$$

The deposition velocity depends on the particle size and on the structure of the turbulent boundary layer of the flow above the surface. This is parameterized by the friction velocity, u^*. Figure 8 (see page 105) shows the deposition velocity as a function of the particle diameter and the friction velocity. As a rule of thumb the friction velocity is in the order of 5 to 10 % of the bulk air flow velocity. For normal workplace conditions $u^* < 10\ cm/s.$

In the small particle size regime and in stagnant air ($u^* = 0$), the concentration boundary layer is formed by the Brownian particle motion only. The concentration

gradient in this case is flatter than the average concentration gradient developing under turbulent conditions ($u^* > 0$). Here, turbulent eddies enter the laminar boundary layer statistically, transporting the particles closer to the wall and, thus, reducing the distance for the particles to be surmounted by Brownian diffusion before reaching the wall. Therefore the particle deposition velocity is larger for turbulent airflow.

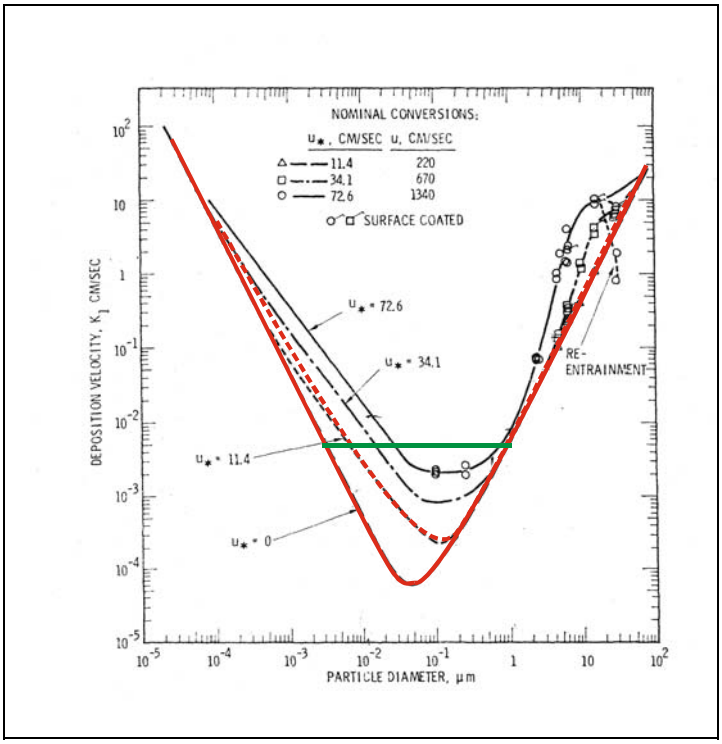


Figure 8:
Deposition velocities of aerosol particles. Left branch: controlled by molecular and turbulent diffusion; right branch: controlled by settling and turbulent impaction

In total, however, it is seen that the UFP size range is more or less the size range of minimum deposition velocity i. e. maximum persistence. Thus, once released into the air ufp at workplaces will have a long residence time. Under well-stirred mixing condition in a ventilated room the loss rate due to particle deposition is given by

$$R_l = \frac{S}{V} V_{dep} \qquad (6)$$

where

S = area of all surfaces inside the room, onto which particles can deposit

V = volume of the room

The loss rate can be compared, for example, with the air exchange rate, Λ. Assuming a room size of 10 x 5 x 5 m^3 and a total surface area of 500 m^2 (250 m^2 from walls, ceiling and floor, plus 250 m^2 from other inner surfaces), a maximum deposition velocity of 0.01 cm/s (10 nm particles, $u^* = 11\ cm/s$), we obtain a value of 0.76 [1/h] for R_l which is considerably smaller than the air exchange rate, Λ, which should be significantly above 1 [1/h] for turbulent flow conditions resulting in $u^* = 11\ cm/s$. Obviously, deposition to surfaces plays no important role for the transport of UFP and thus does not influence the exposure concentration.

Ultrafine particles – measurement techniques [1]

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Nanotechnology is concerned with the manufacture of nanostructured materials and components. It is considered to have a great future. In order to be classed in the realm of nanotechnology, a technological subject must measure at least one of its three dimensions smaller than 100 nm. Thin layers for establishing certain functional surfaces and even the two-dimensional nanowires that have captured the imagination in the field of electronics fall within the field of nanotechnology. Three-dimensional particles are especially interesting here due to their large surface areas and due to their size-related properties (Figure 1).

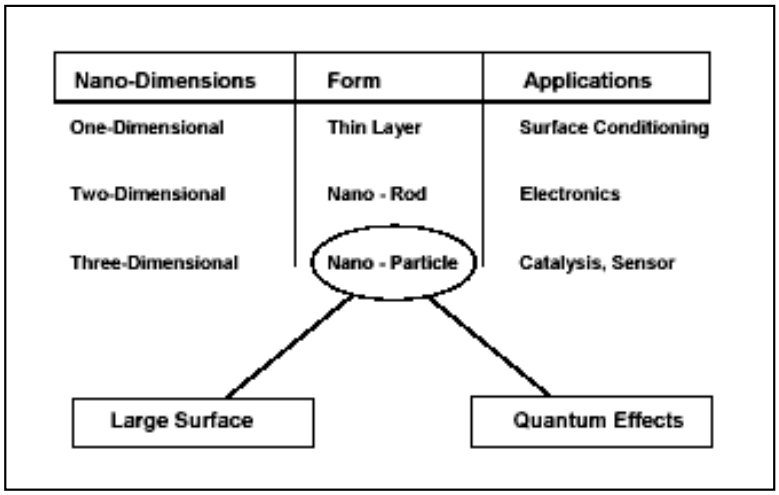


Figure 1:
Forms and applications of nanoparticles

Nanoparticles include solid or liquid particles made up of physically bounded molecules (clusters). In comparison to the related bulk material, nanoparticles have different optical, electrical, chemical, and mechanical properties (Figure 2, see page 108).

[1] Transcription on the basis of the oral presentation; reviewed and authorized by the author.

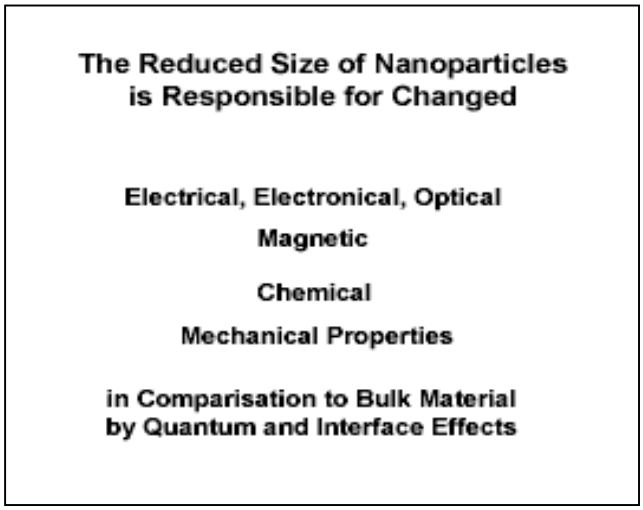
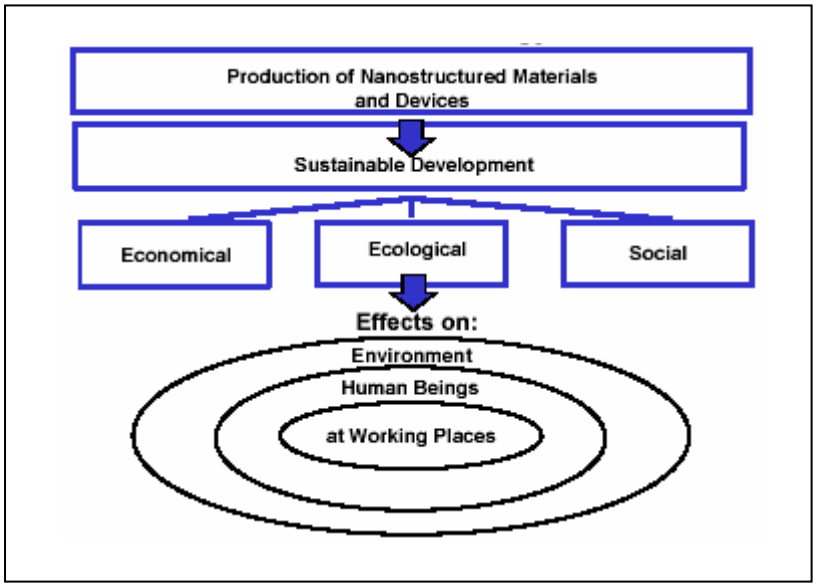


Figure 2:
Properties of nanoparticles

The special properties of nanoparticles can also lead to ecological effects (Figure 3). This has become part of a discussion as to the sustainability of nanotechnology.

Figure 3:
Sustainability of nanotechnology



In Table 1 (see page 109), the properties of a 10 nm particle are compared to those of a 1 μm particle. The size difference is thus 1 : 100. Mathematically, the 1 μm particle contains sufficient matter to create 10^6 10 nm particles. The surface area of the 10 nm particle is 10^{-4}, and the mass 10^{-6} based on the corresponding properties of

the 1 μm particle; in other words, the specific surface is 100 times as large. The intensity of light that is scattered on a 1 μm particle is proportional to dp^2; for the 10 nm particle it is proportional to dp^6, which amounts to a ratio of 10^{-36}.

Table 1:
Comparison of properties for particles of different sizes

Property	Dependency on particle diameter dp	Dust particle	Nano-particle	Nano-particle/ Dust particle
Size		1 µm	10 nm	$\frac{10}{1000} = 10^{-2}$
Number		1	1 000 000	10^6
Surface	$\approx d_p^2$	$3{,}14 \bullet 10^{-12}$ m²	$3{,}14 \bullet 10^{-16}$ m²	10^{-4}
Mass (ρ = 1 g/m³)	$\approx d_p^3$	$5{,}24 \bullet 10^{-19}$ g	$5{,}24 \bullet 10^{-25}$ g	10^{-6}
Scattered light	$\approx d_p^2 \div d_p^6$	$\approx d_p^2$	$\approx d_p^6$	10^{-36}

Figure 4 (see page 110) gives a non-exhaustive list of parameters for characterising aerosols. These characteristics are also distributed over different properties, which makes it difficult to describe the state of an aerosol. The most important property is the particle size, and this is mostly given as the diameter even for non-spherical particles. The diameter is then the equivalent diameter, its value depending on the physical process behind the measuring principle. Figure 5 (see page 110) shows the number, surface, and volume size distribution of a typical atmospheric aerosol.

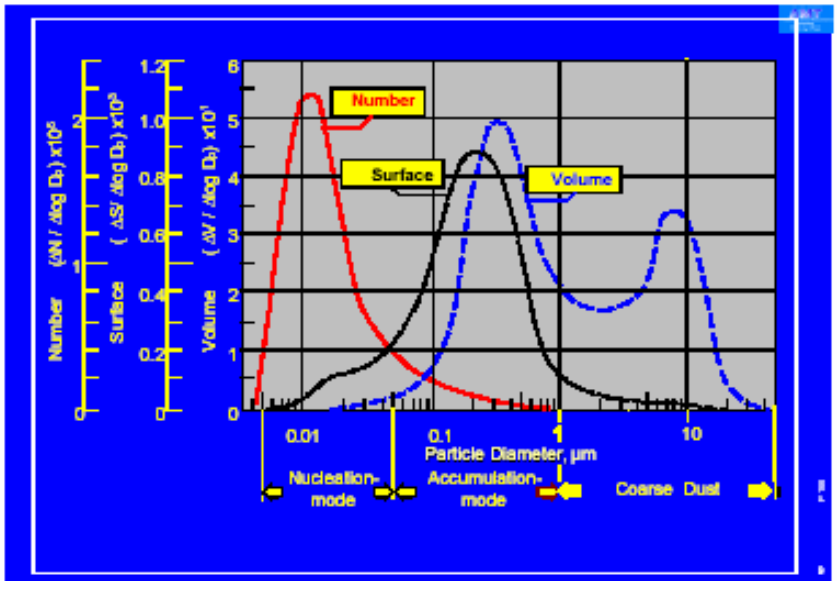
Figure 4:
Parameters for characterising aerosols

Measurement Quantities:
- Number
- Diameter
- Surface
- Volume
- Mass
- Composition
- El. Charge
- Intensity of Scattered Light

Concentration Measures: $\frac{x}{m^3}$
- Number Concentration

Particle Size Distribution:
- Number (Concentration) – Size Distribution

Figure 5:
Number, surface, and volume size distribution for
a typical atmospheric aerosol



It is clear that nanoparticles contribute little to mass, and that they must thus be counted. The particles are collected as deposits (on filters, baffles) to determine their mass concentration, and their mass is determined by weighing, by β-radiation

absorption or by the change in the resonating frequency of a vibrating filter (TEOM) (Figure 6).

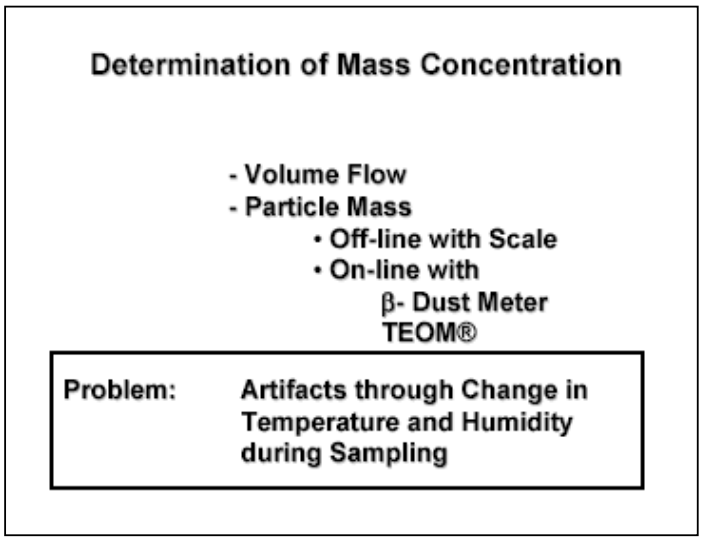


Figure 6:
Determining the mass concentration

The greatest obstacles here are the artefacts that arise and that are particularly significant for small particles. Due to the low masses involved, determining the chemical composition of nanoparticles requires a very sensitive analytic method, such as the total reflection x-ray fluorescence method (TXRF). Using this requires that the particles be distributed evenly on a smooth flat surface (Figure 7).

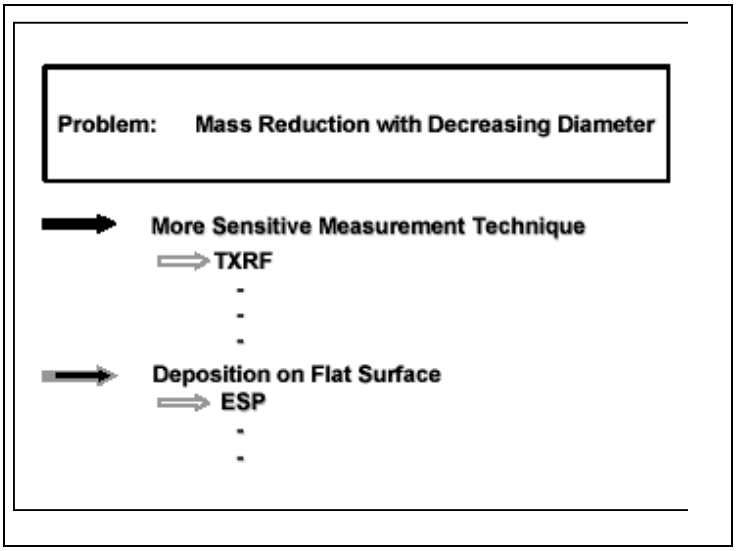
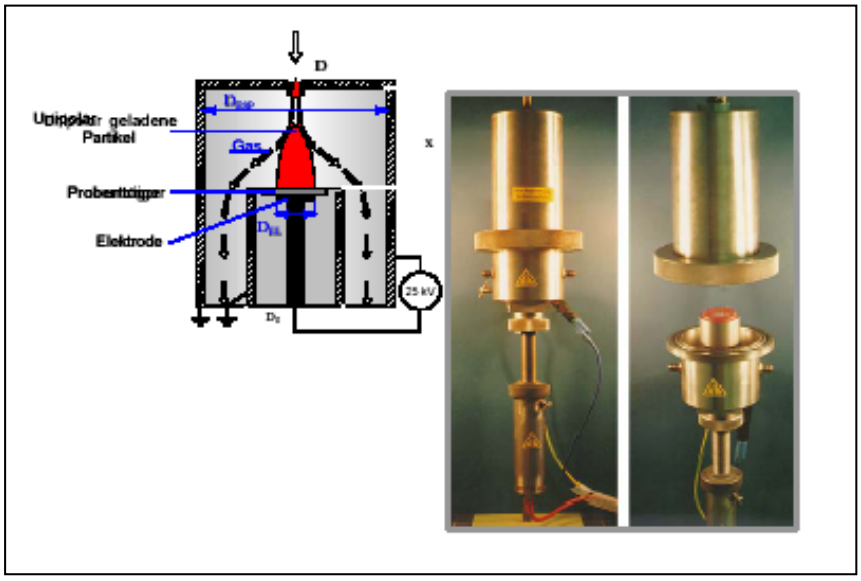


Figure 7:
Determining the chemical composition of particles

This can be done using equipment such as the electrostatic precipitator (ESP) we have developed, and which is now commercially available (Figure 8). There is a voltage of 25 kV between the chamber wall and the middle electrode bearing the sample. The particles, previously given an electrical charge, are transported through the chamber by the electric field and deposited on the sampling surface. Adjusting the flow conditions and electrical field accordingly results in a homogeneous deposition of particles.

Figure 8:
Electrostatic precipitator



Unipolar geladene Partikel = unipolar charged particles,
Probenträger = sampling surface, Elektrode = electrode, Gas = gas

Figure 9 (see page 113) shows the working principle of this device when collecting samples of atmospheric aerosols. Behind the PM_{10} inlet, there are two impactor stages to separate the particle fractions > 2.5 μm and > 0.1 μm; the remaining nanoparticles are given a unipolar charge in a corona discharger and sent to the ESP. One problem here is that the effectiveness of charging small particles (< 30 nm) is no longer 100 % so that we have to apply a correction factor.

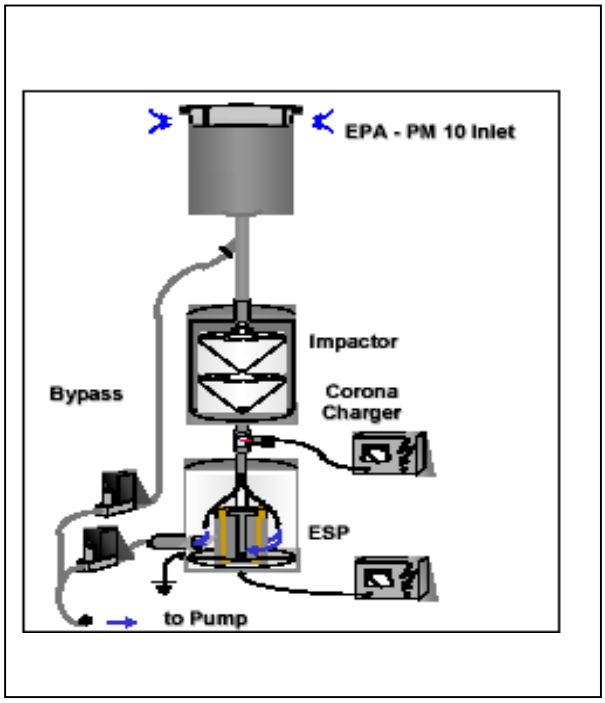


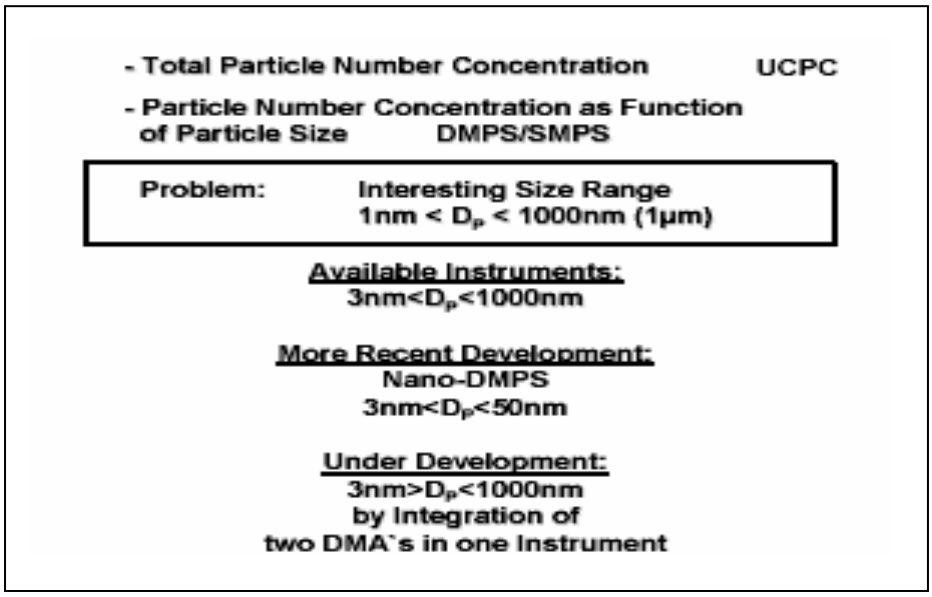
Figure 9:
Working principle of the electrostatic precipitator (ESP)

The nanoparticles collected on smooth substrates can be analysed offline in many different ways. One excellent analytic device is the high resolution transmission electron microscope (Figure 10, see page 114). This allows an exploration of the physical and especially the chemical questions at resolutions down to the atomic scale with the aid of electron energy loss spectrometry (EELS), energy dispersive x-ray microanalysis (EDX), and dark field techniques (HAAF). Yet these systems require quite expensive equipment.

To determine the number concentration of nanoparticles, a condensation nucleus counter is often used (UCPC, ultrafine condensation particle counter). Here, the underlying principle is that particles in a saturated vapour atmosphere grow to such a size that they can be counted using the light scattering method. In order to be able to determine the size distribution of ultrafine particles, a differential mobility analyser (DMA, DMPS, SMPS) is placed before the UCPC, and the particles in the differential mobility analyser are classed according to their mobility and their size at the same charge. Equipment is now available on the market to cover the size range from around 3 nm to 1,000 nm (Figure 11, see page 114).

Figure 10:
High resolution transmission electron microscope

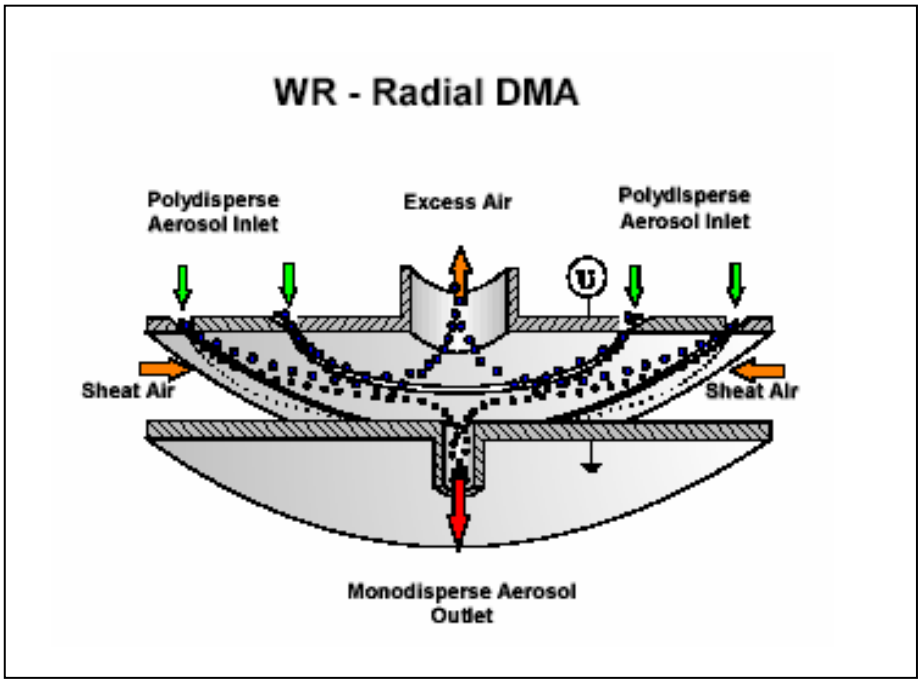
Figure 11:
Determining the size distribution of ultrafine particles



The functional principles of a DMA with plate electrodes is illustrated in Figure 12 (see page 115). Both plates are connected to a voltage supply. The polydisperse aerosol enters through the two ring inlets; radial symmetric clean sheath air enters from the side. The interaction of the electrical field with the flow field leads to a monodisperse

aerosol to exit through the outlet at the bottom; the size of the aerosol particles is determined by the particle mobility in the electrical field. Successively changing the voltage causes particles of corresponding size to exit at the outlet.

Figure 12:
Functional principles behind the differential mobility analyser



Another interesting measuring device is the electrical aerosol detector (Figure 13, page 116) provided by the company TSI. A corona discharger generates ions that are deposited on the particles in the mixing chamber by way of diffusion. Excess ions are removed using an ion trap. The charged particles are then deposited in a Faradays' cage, and the electrical current generated is measured. It is as a first approximation for the sum of the diameters of the deposited particles because the diffusion charging causes a linear relationship between the mean charge per particle and the particle size above 10 nm with a diameter dependency $dp^{1.1}$ (Figure 14, see page 116).

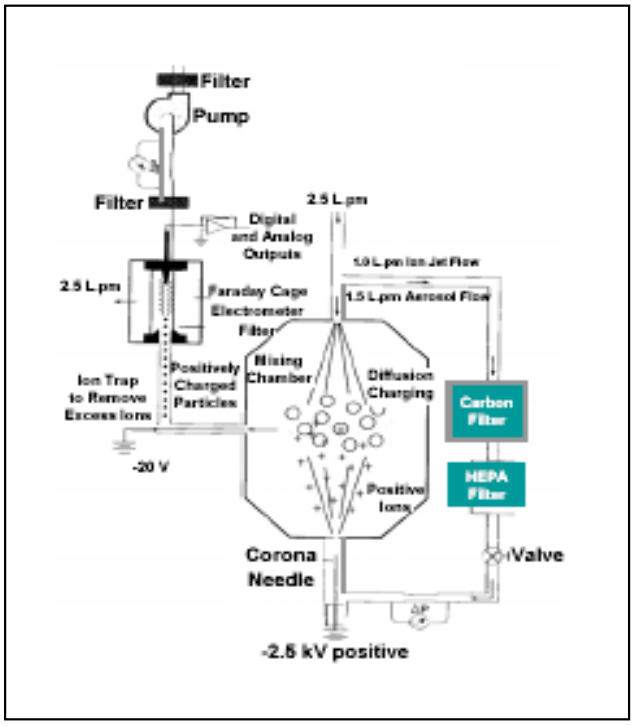


Figure 13:
Electrical aerosol detector

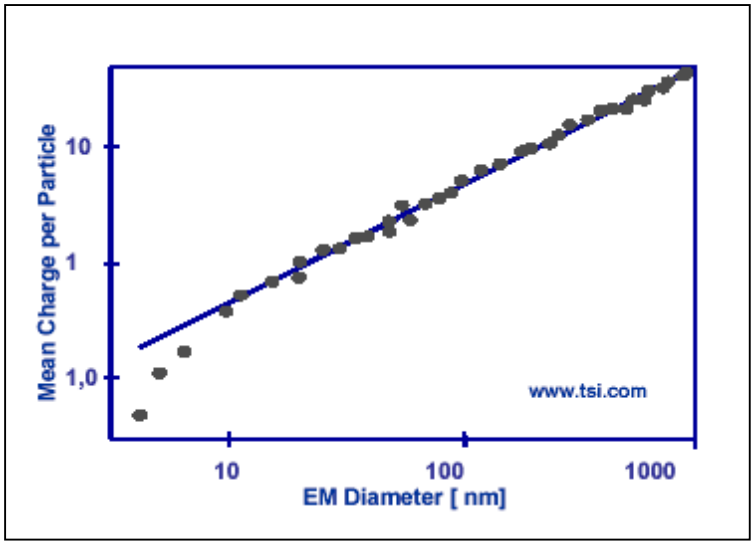


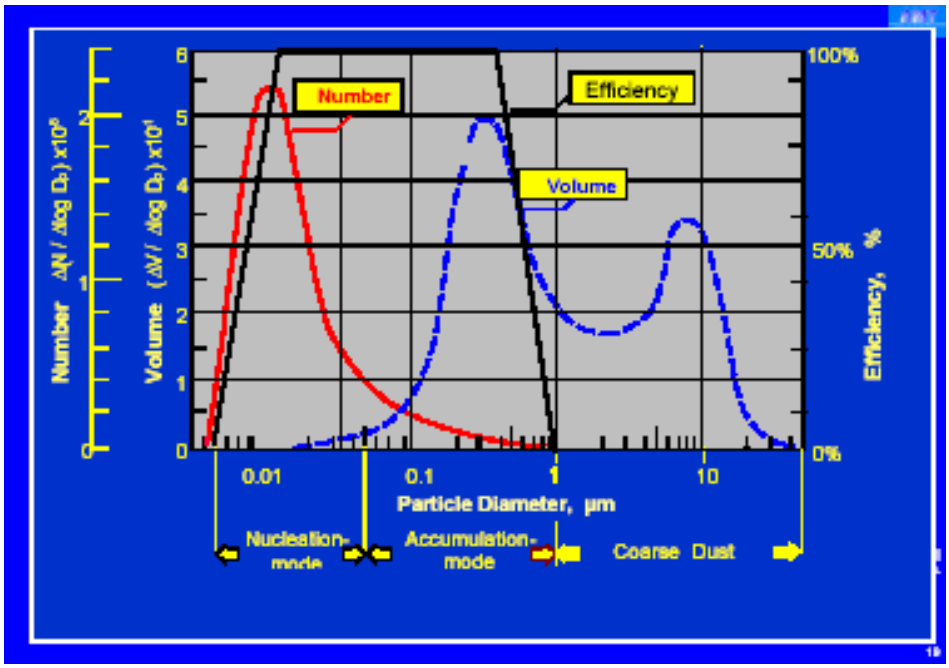
Figure 14:
Relationship of particle charge and particle size

The sum of the diameters of the particles is assumed to be effect-relevant in the context of inhalation. Every measuring device has upper and lower measuring limits in terms of the particle sizes detected. Figure 15 (see page117) provides an example of the effectiveness (right-hand ordinate) of a measuring device as it relates to particle size. The upper limit is important for the measurement of the mass (or the volume). In the given example, the upper limit does not influence the results of the measurements

of the numbers, but the lower limit must be taken into consideration when interpreting the measurements taken with this device. The level of the measurement limits depends on the type of device, and this level may even be different for different devices of the same type.

Additional information on measurement devices and their characteristics may be found in the article "Instrumentation and Measurement Issues for Nanometer Particles: Workshop Summary" [1].

Figure 15:
Efficiency of particle measurement as related to particle size



The respective particle standards are important for the measurement techniques used for ultrafine particles. These are needed for verifying and improving the accuracy and precision of the measured results, for support when developing new instrumentation, and for promoting nanotechnology. Unfortunately, almost nothing is currently available in this field. One standard for particle size is provided by the National Institute for Standards (NIST) in Washington, DC – a standard for polystyrene spheres with an average size of 100.7 nm that are measured using the DMA technique (Figure 16, see page 118). Attempts have been made to use dendrimers to cover the size range

between 3 nm and 15 nm. This procedure uses synthetic three-dimensional dendrite macromolecules in spherical form. The procedure is still in development.

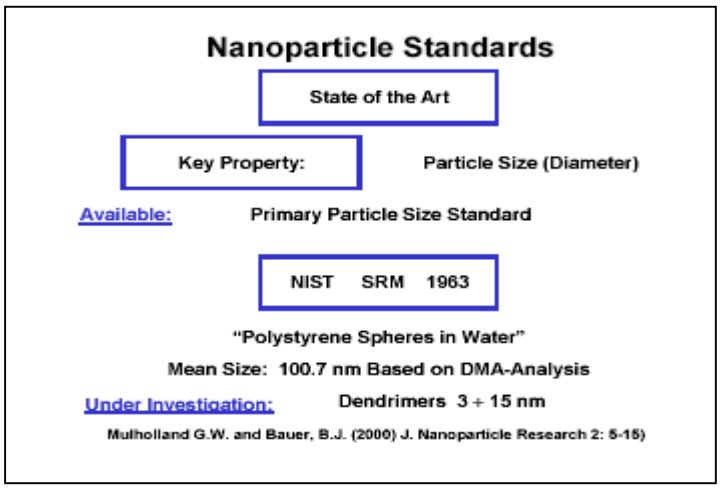


Figure 16:
Standard for the particle size

Yet particle size is just **one** parameter that we have a standard for. No standards are available in contrast for number concentration. The only thing that can be done here is a standardized dilution of a given aerosol. But this only produces relative values; the actual number concentration remains unknown. For the measurement techniques for use on nanoparticles, many problems still need to be solved and much work still needs to be done. Figure 17 summarises the most important tasks ahead.

Figure 17:
Required developments in the measuring techniques and technologies for ultrafine particles

References

[1] *Pui, D. Y. H.; Brock, J. R.; Chen, D.-R.; Fissan, H.; Frisbie, C. D.; Lyman, C. E.; Miller, J. C.; Mulholland, G. W.; Pecora, R.; Preining, O.; Vo-Dinh, T.*: Instrumentation and measurement issues for nanometer particles: Workshop Summary. J. Nanoparticle Res. 2 (2000), p. 103-112

Describing ultrafine particles using electron microscopy [1]

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1 Problem

Animal experiments indicate that there are increased biological effects caused by ultrafine particles with a diameter of D < 100 nm that are not only to be expected from free aerosol particles, but also from their aggregates and agglomerations (described below only as "aggregates" for the sake of simplicity).

Measurements of the concentration of all particles of a diameter D < 200 nm have so far been conducted using a mobility particle sizer (MPS). But this frequently-used method does not distinguish between compact particles and aggregates.

The results of such MPS measurements should thus be compared with a characterisation by transmission electron microscopy (TEM) where the number of all primary particles including those in the aggregates are recorded. The stability of such aggregates in aqueous suspension also needs to be explored.

2 Materials

Measurements were taken at the following aerosols:

- from welding fumes from manual metal arc welding (MMA) of mild steel (MS) and stainless steel (SS)

[1] This project was completed under co-authorship of *S. Podhorsky* [1)], *B. Brückel* [1)], *D. Dahmann* [2)], *G. D. Hartfiel* [2)] and *H.-J. Woitowitz* [1)]. It was supported by the Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA – the German Federal Agency for Occupational Safety and Occupational Medicine) as project No. F 1804
1) Institute and Outpatient Clinic for Occupational and Social medicine (IPAS), Giessen
2) Institute for Research on Hazardous Substances (IGF), Bochum

- from welding fumes of metal inert gas welding (MIG) of mild steel, stainless steel, and aluminium (Al)
- from diesel soot from engines with and without particle filters
- from sandstone dust
- from carbon black (CB, Printex 90), cf. [1 to 4].

3 Method

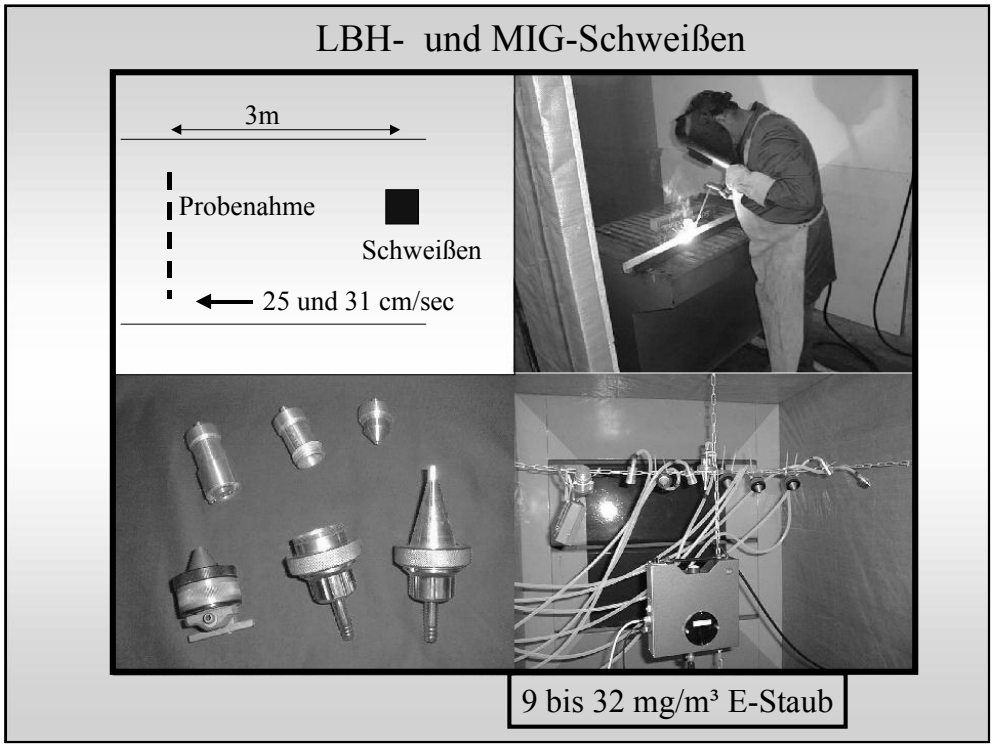
Nucleopore filters were loaded with air samples taken on samplers for the inhalable and the respirable fraction as well as with open filter mounts at low air velocity both at workplaces and the test facilities at the laboratories in Dortmund of the Institute for Research on Hazardous Substances (IGF – Institut für Gefahrstoffforschung) in Bochum.

Samples were also taken by passive collection on TEM grids covered with a Formvar film. In the laboratory studies, MPS measurements were also conducted in parallel (SMPS supplied by TSI). The analysis of the filters was done under both scanning and transmission electron microscopes (SEM and TEM) at magnifications of 80,000x manually as well as by digital picture analysis. The number of aggregates and of primary particles – including those in the aggregates – were determined in parallel.

Figure 1 (see page 123) shows the welding test bench, the sampling heads used, and the spatial arrangement during sampling. The sampling devices were situated at 3 m away from the welding area.

Figure 2 (see page 123) illustrates the different particle and aggregate forms found during MIG welding on aluminium, diesel soot, carbon black, and for sandstone dust at 10,000x magnification under the scanning electron microscope. The pore widths of the nuclear pore filters was 0.2 μm (right side) and 0.4 μm (left side).

Figure 1:
Welding test bench, sampling heads used, and their placement for sampling



LBH- und MIG-Schweißen = MMA and MIG welding, Probenahme = sampling, Schweißen = welding, 9 bis 32 mg/m³ E-Staub = 9 to 32 mg/m³ inhalable dust

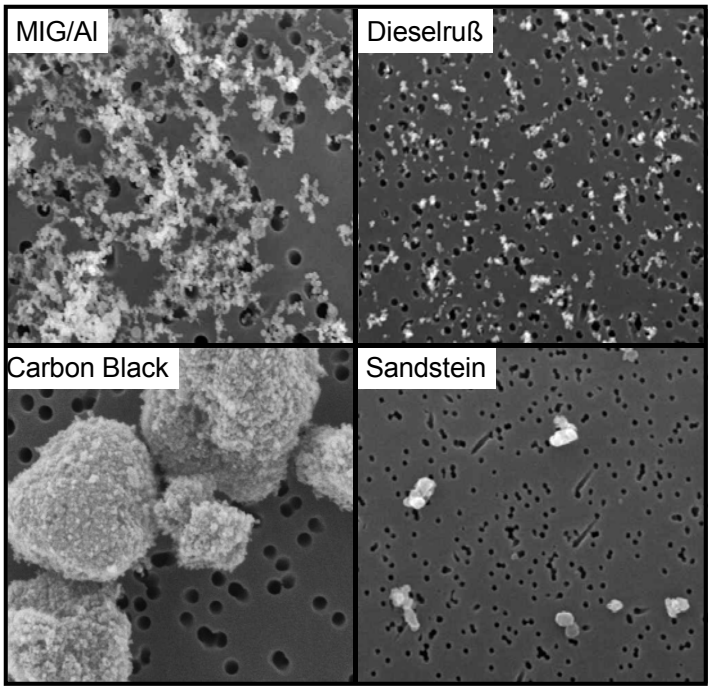
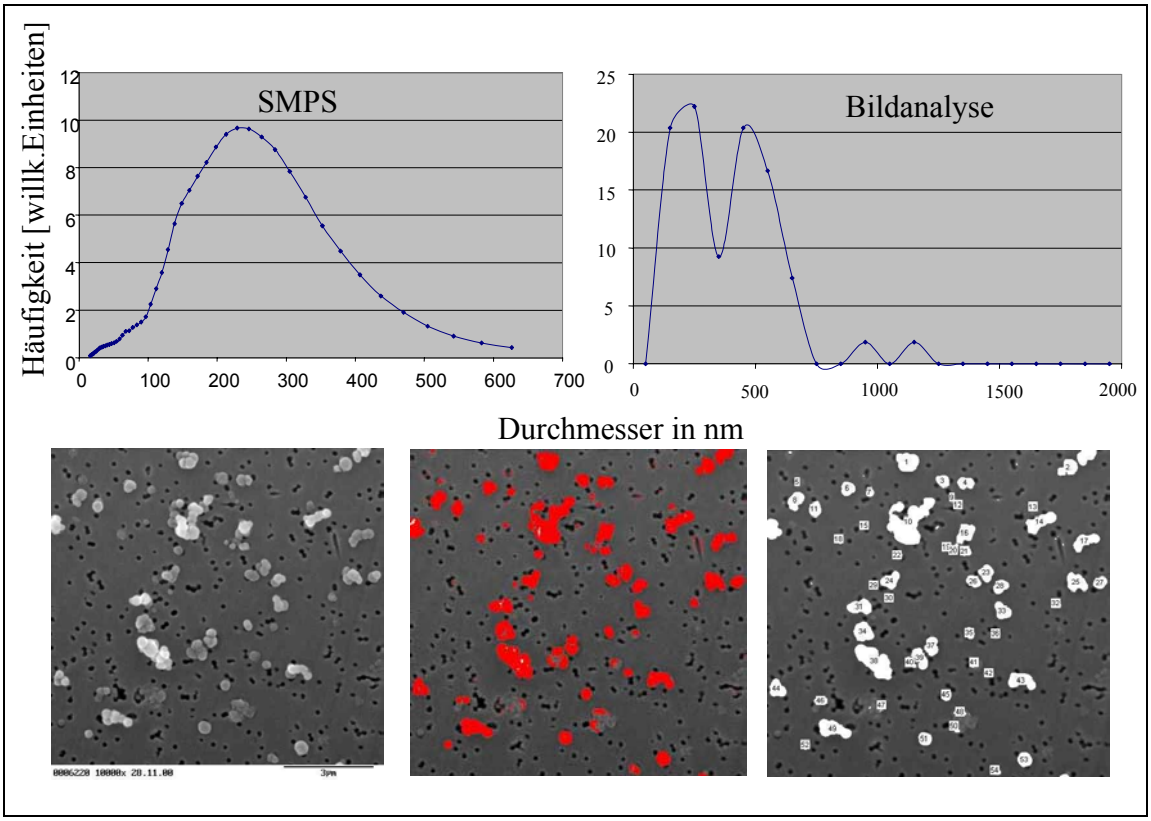


Figure 2:
Different particle and aggregate forms under the scanning electron microscope at a magnification of x10,000. The size of each photo is about 10 x 10 μm
Dieselruß = diesel soot
Sandstein = sandstone

Figure 3 shows the particle size distribution for welding fumes from manual arc welding on construction steel measured using the SMPS technique (scanning mobility particle sizer) in contrast with the measurements obtained using picture analysis for SEM images at 10,000x magnification. It is clear that the curves almost correspond with each other if we bear in mind that only relatively few objects were evaluated in the picture analysis.

Figure 3:
MMA/MS welding: aggregate diameter using SMPS
and picture analysis of SEM photos (x10,000, SCION)

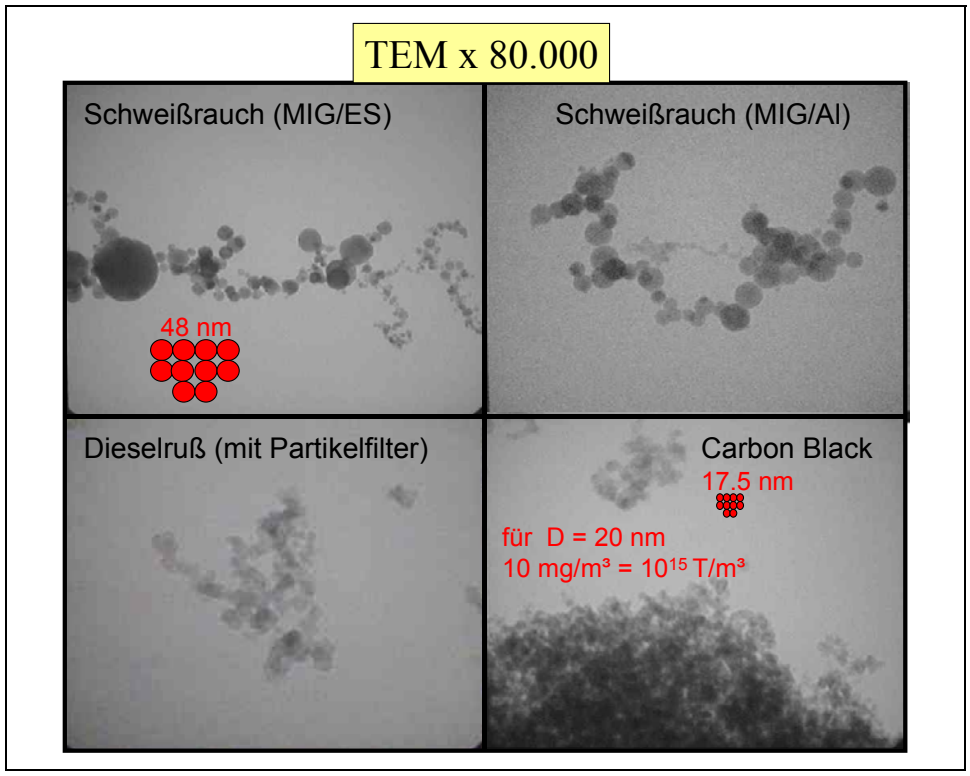


Häufigkeit (willk. Einheiten) = occurrence (arbitrary units),
Bildanalyse = picture analysis, Durchmesser = diameter

The structure of aggregates can be best studied using TEM on TEM grids covered with Formvar film that has been loaded from the aerosol immediately beforehand by diffusion precipitation. Figure 4 (see page 125) shows examples of aggregates from welding fume particles from MIG welding on stainless steel and on aluminium, from diesel soot, and from carbon black. For comparing the sizes in question, dots are

drawn over the pictures to correspond to diameters of 48 nm and 17.5 nm. The example of carbon black shows that the large aggregate is formed around small primary particles. Assuming that these are 20 nm particles of a density of 2 g/cm³, a mass concentration of 10 mg/m³, which we found in the test with the continuous drop tube, would correspond to 10^{15} particles/m³.

Figure 4:
TEM images of aggregates of different ultrafine dusts

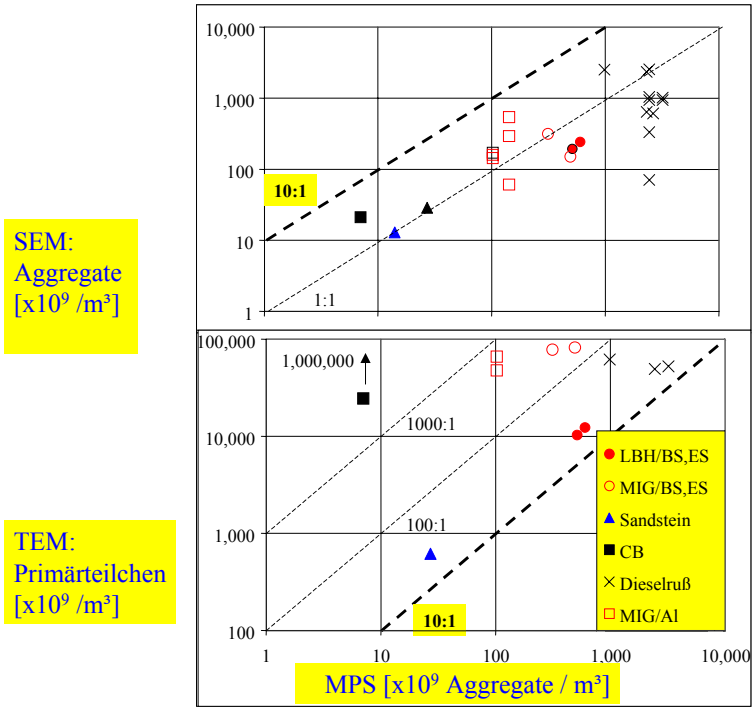


TEM = SEM, Schweißrauch = welding fume,
Dieselruß (mit Partikelfilter) = diesel soot (with particle filter)

Figure 5 (see page 126) illustrates an initial comparison of the results of SMPS with those of electron microscopy for different aerosols sampled on nucleopore filters. In the SEM samples at 10,000 to 20,000x magnification, all objects – even aggregates – were counted independently of whether or not they were formed from primary particles, as is also the case for SMPS. It is obvious that the results are more or less symmetrical with the identity line, but with large variations. Under the TEM, all primary particles – even those within the aggregates – were counted within individual photo-

graphed areas at 80,000x magnification. These estimates show that the aggregates for sandstone dust, MMA welding, and also diesel soot are made up of relatively few primary particles, whereas the number of primary particles per aggregate for MIG welding is between around 100 and 1,000, and for carbon black it is up as high as 100,000.

Figure 5:
Laboratory trials: comparison of the results from the mobility spectrometer (MPS) with those from the electron microscope [1]



Aggregate: aggregates; Primärteilchen: primary particles; LBH: MMA (metal arc welding); BS: MS (mild steel); ES: SS (stainless steel); Sandstein: sand stone; CB: carbon black; Diesel-ruß: diesel soot; MIG: metal inert gas welding; Al: aluminium

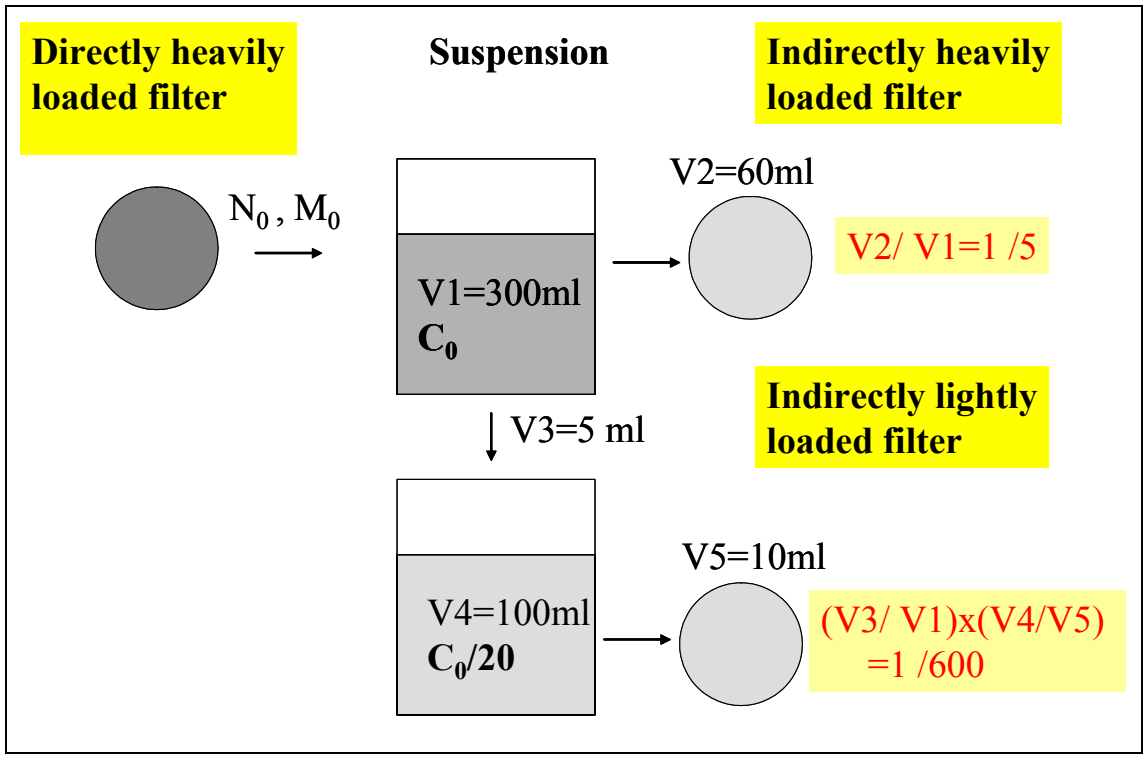
As a next step, we attempted to integrate and standardise the two methods of electron microscopy in a single TEM evaluation procedure (Figure 6, see page 127).

Aside from the direct method for evaluating the sampling substrate under the electron microscope, where the sampling substrates are studied under the electron microscope directly after the appropriate preparation, there is also the indirect preparation method (Figure 7, see page 127).

Figure 6:
Excel form for TEM analysis (10 to 25 fields, x40,000)

Excel-Form for TEM-analysis (10 to 25 fields, 40,000x)	
Input:	• Sampling, preparation (indirect, as needed) • Weighing • Counting and measuring the particles • Assignment to aggregates
Results:	•Mass concentration •Particle concentration •Aggregat concentration Plausibility test
Analysis of the primary particle	• Number- • Surface- • Mass *) - } weighted diameter • Surface concentration • Mass concentration*)
Analysis of the aggregates	• Average size, number of primary particles per aggregat • incomplete proportion in the counting field
Error margin: coefficients of variation:	1. Aggregates per field (Poisson and median test) 2. Particles per aggregat (Log normal and median test) 3. Primary particle count from 1. und 2.
*) Volume x estimate of densitiy	

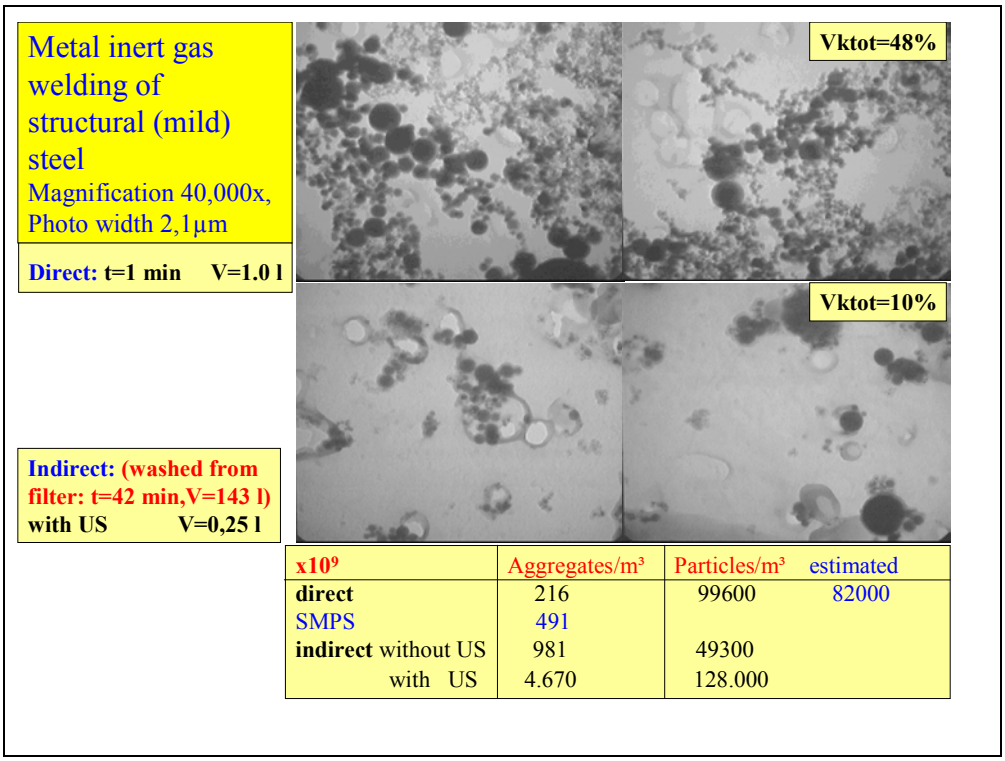
Figure 7:
Indirect preparation method



For this, a highly loaded measuring filter is washed with 300 ml distilled water and 1 % propyl alcohol under ultrasound. From the resulting suspension, part of the volume either immediately can be filtered out and studied or can be diluted first in a defined amount and then run through another ultrasound treatment to break up the aggregates. Afterwards part of the volume of this suspension is then filtered out and studied.

The effect of the two preparation methods is shown in Figure 8 using the example of metal inert gas welding on mild steel under the TEM. The upper part of the figure shows the results of the direct method for a sampling period of 1min and a sample air volume of 1 l. The lower part of the figure shows the results of the indirect method. The duration of the air sampling is 42 min. The indirect preparation with additional ultrasound treatment results in a filter that is loaded with 1/600th of the original dust amount.

Figure 8:
Comparison of direct and indirect preparation methods
for metal inert gas welding on mild steel (US = ultra sound)



x10⁹	Aggregates/m³	Particles/m³	estimated
direct	216	99600	82000
SMPS	491		
indirect without US	981	49300	
with US	4.670	128.000	

As can be seen in the two evaluations of these two samples shown in Figure 9, the observed number of aggregates per evaluated field (left) very well matches the numbers expected in terms of Poisson's distribution; after indirect preparation, the observed number of primary particles per aggregate especially closely match the expectations of the lognormal distribution hypothesis. The combined coefficient of variation is 48 % for the direct preparation method, and 10.4 % for indirect preparation.

Figure 9:
Primary particles and aggregates in ultrafine dusts from metal inert gas welding on construction steel using the direct and indirect methods

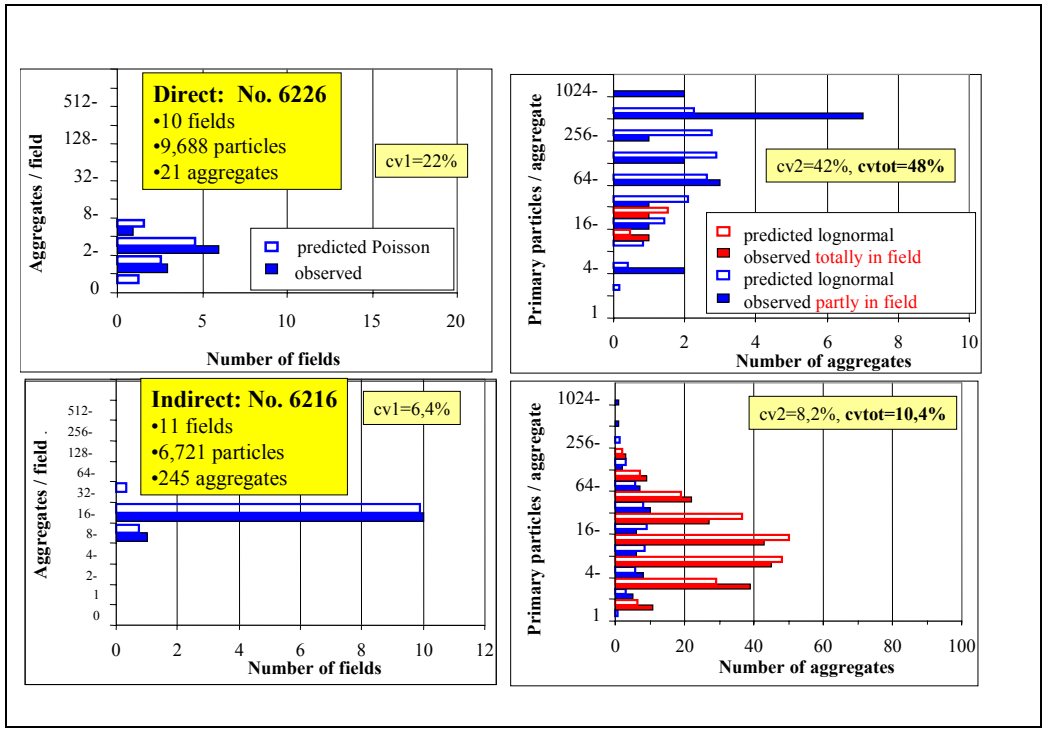
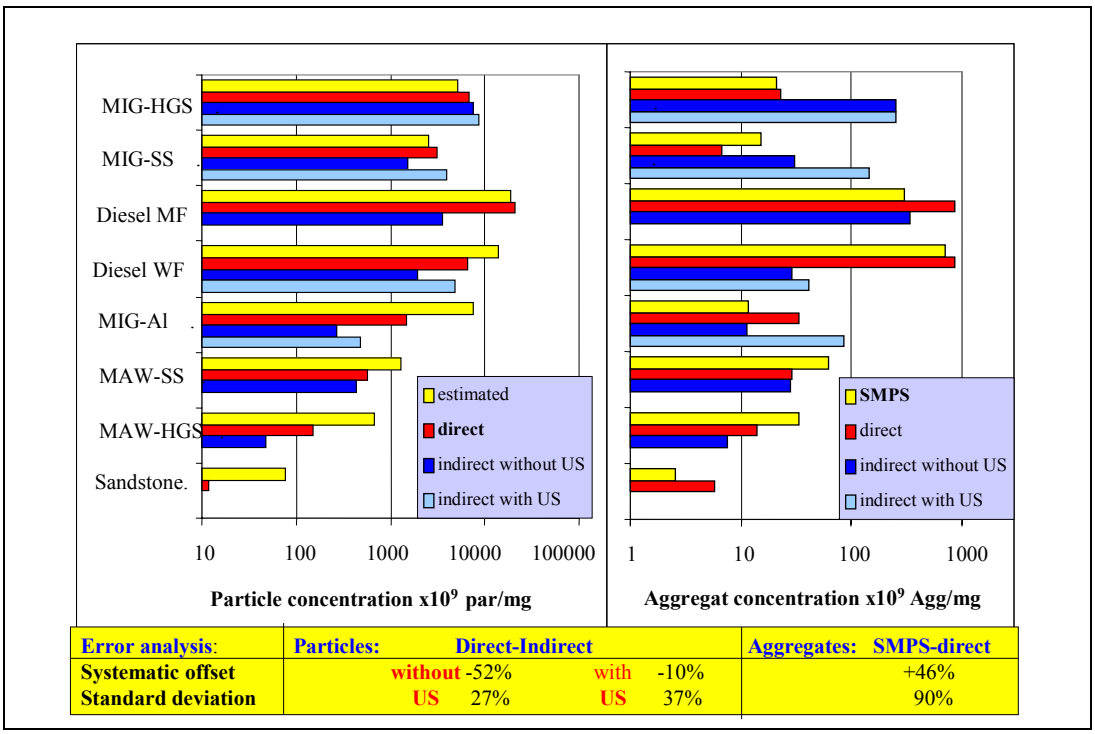


Figure 10 (see page 130) shows the results for the different aerosols after direct and indirect preparation summarized for the primary particle concentration (left) and the aggregate concentration (right). The highest particle number concentrations and aggregate number concentrations are found in diesel soot (with and without particle filters) at 10^{13} particles/mg and up to 10^{12} aggregates/mg, respectively; the lowest concentrations are found in sandstone dust. There are marked differences between the aggregate concentrations registered with SMPS and using direct preparation when compared to the indirect preparation method. In the latter case, an increase in the

aggregate concentration by a factor of 10 is observed for MIG welding on mild and stainless steel; a decrease is observed in the diesel soot with particle filter. This allows us to determine whether the aggregates decompose or stick together when in aqueous suspension.

Figure 10:
Particle and aggregate concentrations, direct preparation, and indirect preparation with and without ultrasound



US: Ultrasound, MF: filtered, OF: unfiltered

The conclusions from these studies are:

- The MPS finds ultrafine particles in each of the aerosols.
- The aggregate concentrations of the MPS are confirmed by the SEM at around 10,000x magnification and by the TEM at around 40,000x magnification.
- The concentration of the primary particles counted with the TEM is on average at around half of the earlier estimated quantities.

- These exceed those of the aggregates by factors of around 3 for sandstone, 10 to 20 for diesel soot and MMA, 100 to 300 for MIG welding, and 10^5 for carbon black.
- The number of primary particles per mg of the inhalable fraction depends on the type of the aerosol. $1 \cdot 10^9$ primary particles result for sandstone compared with $1{,}000 \cdot 10^9$ primary particles for diesel soot.
- For carbon black, the result per mg is 10^9 aggregates and $> 14{,}300 \cdot 10^9$ to $100{,}000 \cdot 10^9$ primary particles.
- In comparison to direct preparation, indirect preparation produces nearly the same primary particle concentrations. In contrast, an increase in the concentration of aggregates is observed for MIG welding and a decrease in concentration of aggregates is observed for diesel soot.

References

[1] *Rödelsperger, K.; Brückel, B.; Podhorsky, S.; Dahmann, D.; Hartfiel, G. D.; Woitowitz, H.-J.*: Characterisation of ultrafine particles with electron microscopy. In: *Heinrich, V.; Mohr, V.* (eds.): Crucial issues in inhalation research – mechanistic, clinical and epidemiologic. INIS Monographs. Fraunhofer IRB, Stuttgart 2002, p. 221-232.

[2] *Rödelsperger, K.; Podhorsky, S.; Brückel, B.; Dahmann, D.; Hartfiel, G.-D.; Woitowitz, H.-J.*: Charakterisierung von Aerosolen ultrafeiner Teilchen für den Arbeitsschutz. 43. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin e. V. Dresden. p. 631-634. Fulda, Rindt-Druck 2003

[3] *Rödelsperger, K.; Podhorsky, S.; Brückel, B.; Dahmann, D.; Hartfiel, G.-D.; Woitowitz, H.-J.*: Charakterisierung von ultrafeinen Partikeln für den Arbeitsschutz. Abschlussbericht für das Projekt F1804. Hrsg.: Bundesanstalt für den Arbeitsschutz und

Arbeitsmedizin (BAuA), Dortmund. Bremerhaven: Wirtschaftsverlag NW, Verlag für neue Wissenschaft 2003

[4] *Rödelsperger, K.; Podhorsky, S.; Brückel, B.; Dahmann, D.; Hartfiel, G.-D.; Woitowitz, H.-J.*: Measurements of granular ultrafine bio-durable particles for work-place protection. Eur. J. Oncol. 8 (2003) No. 2, p. 103-112

A thermal precipitator as personal sampler [1]

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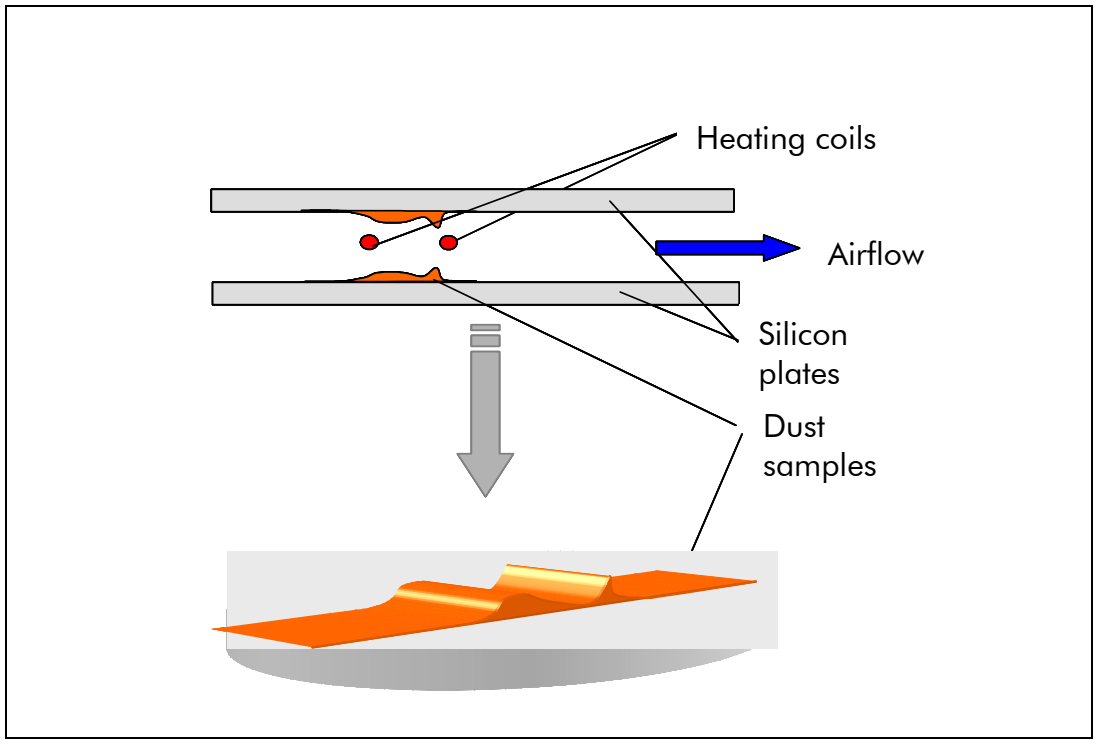
We have reduced and redesigned the thermal precipitator, well-known for decades, to such an extent that it can now be used as personal sampler and operated for the duration of a work shift without the need of fresh batteries. The working principle here (Figure 1) is for two heating coils to be placed very close together between two parallel silicon plates that are also very close together. The aerosol passes through the gap between the silicon plates at a rate of 0.5 ml/min. The ultrafine particles are deposited on the silicon plates due to temperature gradients.

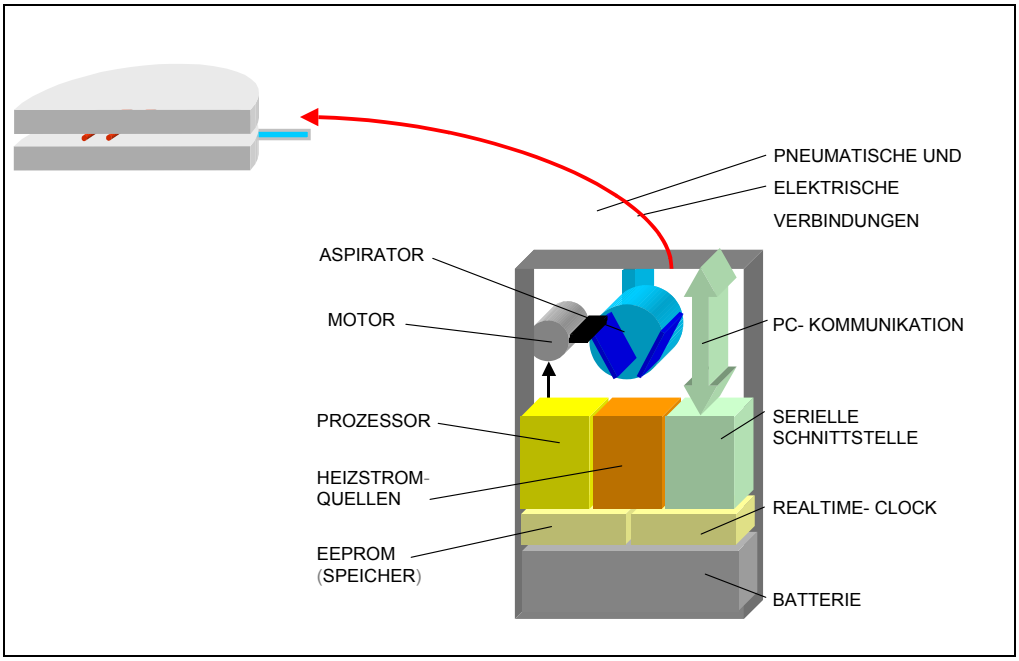
Figure 1:
Principle behind the portable thermal precipitator



[1] Version produced on the basis of an oral request; reviewed and authorized by the author.

The technical concept is shown in Figure 2; the device is depicted in Figure 3.

Figure 2:
Technical concept behind the personal thermal precipitator



Prozessor = processor, Heizstromquellen = heating power source, Speicher = memory, pneumatische und elektrische Verbindungen = pneumatic and electrical connections, serielle Schnittstelle = serial interface, Batterie = battery, Speicher = memory, PC-Kommunikation = PC communication

Figure 3:
Thermal precipitator as personal sampler

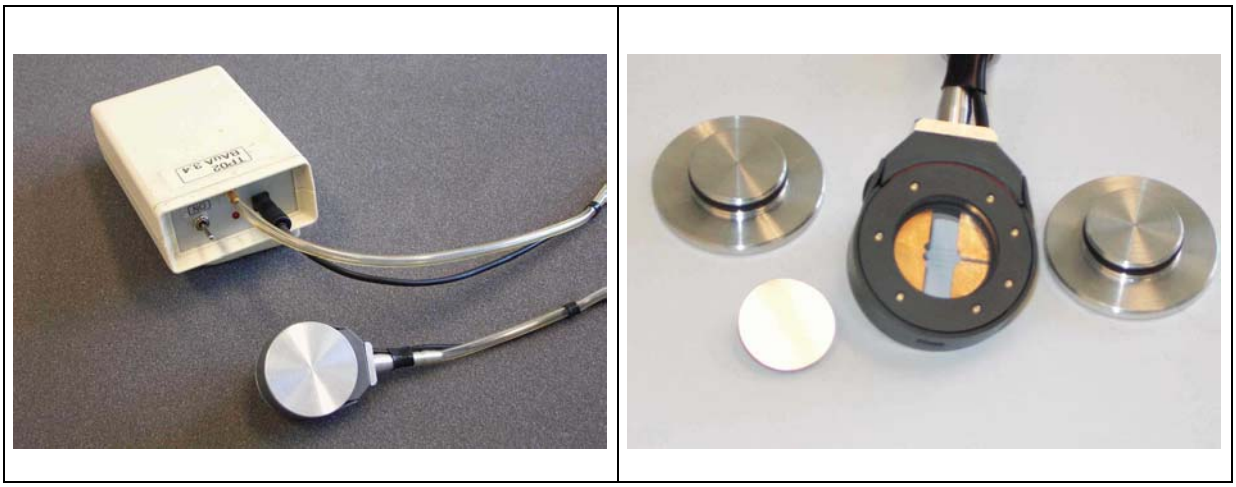


Figure 4 shows how the device is used as personal sampler. In this example, the sampling head is attached to the welder's facial shield; the power unit is attached to the clothing. The device features

- ❒ easy wearability
- ❒ simple handling (easy to change the preparation surfaces)
- ❒ recording of an entire shift possible without need for battery change
- ❒ non-critical use at higher concentrations

Figure 4:
Practical use of the small portable thermal precipitator

Inasmuch as the particles are not changed by the temperature (droplets), this technique allows to take a representative sample of ultrafine particles. Afterwards, the dust strips on the silicon plates are evaluated using an electron microscope in combination with image evaluation software.

Discussion

An important question about measurement techniques at the workplace is that of what the lower particle size limit should be. In other words, how small are the particles that can be found at the workplace? Figure 10 together with Figure 11 in the article by *Koch* can help answer this question: If we consider that the time period between the creation of the particle at the source and its inhalation (receptor) can be assumed to be ≥ 10 seconds, even at low concentrations of just a few $\mu g/m^3$ and a particle size of 1 nm at the source at the workplace (near the receptor), 1 nm particles can no longer arise. At higher concentrations, the average particle diameter at the location of the receptor increases through the process of coagulation as described in Figure 10. On the other hand, it must be kept in mind that particles smaller than around 10 nm are deposited mainly in the extra-thoracic regions of the respiratory tract. If neuronal transport really does occur from these regions in the nose into the brain as several studies suggest, the particles smaller than 10 nm should be taken into account when taking measurements. This would also lead to the conclusion that particle sizes down to around 5nm need to be considered when measuring ultrafine aerosols at the workplace. One suitable sampling device for this purpose is the thermal precipitator, as it allows for smooth collection of particles from the nanometre size range up to several μm in size that may then be studied further under the electron microscope. The vapour pressure of the particles here has to be negligible so that they are not changed in the temperature gradient field of the thermal precipitator.

Low pressure impactors, such as the Berner impactor or ELPI (Electrical Low Pressure Impactor), are quite useful for simple aerosols with low volatility. Yet when taking samples, aerosols with complex structures can undergo phase changes and be influenced by moisture, altering the particle morphology and causing artefacts to arise.

When the measurement results are compared – no matter if these were taken with the same or with different measuring procedures – the size range must be taken into consideration, especially at the lower limits of the recorded particle size range. When using electron microscopy to study ultrafine particles on nuclear pore filters

(e. g. Nuclepore), it must be kept in mind that particles that are smaller than the pores can also be deposited on the inside of the pores where they cannot be studied directly under the microscope.

Occupational safety and environmental protection in the industrial laser beam ablation process [1]

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This presentation reports on a research project that was initiated and supported by the German Federal Ministry for Education and Research (Bundesministerium für Bildung und Forschung – BMBF) and by the German engineers' association (Verein Deutscher Ingenieure, VDI). Also contributing to the project were the BG Institute for occupational safety and health – BIA, which also took on the project leadership role, the laser centre in Hanover (Laser Zentrum Hannover – LZH), and the institute for hygiene and occupational medicine (Institut für Hygiene und Arbeitsmedizin – IHA). Project partners from industry are shown in Figure 1.

Figure 1:
Project partners from industry

[1] Transcription on the basis of the oral presentation; reviewed and authorized by the author.

The project was concerned with the emissions of aerosols and other hazards caused by material processing using lasers under real-world workplace conditions (Figure 2).

Figure 2:
Hazards of laser material machining and processing to workers and the environment

Partners were selected from different parts of the project group to deal with

- precision machining of metal surfaces
- precision drilling and removal of metallic and ceramic materials
- precision structuring of glass and thin layers using laser beams
- precision surface cleaning of technical and natural materials.

Figures 3 to 5 (see pages 141 and 142) show examples of material processing using lasers. The principle at work here is that the laser beam is applied to the material surface, heating a discrete small part of the surface with concentrated energy causing the material to vaporise. The by-products formed in recondensation, are potentially toxic; the health risk is an open question in occupational hygiene and occupational medicine.

Figure 3 shows the example of a very small, very precise hole drilled in metal using laser technology, much as such a hole might be needed in modern fuel injection systems. Figure 4 shows a hole drilled in diamond using lasers.

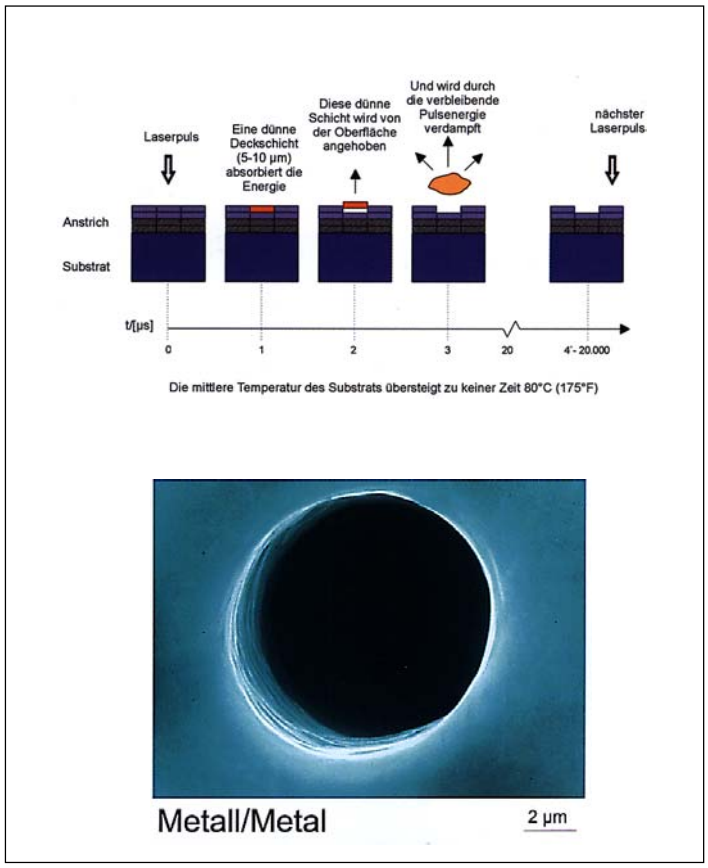


Figure 3:
Precision metalworking using copper vapour lasers

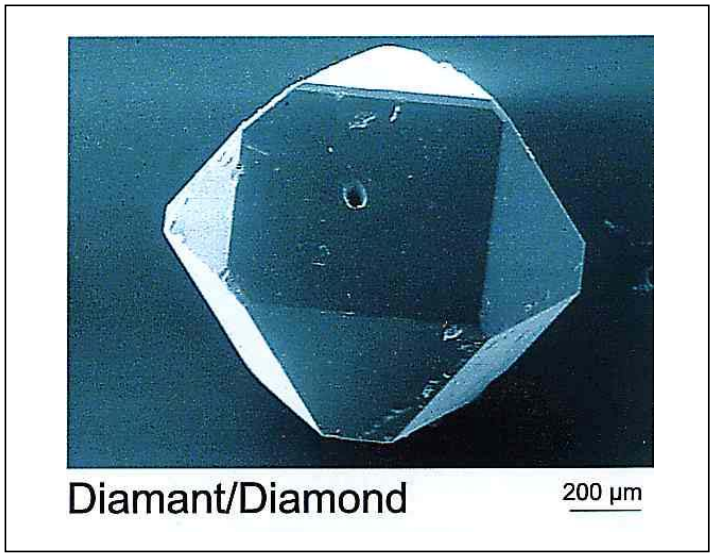


Figure 4:
Precision diamond cutting using copper vapour lasers

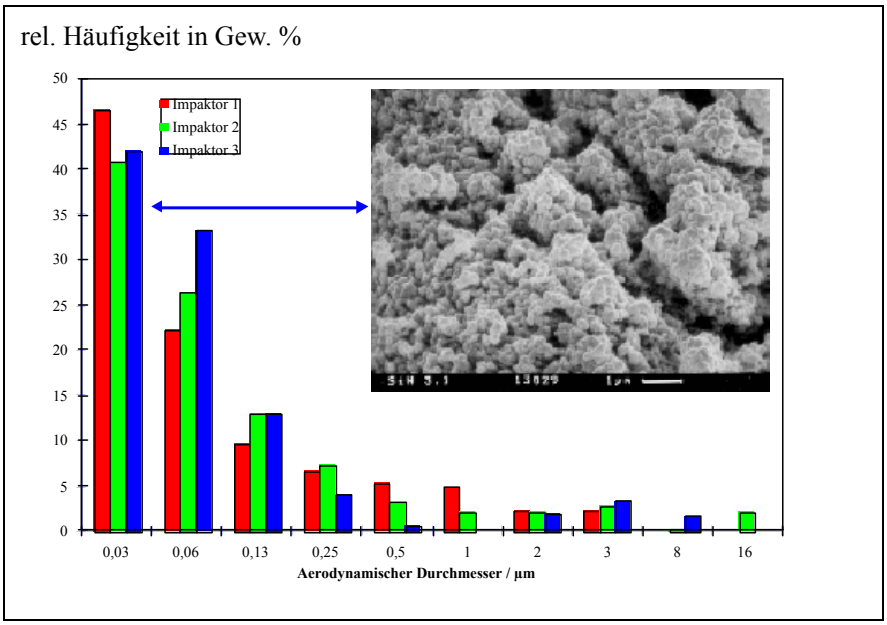
Ceramics are materials very difficult to process. In particular, ceramic composite materials are high-tech materials that are used in modern engines and turbines and several other specialised technical fields. These ceramics can be drilled, cut, structured, and smoothed using laser beams (Figure 5).

Figure 5:
Precision machining of ceramics using copper vapour lasers

During the surface machining of a ceramic material (Figure 6), dust measurements were taken using cascade impactors (Figure 7, see page 143).

Figure 6:
Surface machining of ceramics

Figure 7:
Results of the dust measurements taken during ceramic surface machining



rel. Häufigkeit in Gew. % = relative occurence in weight-%,
Impaktor = impactor, aerodynamischer Durchmesser = aerodynamic diameter

The largest portion of the particles (shown in weight-%) was the size classes of 100 and 50 nm in aerodynamic diameter. The respirable dust concentrations lay below 0.09 mg/m³, which can be ascribed to the effective protective measures of enclosing the procedure in a casing, vacuuming the materials off locally at the source, and vacuuming the processing cabin (Figure 8).

Example: Surface machining of ceramics

Respirable dust fraction: 0.09 mg/m³

Respirable dust DFG: 1.5 mg/m³ (now 3 mg/m^3)

4,13 mg/m³ worst case without protective measures
Hygienic values for ultrafine dusts currently in processing

Protective measures:
Closed encasement for the procedure
Local vacuuming at the source
Vacuuming of the processing cabin
Separator in the work area (clean air return)
Fresh air and exhaust for the work area

Figure 8:
Protective measures used in the surface machining of ceramics

Figure 9 (see page 145) shows the median particle sizes of the aerosols that arise in 19 different industrial laser procedures arranged in terms of the type of materials that are processed; Figure 10 (see page 145) shows the corresponding emission and exposure values.

Summary

1. The emission measurements for all the studied procedures indicated a high proportion of fine dust particles (alveolar dust). The median particle diameter depends on the type of material being processed:
   Organic materials > metals > ceramic materials.

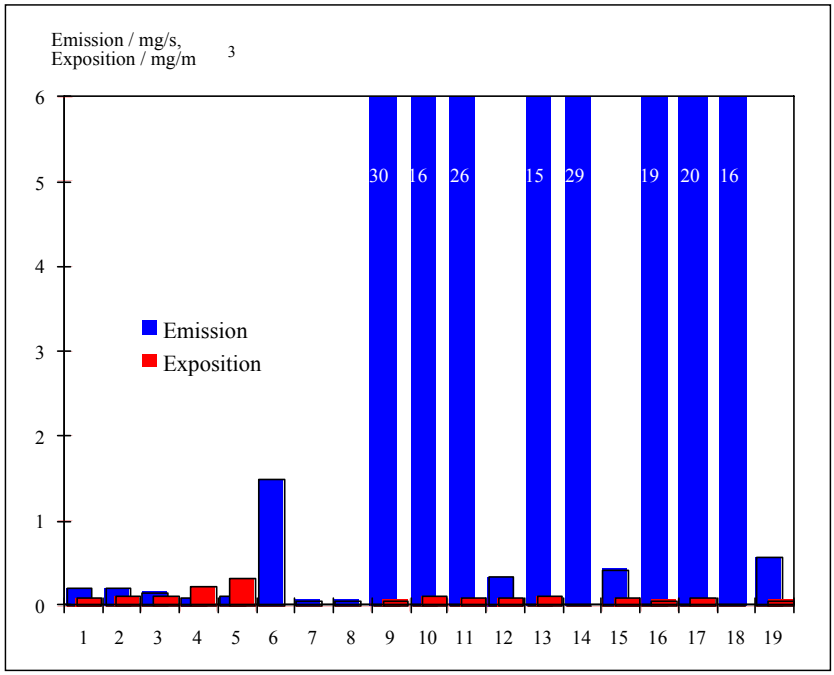
2. Laser machining and processing of metals and plastics at times produces large quantities of ultrafine dust (emissions). One example is ceramic materials: some 40 weight-% of particles with an aerodynamic diameter of ≤ 0.03 μm.

3. In the exposure measurements, no elevated concentrations could be found under normal conditions when using available enclosures and other protective equipment. Eliminating the protective equipment produced a measurement of (in one worst case) 4.13mg/m^3 of respirable dust.

4. All of the procedures studied can be considered to be safe in terms of the hazards investigated here during normal operation and at the current state of our knowledge.

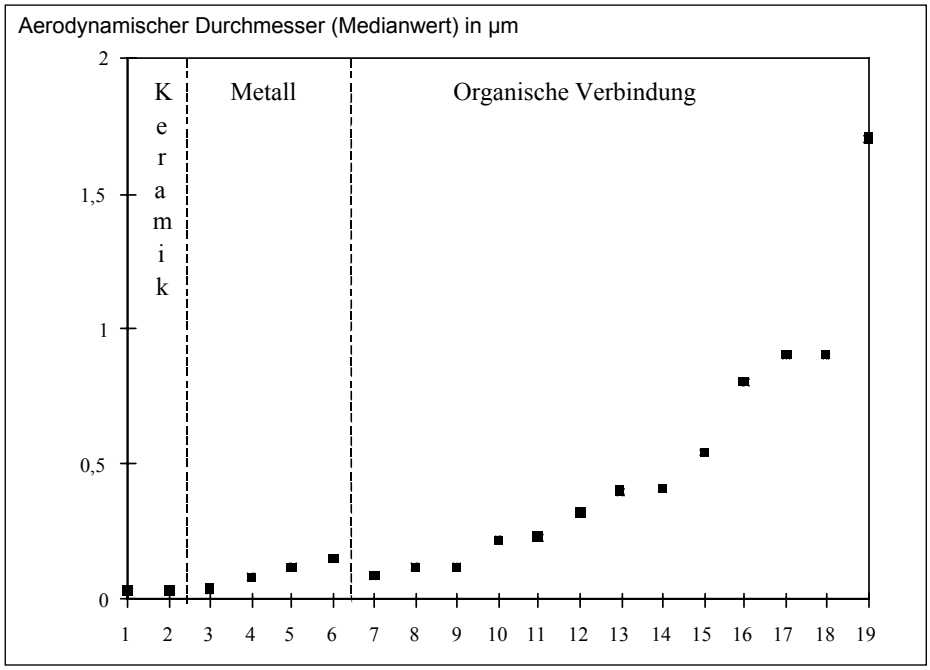
5. In the set-up and trial operations, special attention must be paid also to the hazardous substances side. Much higher concentrations may arise.

Figure 9:
Emission and exposure measurements in the 19 facilities under study that also use laser machining and processing



Emission = emission
Exposition = exposure

Figure 10:
Median particle size in 19 facilities where laser processing is in use, sorted by type of materials being processed



Concluding remarks

1. Small firms using laser processing were not studied; when the author visited such so-called job shops that produce large quantities of parts as piecework, the work hygiene conditions appeared to be in a very poor state.

2. Laser manufacturers also sell their equipment without air suction devices. One query found that around 50 % of the devices are sold "inexpensively", or in other words, without such equipment (from a remark in a discussion at a working colloquium at the LZH in Hanover in the spring of 2000).

3. The significance of polycyclic aromatic hydrocarbons (PAH) on the surface of the dusts needs more intensive research.

4. Laser dusts have an indefinable surface quality that is not predictable merely by looking at the compounds of the materials being processed ("bulk"). Positive and negative changes to the toxic potential have both been found [1].

References

[1] *Bruch, J.; Rehn, B.* et al.: Industrial hygienic evaluation of emission of laser processing. ILSC ´97 Orlando (Florida). Ed.: Laser Institute America, LIA. Vol. 3, p. 269-278

Ultrafine particles at industrial workplaces [1]

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This paper uses the example of workplaces in the carbon black industry to illustrate methods for studying ultrafine particles at industrial workplaces. Quasi-online instruments, such as SMPS (scanning mobility particle sizers), APS (aerodynamic particle sizers), and TEOM® (tapered element oscillating microbalance) were used to measure the number size distribution and mass concentration (Figure 1) at different workplaces. Manual filtration samplers were also used at the workplaces to verify the PM_X mass concentrations obtained by the TEOM® and to analyse the loaded filters chemically for TC (total carbon) and EC (elemental carbon).

- Number size distribution; SMPS and APS
- PM_x mass concentration with TEOM (online) and manual filtration samplers
- Chemical analysis for TC and EC
- Number size distribution and PM_x mass concentrations online in parallel at a workplace and a reference point

Figure 1:
Measuring devices used for measurements at carbon black industry workplaces

Parallel to the measurements at the workplace, the number size distributions and PM_x mass concentrations were measured at an outside station for comparison. This made it possible to take the outdoor air influences on the workplace measurements into consideration.

[1] Transcription on the basis of the oral presentation; reviewed and authorized by the author.

Figure 2 shows a semiautomatic packing facility filling carbon black into bags, weighs them, and then packages these bags into larger packing units. The online instruments were inside the two white housings on the left beside the conveyor belt.

Figure 2:
Measurement instrument setup at a semi automated packing facility

Figure 3 (see page 149) shows the mass concentrations in $\mu g/m^3$ as measured with the TEOM for PM_{10} dust concentrations over time, both for measurements taken outside (in light grey) and at the workplace itself (in black). The beginning and the end of the shift and the lunch break can easily be detected in the graph.

In Figure 4 (see page 149), the corresponding graph of the particle concentration over time is given in cm^{-3}. The upper curve displays the particle size range of 15 nm to 100 nm (ultrafine particles); the middle curve displays the range of 200 nm to 700 nm; and the lower curve displays the size range of 2.5 μm to 10 μm. This figure shows that the number concentration of the larger particles (2.5 μm to 10 μm), as with the PM_{10} mass concentration (Figure 3), reflects the workplace activity. This interdependency is not found for the accumulation class (0.2 to 0.7 μm) and for the number of ultrafine particles.

Figure 3:
Mass concentration at facility 1

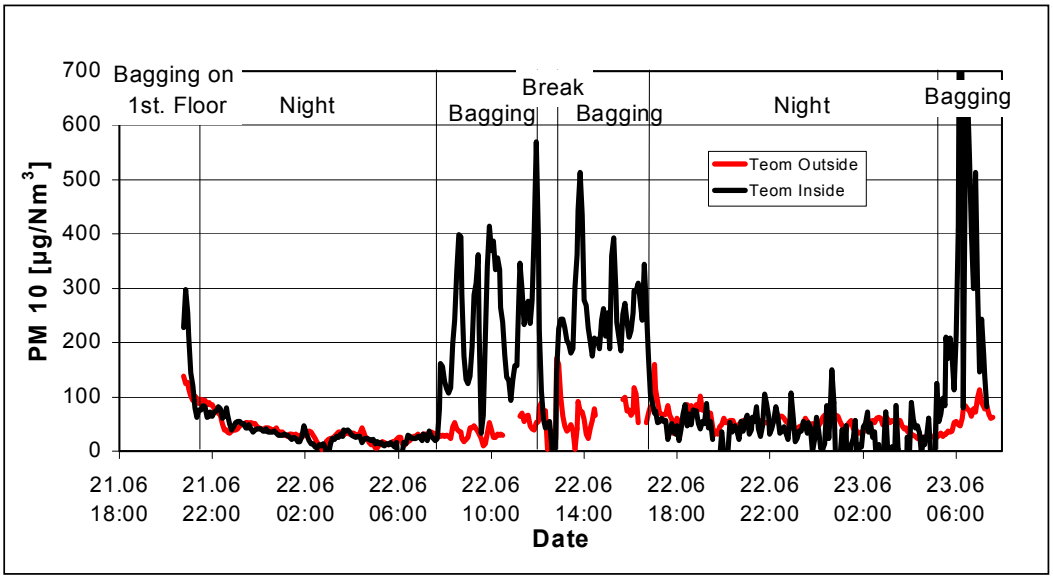
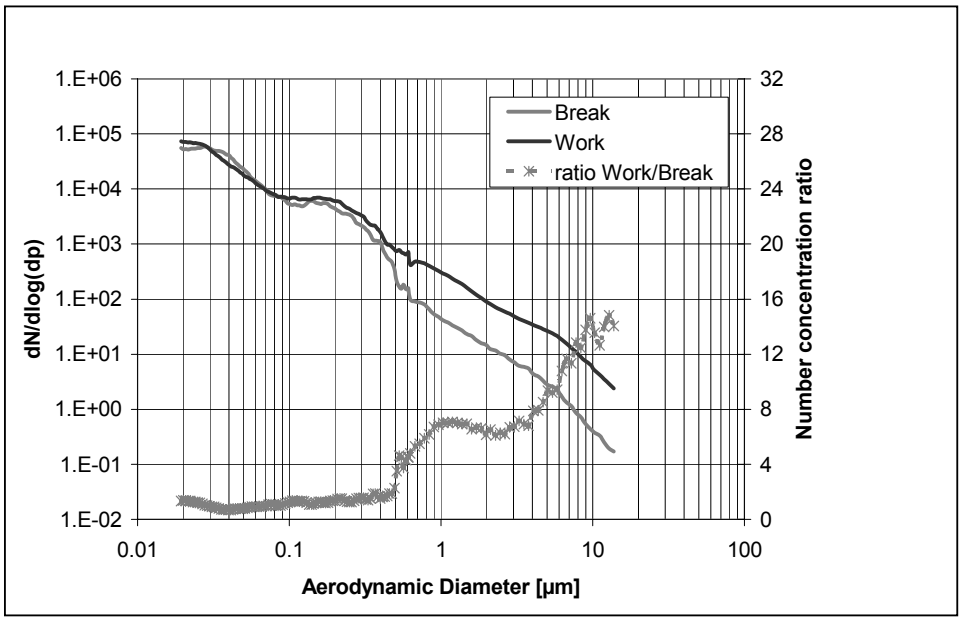


Figure 4:
Particle concentration at facility 1 over time

Figure 5 (see page 150) shows the average number size distribution that was measured at facility 1 both during the work phase and during the break. The lower curve (right-hand scale) shows the ratio of the two particle size distributions. This

"relative" particle size distribution (ratio) is thus the size distribution of the particles emitted by process.

Figure 5:
Average number size distribution during the work phase and during the break at facility 1



The curve makes it clear that no appreciable particle emissions from the work process are present up to around 500 nm. The size of the emitted particles is mainly around 1 μm and around 10 μm and larger.

Figures 6 and 7 for facility 2 (see page 151) correspond to Figures 4 and 5 for facility 1. These show the relationships at facility 2, whereby the outdoor air was also measured here (at around 500 to 600 m away from the facility).

The comparison of the PM_x mass concentrations in the outdoor air (comparison point) and at the workplace gives a picture similar to that of Facility 1. The influence of workplace activity on particle concentrations (2.5 to 10 μm) can be easily seen in Figure 6.

In contrast to facility 1, elevated ultrafine particle concentrations can also be discerned (Figure 7).

Figure 6:
Particle concentration at facility 2 over time

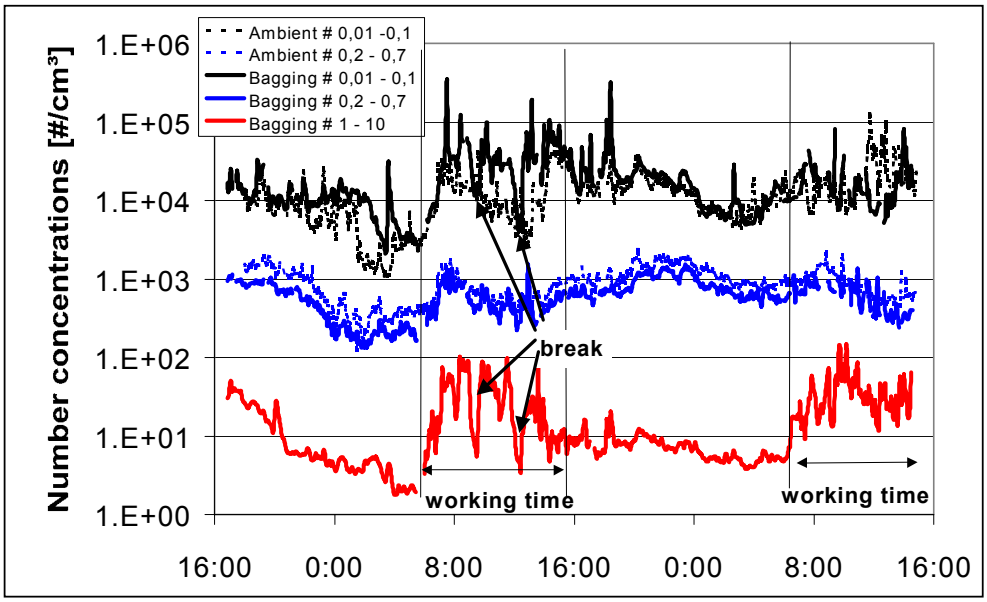
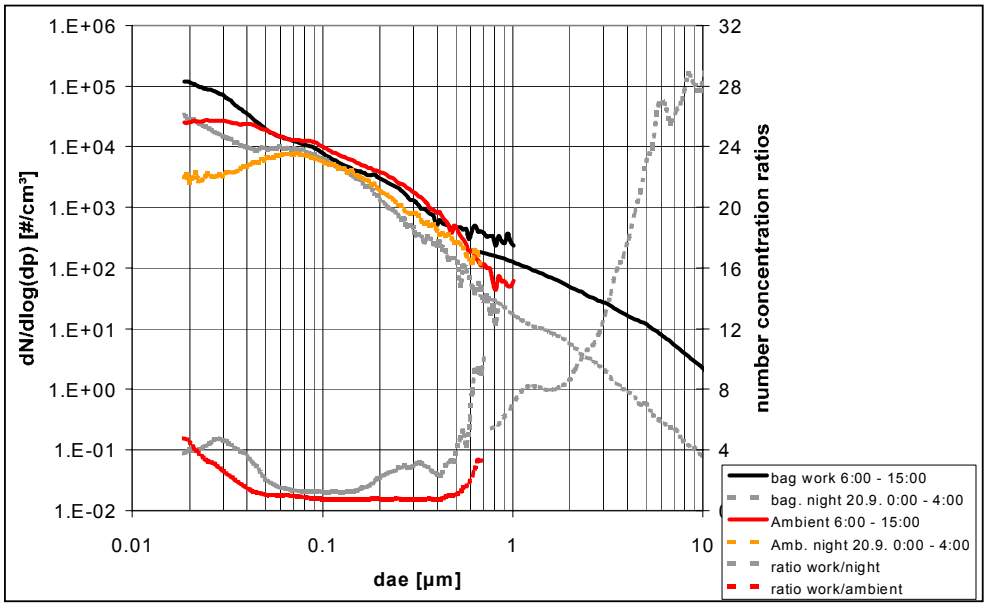


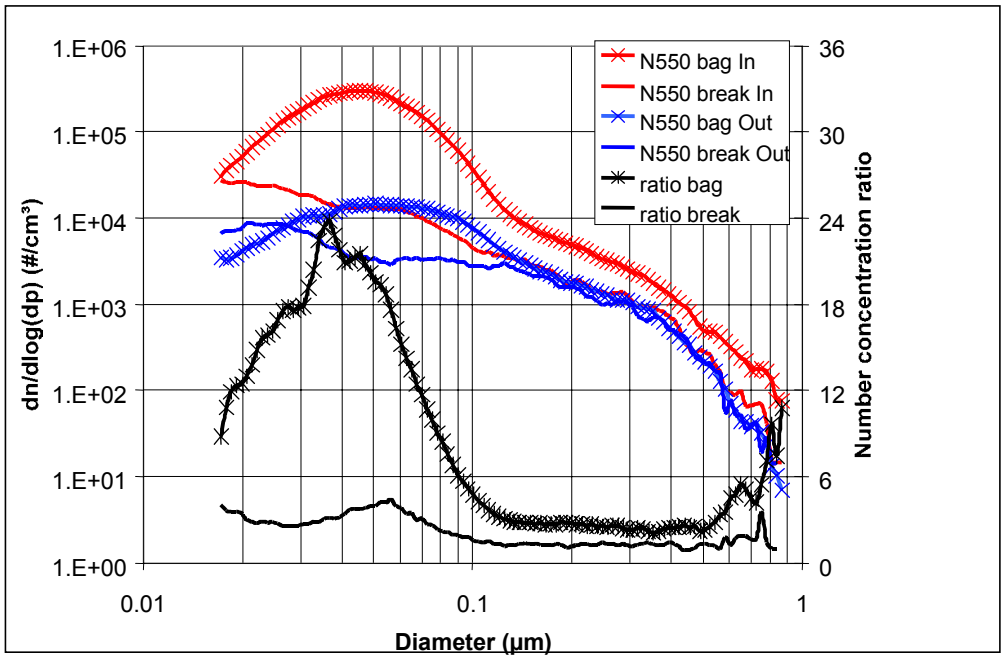
Figure 7:
Average number size distribution during the work phase
and during the break at facility 2



In Figure 8 (see page 152), the particle number size distributions and their inter-relationships at facility 3 are shown. As at facility 2, elevated number concentrations

of ultrafine particles were also measured here. The increase in the number of ultrafine particles was markedly higher at facility 3 than at facility 2.

Figure 8:
Particle concentration at facility 3 over time



At facility 3 measurements were taken both inside and outside the facilities (Figures 8 and 9). The curve of the soot concentration (BCopt) shown in Figure 9 (see page 153) was determined using optical density measurements of carbon black layers. On the basis of the recorded workplace activity and detailed analyses (e. g. Figure 9, sporadic maxima of the soot concentrations without elevated PM_x mass concentrations), it was found that the elevated concentrations of ultrafine particles correlated to forklift truck activity. The particle number size distributions in Figures 10 and 11 (see pages 153 and 154) were thus determined at a time when no other workplace activities occurred. These measurements showed that the forklift trucks are a source of ultrafine particles, with lower particle emissions for gas-powered forklifts (Facility 2, Figure 10) than for diesel fork lift trucks (Facility 3, Figure 11).

Figure 9:
PMs and BC mass concentrations at facility 3

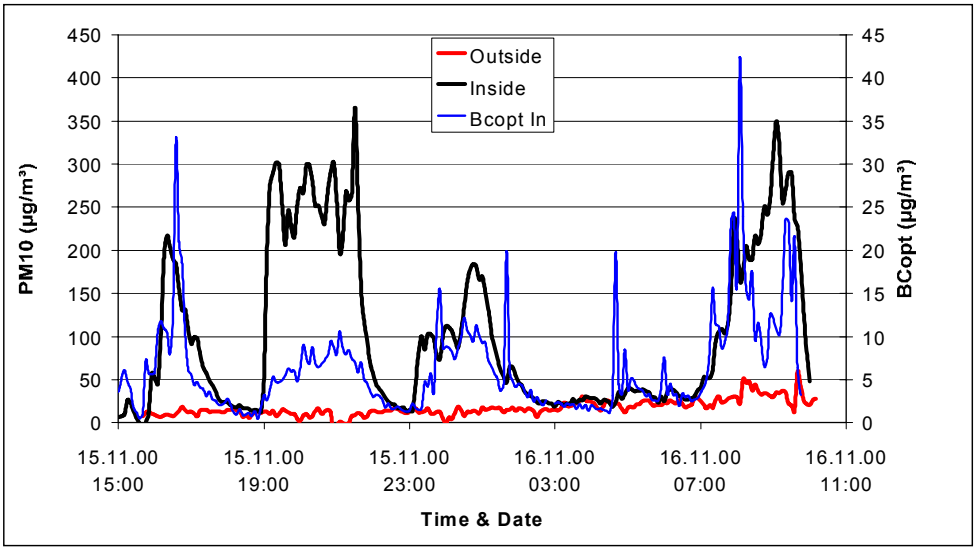
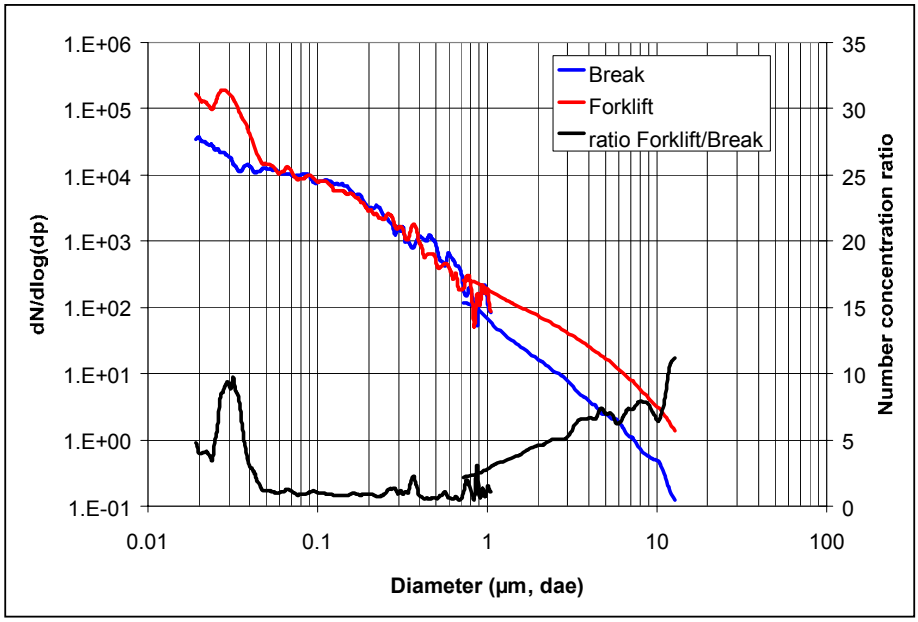
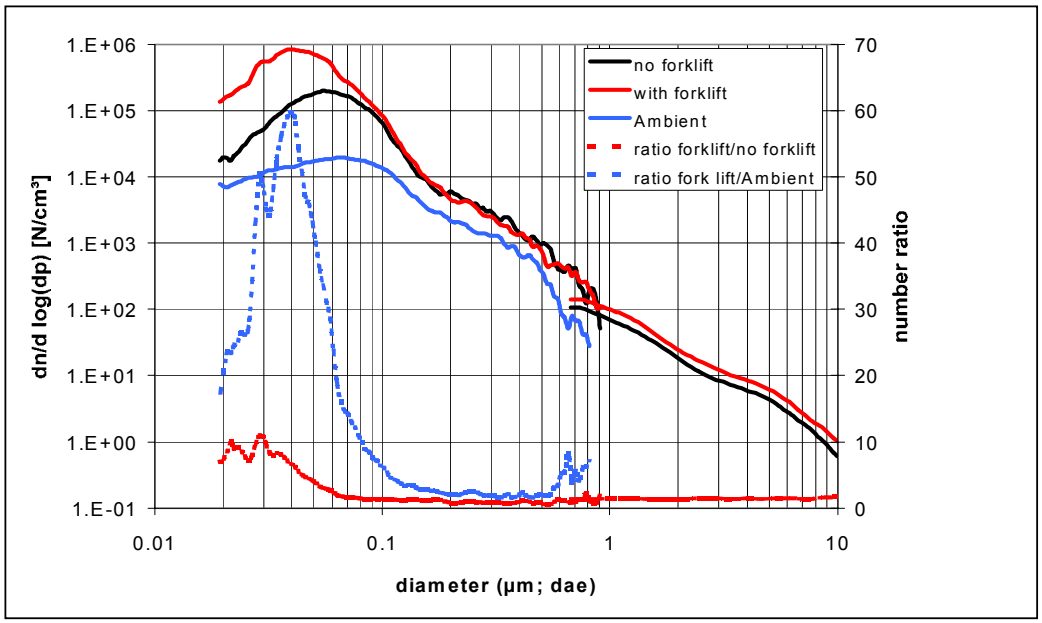


Figure 10:
Particle number size distribution, propane gas-powered forklift truck at facility 2



Only discontinuous sources of particles can be recorded by using the method of comparing working phases to break periods or workplace to outdoor air during the workday as described so far.

Figure 11:
Particle number size distribution; diesel forklift truck at facility 3



By comparing the outdoor air to that of the workplace over longer intervals – even outside active working hours – continuous sources can also be found, and their particle emission can be described. This approach thus also identifies an additional source of ultrafine particles: continuously run small gas heating units which were used at facility 3 to keep the facilities warm. Not all the ultrafine particles found in the air at a given workplace must thus originate from the work process itself. Finding all the different potential sources of emissions requires further investigation.

Figure 12 (see page 155) shows measurements from the reactor area in carbon black production during two different time periods – period A and period B. Although the reactor was run continuously without any changes, the measurements taken at different times were different. The particle size distributions for concentrations < 10,000/cm³ both within and outside the reactor area are similar; the same is true for concentrations > 20,000/cm³ (Figure 13, see page 149). This leads to the suspicion that changes in the wind direction caused the differences shown in Figure 12. A street was located around 300 m away from the facility: another source of pollutants outside the facility.

Figure 12:
Measurements within the reactor area at facility 2
during two different periods

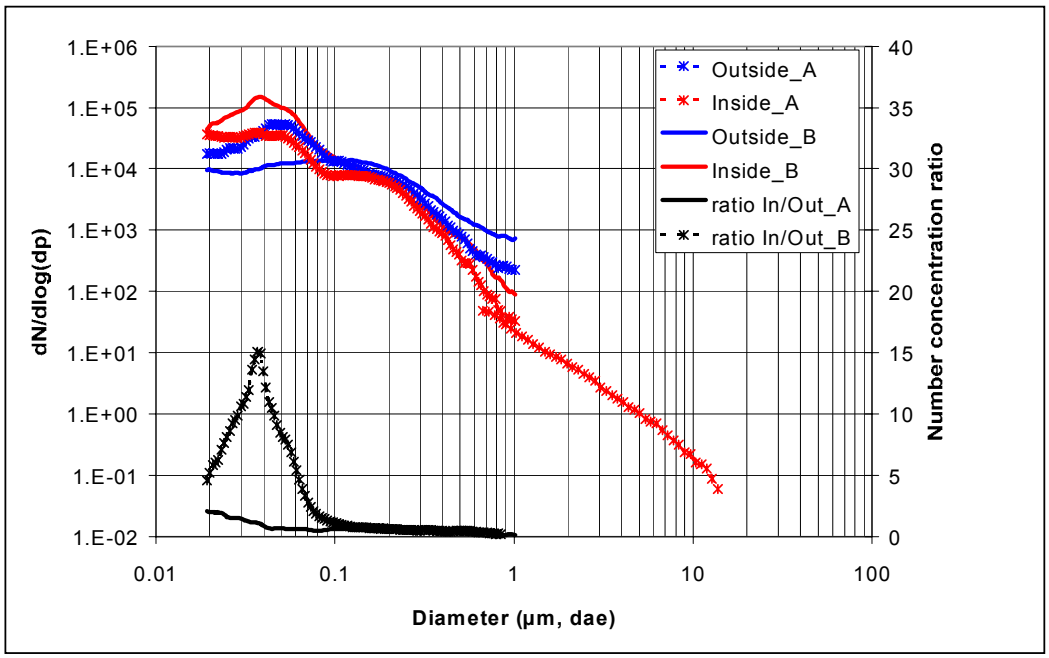
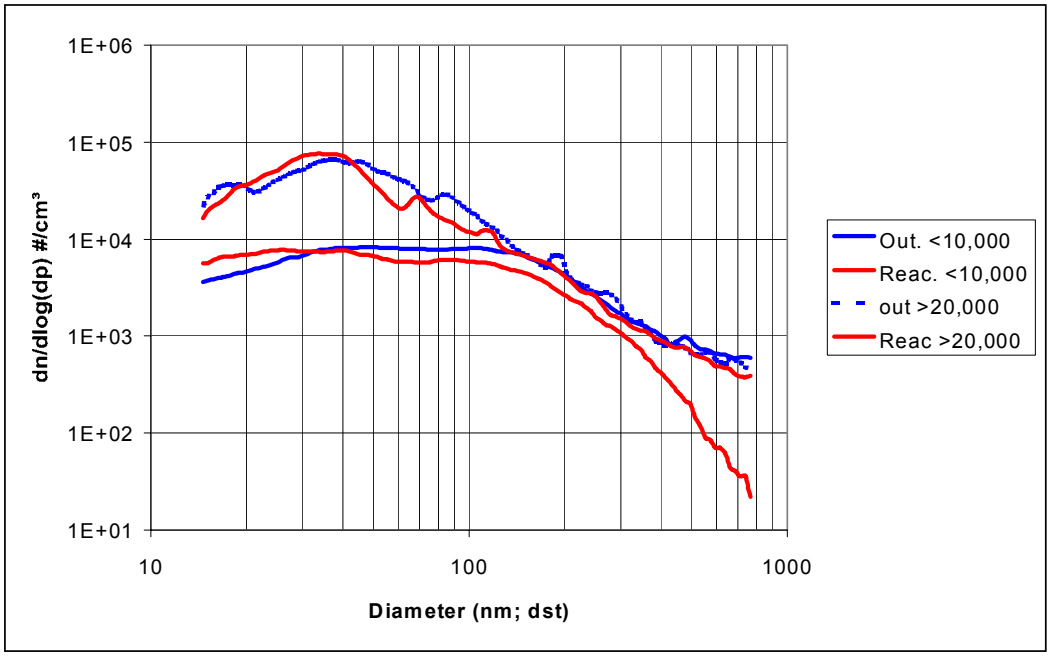


Figure 13:
Number size distribution at facility 2



Summary

- Packing increases the number concentrations mainly for particles > 0.4 μm.
- Influencing factors included packing speed, workplace ventilation, and location of sampling.
- At facility 1, no increase is discernible in the number concentrations of ultrafine particles.
- Ultrafine particles found at facilities 2 and 3 are explained by emissions from fork-lift trucks and gas heaters.
- Ultrafine particles in the reactor area at facility 2 are explained by a source outside the facility (probably road traffic).
- When taking measurements at workplaces, it is important to be able to distinguish continuous from discontinuous sources and to identify sources at the workplace and outside influences.
- Potential methods for conducting such studies are shown.

Ultrafine particles created by welding and allied processes

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1 Introduction

During welding and allied processes mixtures from gaseous and particulate substances are formed by means of chemical and physical processes from materials (base and filler metals), auxiliary materials, impurities etc. The chemical composition of the particulate substances mainly depends on the materials. The amount of particles depends on the combination of the processes and materials used. In each group of processes different particle sizes with different particle morphology are formed. On one hand, the toxicology of the mixtures depends on the chemical composition, on the other hand on the size of the particles formed (particle diameter).

2 Particle size, morphology, chemical composition

2.1 Welding – particle size, morphology

During welding (manual metal arc welding, gas-shielded metal arc welding, tungsten inert gas welding) particulate substances are formed with a particle size (aerodynamic diameter) of $< 1\ \mu m$, mostly even $< 0.1\ \mu m$, generated predominantly from the welding consumables. In practice they are referred to as "welding fumes". The contingent of particles $< 0.1\ \mu m$ is called ultra-fine particles. Welding fumes are definitely respirable.

Comprehensive studies concerning particle size, morphology and chemical composition of welding fumes were carried out on a national as well as on an international level. These studies lead to the conclusions explained in the following.

During manual metal arc welding with covered electrodes the majority of the particles have a size between 0.02 and 0.4 µm. These particles are partly agglomerated.

During gas-shielded metal arc welding the maximum of the particle size distribution is in the range between 0.01 and 0.05 µm. Only very few individual particles reach sizes greater than 0.2 µm. Here as well agglomerated particles are found.

Electron microscope examinations of welding fumes showed that the individual particles have a spherical shape. Secondary particles are formed by flocculation of spherical primary particles. Thus, for example during manual metal arc welding of stainless steel, mainly two types of particle chains are formed, namely chains with very fine particles up to 0.05 µm and chains with larger particles up to 0.4 µm. The length of both chain types may be several micrometers. The agglomerates of primary particles are in the range of up to 0.5 µm. Some examples for the size, form, and shape (morphology) of welding fume particles are shown in table 1.

Table 1:
Particle size, form, and morphology of welding fumes (examples)

Procedure	**Material**	**Particle**			
		Individual particle form	**Size**		
			Individual particle (diameter)	**Chains (length)**	**Agglomerates (diameter)**
Manual metal arc welding with covered electrodes MMA	Cr-Ni steel	spherical	up to 50 nm	several µm	up to 500 nm
			up to 400 nm	several µm	
Gas shielded arc welding MAG/MIG	Cr-Ni steel	spherical	up to 10 nm	to 100 nm	up to 100 nm
	Aluminium alloys	spherical	10 to 50 nm up to 400 nm	n.a.	n.a.
					
n.a. = not available					

During MIG welding on aluminium alloys, the particles found in the welding fumes have particle sizes of < 0.4 µm nearly without exception. The majority of these particles have sizes between 0.01 and 0.05 µm. Examples of electron micrographs of welding fumes are shown in Figures 1 and 2 (Figure 2, see page 160).

The maximum of the particle size distribution during MAGC welding is in the range of 0.01 to 0.05 µm. Only very few particles have a particle size of 0.2 µm or larger. The individual particles are nearly all smaller than 0.4 µm.

During gas-shielded metal arc welding of stainless steel, chains and agglomerates of relatively homogeneous particle sizes are formed. The particle size is up to 0.01 µm. The chains and agglomerates have sizes in the range of up to 0.5 µm. Morphological studies suggest that individual welding fume particles do not have a homogeneous composition.

Figure 1:
Electron microscope photo of welding fume particles formed by MIG welding on aluminium alloys

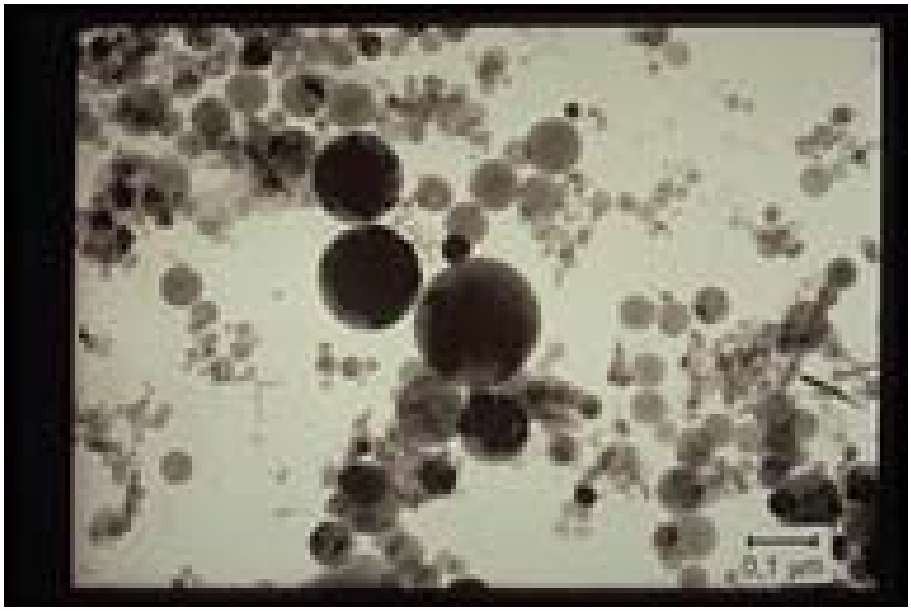
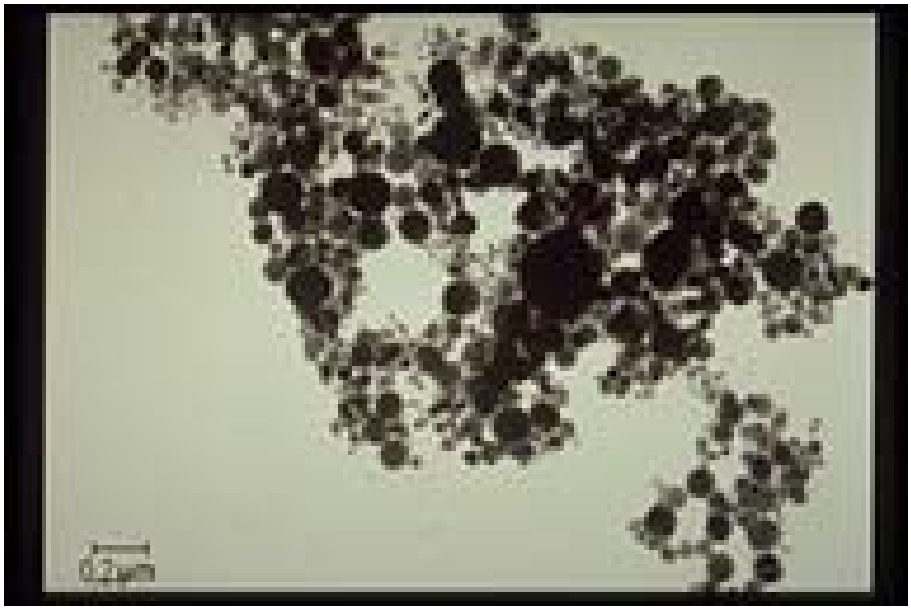


Figure 2:
Electron microscope photo of welding fume particles formed by MAGC welding



Studies on the characterisation of welding fumes were as well carried out by the American Welding Society (AWS) during manual metal arc welding and during metal active gas and metal inert gas welding using different welding consumables (electrodes, wires).

The following process and material combinations were used:

1. Manual arc welding with unalloyed electrode
2. Manual metal arc welding with unalloyed basic electrode
3. Metal active gas welding with low alloyed steel wire and inert gas: carbon dioxide
4. Metal active gas welding with low alloyed flux-cored wire and shielding gas: argon/carbon dioxide
5. Manual arc welding with high alloyed Cr-Ni covered steel electrode
6. Metal inert gas welding with aluminium-alloyed wire.

The studies of the welding fumes showed that for

- low alloyed consumable 61.9 %
- high alloyed Cr-Ni consumable 75.3 % and
- aluminium-containing consumable 29 %

of the number of particles in the welding fumes were < 0.2 µm.

The proportions describes above are distributed over the total mass of all particles of a welding fume (see above), as follows:

- 5.4 % in the welding fume of the low alloyed consumable
- 15.9 % in the welding fume of the high alloyed Cr-Ni support materials
- 1 % in the welding fume of the aluminium-containing support materials.

For percentage of the relevant surface in comparison to the total surface area of all particles < 1 µm is 25.9 %, 42.3 %, and 11.3 %, respectively. Tables 2 to 4 (Tables 3 and 4, see page 162) show the particle size distributions for some of the welding fumes mentioned above.

Table 2:
Particle size distribution in the welding fume;
E6010 (unalloyed welding consumable)

Particle diameter Ø in µm	< 0.2	< 0.4	< 0.6	< 0.8	< 1.0	≥ 1.0
Number	620	331	38	6	2	5
% of number	61.9	33.0	3.8	0.6	0.2	0.5
% of mass (Ø < 1 µm)	9.1	47.9	23.6	9.4	9,9	-
% of surface area (Ø < 1 µm)	25.9	49.6	16.3	6.3	1.9	-
% of total mass	5.4	24.2	15.5	4.3	4.1	46.6

Source: AWS study

Table 3:
Particle size distribution in the welding fume
E308-16 (high alloyed Cr-Ni consumable)

Particle diameter Ø in µm	< 0.2	< 0.4	< 0.6	< 0.8	< 1.0	≥ 1.0
Number	800	251	9	0	1	2
% of number	75.3	23.6	0.9	0	0.1	0.2
% of mass (Ø <1 µm)	16.8	46.7	8.2	0	28.1	-
% of surface area (Ø <1 µm)	42.3	49.3	6.2	0	2.2	-
% of total mass	15.9	38.7	7.5	0	8.2	29.7

Source: AWS study

Table 4:
Particle size distribution in welding fumes
E5356 (aluminium welding additive)

Particle diameter Ø in µm	< 0.2	< 0.4	< 0.6	< 0.8	< 1.0	≥ 1.0
Number	289	434	195	46	24	10
% of number	29.0	43.5	19.5	4.6	2.4	1.0
% of mass (Ø <1 µm)	1.4	15.1	32.5	22.2	28.8	-
% of surface area (Ø <1 µm)	11.3	33.3	30.4	15.1	9.9	-
% of total mass	1.0	10.6	22.8	15.6	20.2	29.8

Source: AWS study

These studies also show that the average diameters of all particles are between 0.1 and 1 µm, thus lying within the respirable range. Only a few particles are > 1 µm and many particles only have a size of 0.01 µm. Analysis of the chemical composition of the particles shows that there are significant variations. Therefore it must be anticipated that the toxicity of these fumes differs significantly.

As to the particle size distributions in the studied fumes, it was found that they are rather similar. The type of the consumables used, the chemical composition of the welding fumes, or the chemical composition of the individual particles seem to have little effect on the particle size distribution, for example

- the average diameter of all particles (in terms of the number of individual particles) is from 0.14 to 0.33 µm,
- the average diameter of all particles (in terms of the surface of individual particles) is from 0.21 to 0.41 µm,
- the average diameter of all particles (in terms of the volume of individual particles) is from 0.34 to 0.64 µm.

There is little variation in the average particle diameter among the chemical categories in a given fume, for example, 0.09 to 0.54 µm for E6010; 0.06 to 0.30 µm for E70S-3; and 0.06 to 0.27 µm for E308-16.

The reverse is also true. There is little variation among the different fumes for a given chemical category. These diameters are for example 0.14 to 0.17 µm for Fe; 0.13 to 0.20 µm for Fe-Mn; and 0.11 to 0.18 µm for K-Fe.

For these representations 1 µm was set as upper limit. 90 % of the particles have a diameter of < 1 µm. The number of particles that are > 1 µm is so low that the diameters determined by the data are statistically insignificant.

2.2 Chemical composition of the fumes

The chemical composition of the fumes was evaluated in the AWS study by means of three methods: X-ray diffraction of the bulk fume, STEM analysis of few individual particles, SPEC analysis of a large number of particles. A wet chemical analysis was also carried out.

For the above-described welding fume types, these methods enable the specification of the relation between the chemical composition and the main categories of particles. Table 5 (see page 164) shows the chemical composition of the particles for six different welding fumes, classified according to main categories. Table 6 (see page 165) shows the chemical compositions of the same welding fumes established by the wet

analysis. Table 7 (see page 165) shows the specific surface area of welding fumes with different chemical compositions.

Table 5:
Chemical composition of the particles in different welding fumes

MMA[1] with unalloyed electrode (E6010); composition according to category			
Main category	Percentage of the particle number in %	Mean diameter in µm	Composition in %
Fe/low Si	31	0.188	Si(36) Mn(4) Fe(56)
Fe/high Si	10	0.245	Al(21) Si(46) K(9) Fe(21)
Fe-Mn	16	0.202	Si(36) Mn(14) Fe(44)
Ca-Fe	8	0.169	Si(37) Ca(13) Fe(43)
MMA[1] with unalloyed basic electrode (E7018); composition according to category			
Main category	Percentage of the particle number in %	Mean diameter in µm	Composition in %
K-Fe	14	0.179	Si(18) K(36) Fe(28)
Ca-Fe	15	0.158	Al(7) Si(17) Ca(25) Fe(37)
K-Ca-Fe	48	0.188	Al(4) Si(10) K(28) Ca(22) Fe(23)
MAGC[2] with lowly alloyed solid wire (E70S-3); composition according to category			
Main category	Percentage of the particle number in %	Mean diameter in µm	Composition in %
Fe	9	0.153	Si(7) Fe(90)
Fe/low Si	14	0.173	Si(19) Mn(6) Fe(76)
Fe-Mn	17	0.129	Si(12) S(4) Mn(13) Fe(62)
Fe-Cr	5	0.129	Si(16) Cr(10) Fe(53) Zn(5)
Fe-Al	6	0.103	Al(18) Fe(69)
K-Fe	6	0.111	Si(6) K(16) Mn(6) Fe(58)
Ca-Fe	10	0.118	Al(7) Si(13) Ca(15) Mn(5) Fe(48)
Fe-rich	8	0.148	Al(4) Si(5) K(6) Fe(71)
MAGM[3] with lowly alloyed flux-cored wire (E70T-1); composition according to category			
Main category	Percentage of the parti-cle number in %	Mean diameter in µm	Composition in %
Fe	14	0.140	Fe(99)
Fe/low Si	25	0.160	Si(25) Fe(72)
Fe-Mn	37	0.178	Si(8) Ti(11) Mn(19) Fe(59)
MMA[1] with high alloyed Cr/Ni electrode (E308-16); composition according to category			
Main category	Percentage of the particle number in %	Mean diameter in µm	Composition in %
Fe-Mn	5	0.166	Si(32) Ti(5) Mn(26) Fe(26)
K-Cr	5	0.155	Al(6) Si(19) K(31) Cr(17) Mn(9)
K-Fe	18	0.169	Si(22) K(27) Mn(10) Fe(22)
K-Cr-Fe	5	0.176	Si(14) K(28) Ti(10) Cr(24) Fe(21)
Ca-Fe	7	0.144	Si(24) Ca(18) Mn(12) Fe(23)
K-Ca-Fe	7	0.159	Si(25) K(20) Ca(15) Mn(6) Fe(17)
K-Mn	8	0.161	Al(6) Si(25) K(29) Mn(22)
K-rich	7	0.174	Si(26) Cl(5) K(50) Ca(5)
Si-rich	6	0.161	Si(56) S(8) K(8)
MIG with Al-containing solid wire (E5356); composition according to category			
Main category	Percentage of the particle number in %	Mean diameter in µm	Composition in %
Al	86	0.327	Al(99)
Al-Cu	7	0.318	Al(65) Cu(35)

[1] MMA = manual metal arc welding; [2] MAGC = MAG with shielding gas CO_2 ; [3] MAGM = MAG with gas mixture Ar/CO_2

Table 6:
Chemical composition of the welding fumes of different processes and materials (according to AWS[1]; *Voitkevich*)

Chemical composition in %	Consumables					
	E6010	**E7018**	**E70S-3**	**E70T-1**	**E308-16**	**E5356**
Cu	—	—	0.4	—	—	0.5
Fe	46.0	24.6	57.0	38.1	10.8	0.2
K	—	12.5	—	0.3	18.9	—
Mn	4.0	4.6	7.8	11.1	6.2	—
Cr	—	—	—	—	5.6	—
Si	7.5	2.8	3.3	5.1	4.9	—
Mg	—	—	—	—	—	5.4
Na	6.3	3.3	—	8.9	10.4	—
Ni	—	—	—	—	0.75	—
Ti	0.2	—	—	0.8	—	—
Al	—	0.9	—	—	—	45.0
Ca	—	20.6	—	—	—	—
F	—	19.5	—	—	16.8	—

1) AWS = American Welding Society

Table 7:
Specific surface areas of the welding fumes of different compositions (according to AWS[1]; *Voitkevich*)

Process	**s in m²/g**	**Fe**	**Mn**	**Si**	**K**	**Na**	**F**	**Ca**
MAG-C[2] (CO_2)	24.6	44.4	16.3	2.0	—	—	—	—
MAG-M[3] (Ar/CO_2)	8.8	17.5	14.5	1.9	26.7	—	16.4	—
MMW[4]	9.8	20.9	7.0	3.6	3.5	14.0	20.0	12.8

[1] AWS = American Welding Society; [2] MAG, low alloyed solid wire; [3] MAG, low alloyed flux-cored wire; [4] MMW, low alloyed electrode

3 Thermal cutting

During thermal cutting (flame cutting, plasma cutting, laser beam cutting) the particulate substances formed from the basic materials have a diameter between 0.03 and – in agglomerated forms – about 10 µm. They are thus larger than welding fume particles, nevertheless mostly respirable. Electron microscope examinations during plasma cutting of different materials (e. g. chromium-nickel containing, aluminium or iron containing materials) show that round particles with diameters of 0.03 to 0.1 µm are agglomerated to larger branched particles with diameters of 0.3 to around 4 µm.

4 Thermal spaying

During thermal spraying (flame spraying, arc spraying, plasma spraying) particle with sizes of up to 100 µm are formed from the spraying consumables. Besides there are particles which are not subject to a physico-chemical process but are only carried away from the spraying consumable. The particle diameters are generally smaller during arc spraying than during flame spraying, they are, however, larger than during plasma spraying. The particles formed during thermal spraying are inhalable. The percentage of respirable particles depends on process and material.

5 Soldering

The particulate substances formed during soldering and brazing (soldering fumes) are generally smaller than those formed during welding. Depending on the process, soldering metals and fluxes used, particles with diameters between 0.01 and 0.15 µm are formed, also ranking among ultra-fine particles.

6 Summary

The welding fumes formed during welding and allied processes have different chemical compositions which mainly depend on the consumables and base materials used. The generated fumes mainly contain particles and agglomerates/chains which are much smaller than 1 µm. The ultra-fine particles thus formed have different

percentages and weight quantities depending on the type of welding fume. As in addition the chemical composition of these fumes is very complex and the toxicological effect of the total welding fume is known to be of a special quality, effective measures are required for welding activities for the protection of both the welder and assisting persons.

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Ultrafine and fine particles in bronze foundries and in welding [1]

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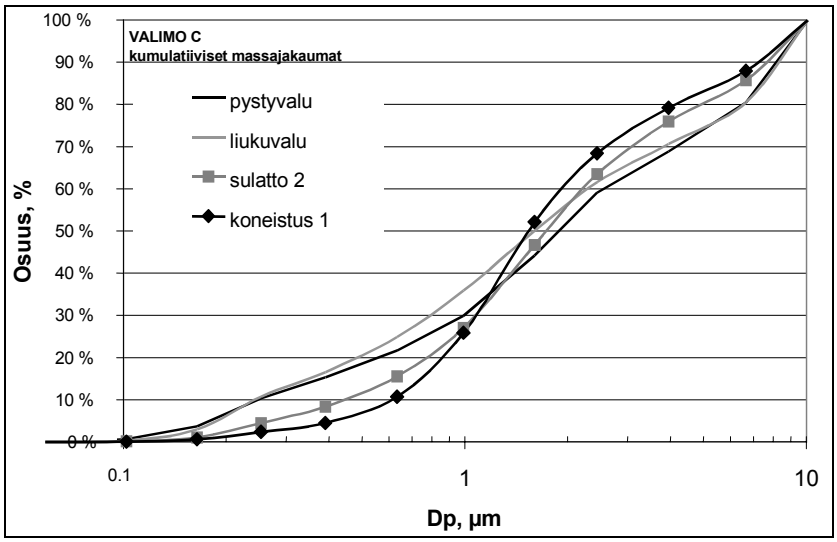
Measurements of ultrafine and fine particles were taken at workplaces in the Finnish metal-working industry using the cascade impactor DLPI (Dekati Low Pressure Impactor) to determine the mass concentration and using the ELPI (Electrical Low Pressure Impactor) to determine the number concentration (and indirectly, the mass concentrations). First is a presentation of several measurement data from a foundry casting bronze with lead content of up to 20 %. Figures 1 to 3 (see pages 170 to 171) show the figures for the mass concentrations of the aerosols at different foundry workplaces; figures 4 to 6 (see pages 171 and 172) show the figures for the number concentrations. It is clear that many fine and ultrafine particles are present in the air; particles $> 2.5\ \mu$m may be ignored due to their low numbers.

The particles that were deposited on the stages of the impactor were analysed for lead and copper (Table 1, see page 173). The ultrafine particle fraction (1 % of the total mass) showed a 3 % weight proportion of lead and an 8 % weight proportion of copper, whereas the fine particle fraction (74 % of the total mass) showed an 83 % weight proportion of lead and a 70 % weight proportion of copper and the larger particle fraction (25 % of the total mass) showed 14 % of the total lead proportion and 21 % of the total copper proportion. The metal contents are thus distributed differently among the different particle size fractions. Approximately 80 % of the metals were found in the ultrafine and fine particle fractions. This could provide an explanation for the problem of the higher lead contents found in the blood of the workers at this foundry.

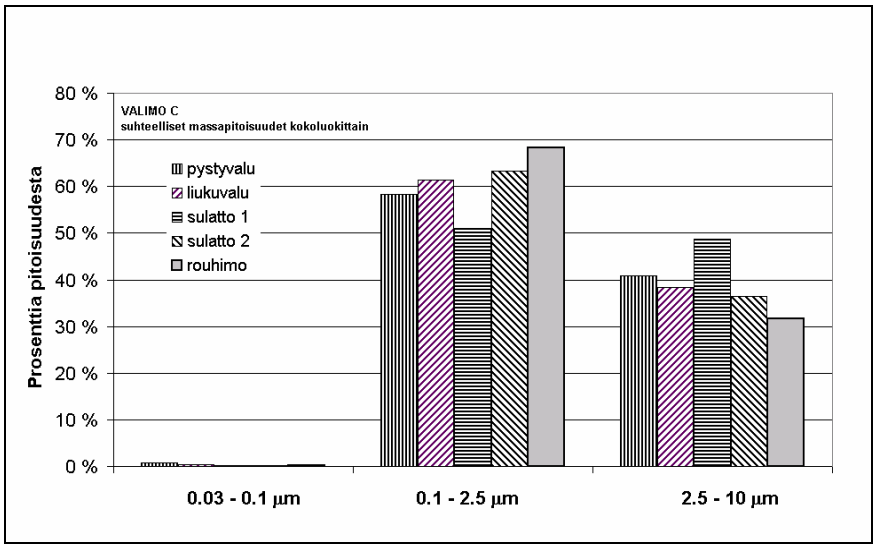
[1] Produced on the basis of the oral presentation; reviewed and authorized by the author.

Figure 1:
Foundry: cumulative mass distribution of the particles as percentages in the different particle fractions (ultrafine, fine, large)



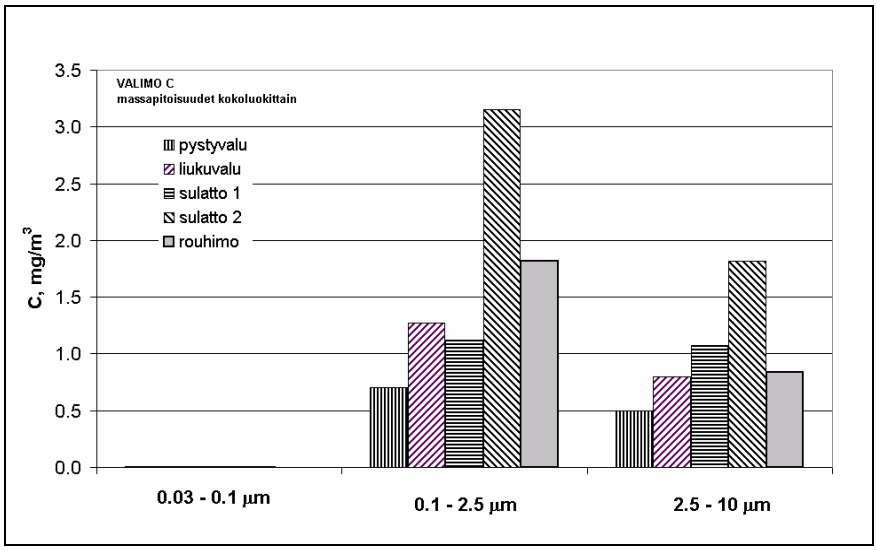
Key, top to bottom
Spun casting (vertical)
Continuous casting
Melting 2
Mechanical processing (fine)

Figure 2:
Foundry: relative mass concentration of the particles as percentages in the different particle fractions (ultrafine, fine, large)



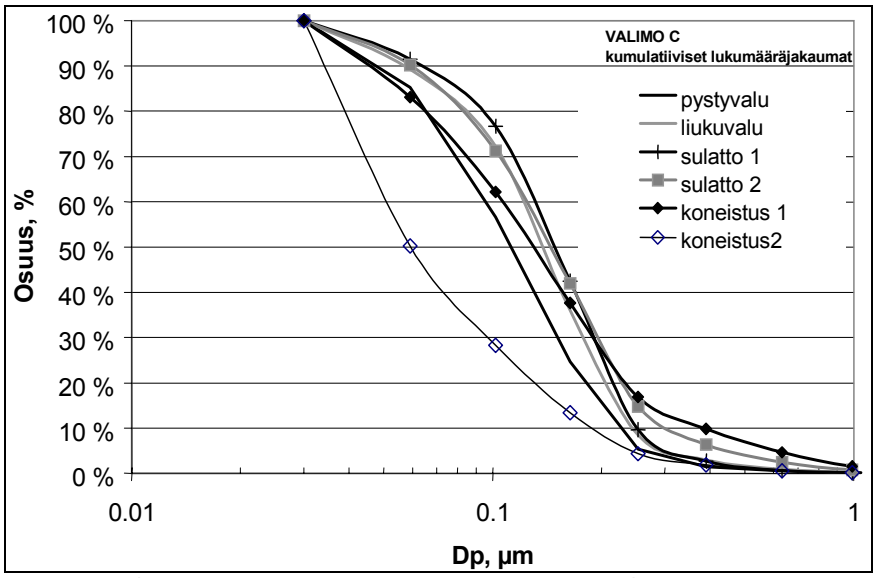
Key, top to bottom
Spun casting (vertical)
Continuous casting
Melting 1
Melting 2
Mechanical processing (coarse)

Figure 3:
Foundry: concentration of the particles in mg/m³ for the different particle fractions (ultrafine, fine, large)



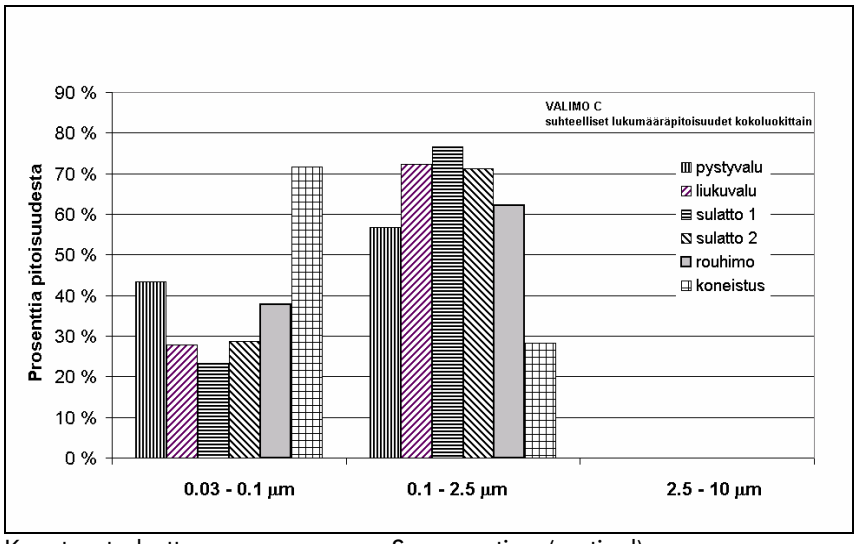
Key: see Figure 2

Figure 4:
Foundry: cumulative number concentration of the particles as percentages in the different particle fractions (ultrafine, fine, large)



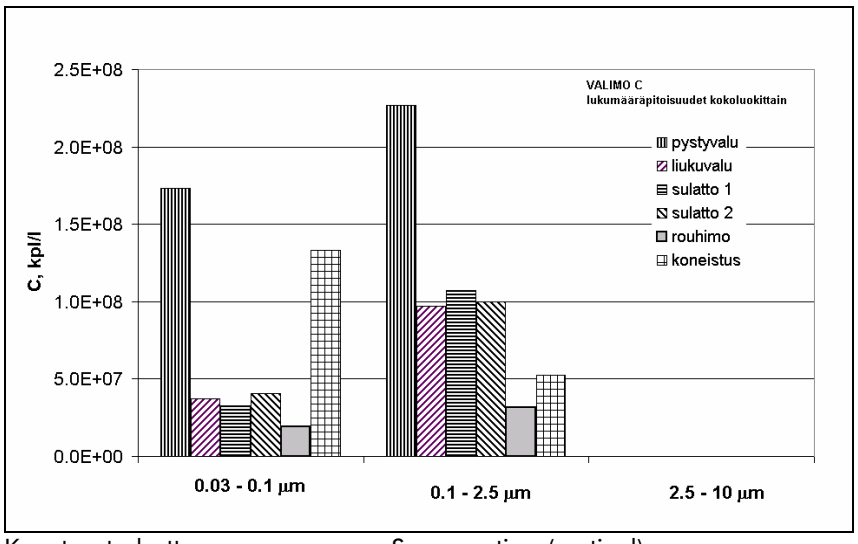
Key, top to bottom:
Spun casting (vertical)
Continuous casting
Melting 1
Melting 2
Mechanical processing (fine) 1
Mechanical processing (fine) 2

Figure 5:
Foundry: relative number concentration of the particles as percentages in the different particle fractions (ultrafine, fine, large)



Key, top to bottom:
Spun casting (vertical)
Continuous casting
Melting 1
Melting 2
Mechanical processing (coarse)
Mechanical processing (fine)

Figure 6:
Foundry: number concentration of the particles as number per litre in the different particle fractions (ultrafine, fine, large)



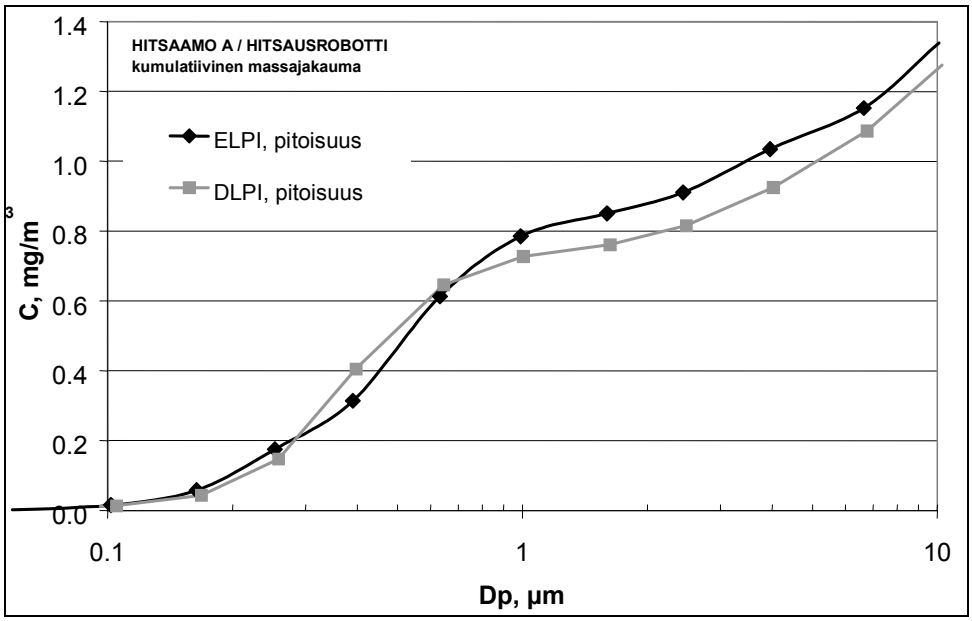
Key, top to bottom:
Spun casting (vertical)
Continuous casting
Smelting 1
Smelting 2
Mechanical processing (coarse)
Mechanical processing (fine)

Table 1:
Particle, lead, and copper mass concentrations and proportions for the different particle fractions; foundry, spun casting

Impactor stage	Cut point, D_{50}	Particles			Lead			Copper		
		Mass concentration	Mass on impactor stage	Mass proportion	Mass concentration	Mass on impactor stage	Mass proportion	Mass concentration	Mass on impactor stage	Mass proportion
	µm	mg/m³	mg	Wt.-%	µg/m³	µg	Wt.-%	µg/m³	µg	Wt.-%
1	0.030		0.02	0.3		< 2.0	< 1		1.1	1.2
2	0.060		0.07	0.9		5.4	3.2		6.4	7.2
ultrafine particles		0.01		1	0.45		3	1.1		8
3	0.105		0.20	2.5		24.4	14.6		22.3	25.3
4	0.168		0.21	2.7		22.2	13.3		18.1	20.5
5	0.258		0.34	4.3		17.2	10.3		10.5	11.9
6	0.397		0.90	11.4		19.6	11.7		5.9	6.7
7	0.645		1.27	16.0		20.2	12.1		2.7	3.1
8	1.004		1.47	18.6		21.0	12.6		1.5	1.7
9	1.626		1.43	18.1		13.6	8.1		1.1	1.2
fine particles		0.81		74	19.3		83	8.7		70
10	2.483		0.88	11.1		8.9	5.3		1.5	1.7
11	4.019		0.48	6.1		5.0	3.0		1.9	2.2
12	6.761		0.33	4.2		4.4	2.6		5.5	6.2
13	10.263		0.32	4.0		5.4	3.2		9.8	11.1
large particles		0.28		25	3.3		14	2.6		21
Total		1.1	7.9	100	23.3	167	100	12.3	88	100

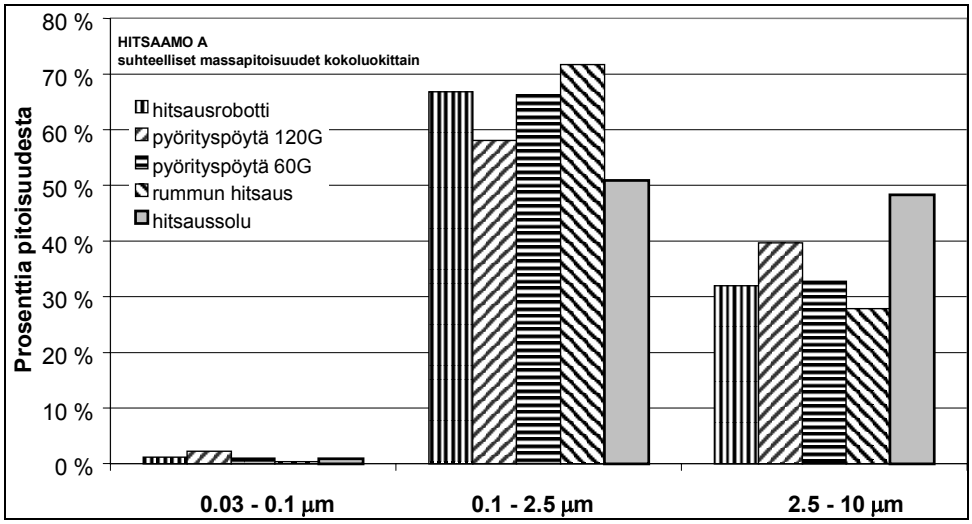
The following figures show the measurement data recorded at welding workplaces. Figures 7 to 9 (see pages 174 and 175) display the mass distribution of the particles, and Figures 10 to 12 (see pages 175 and 176) display the number distribution.

Figure 7:
Welding (welding robot): cumulative mass concentration of the particles as mg/m³ for the different particle fractions (ultrafine, fine, large)



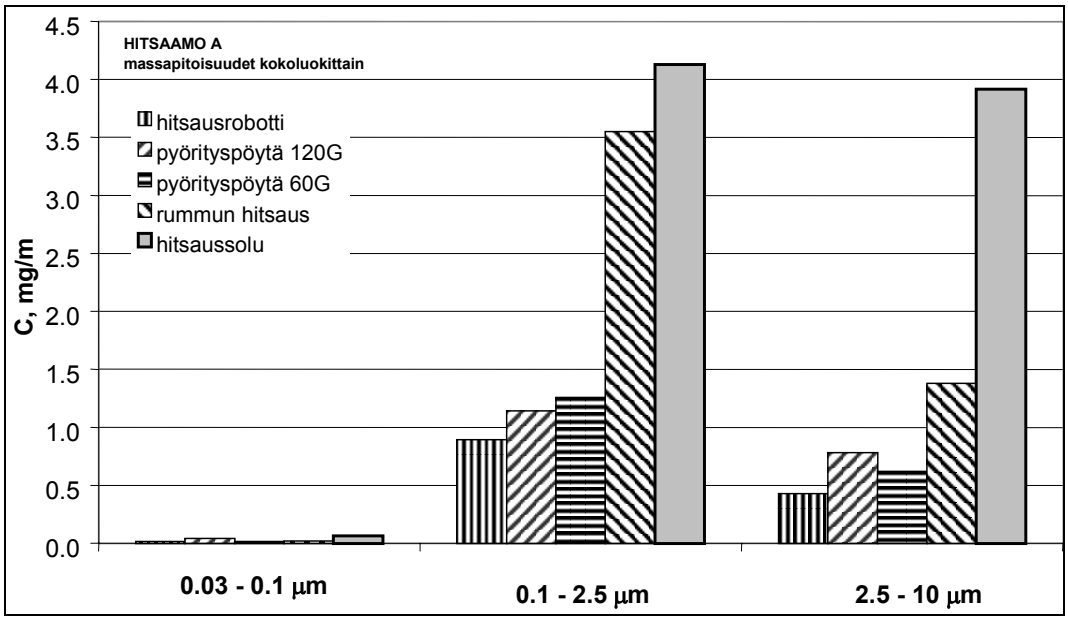
Key, top to bottom
ELPI concentration
DLPI concentration

Figure 8:
Welding: relative mass concentration of the particles as a percentage in the different particle fractions (ultrafine, fine, large)



Key, top to bottom
Welding robot
Welding carrousel 120 G
Welding carrousel 60 G
Welding of a drum
Welding cell

Figure 9:
Welding: mass concentration of the particles as mg/m³ for the different particle fractions (ultrafine, fine, large)



Key: see Figure 8

Figure 10:
Welding (welding robot): cumulative mass concentration of the particles as a percentage for the different particle fractions (ultrafine, fine, large)

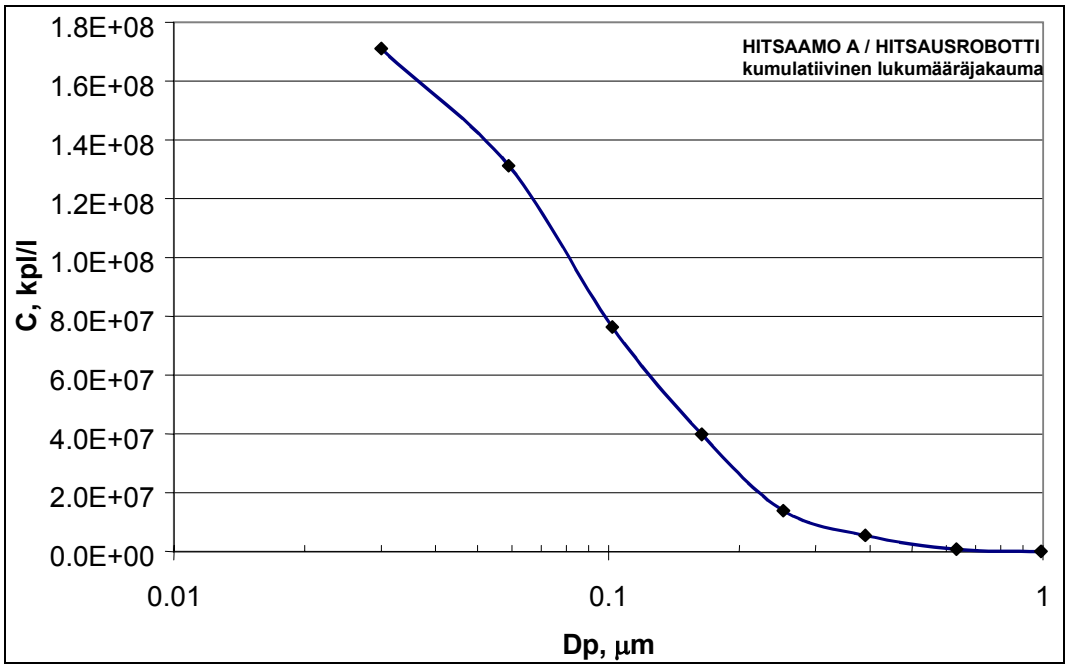
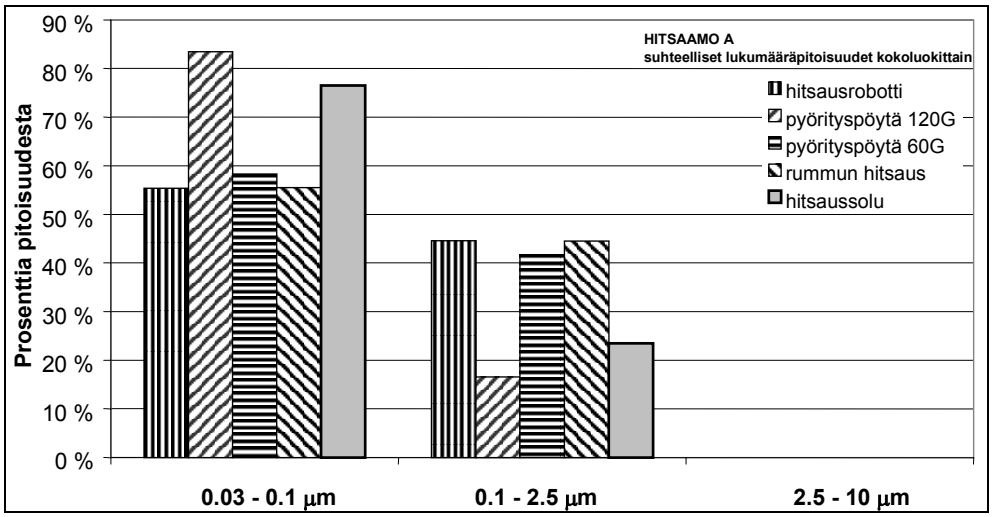
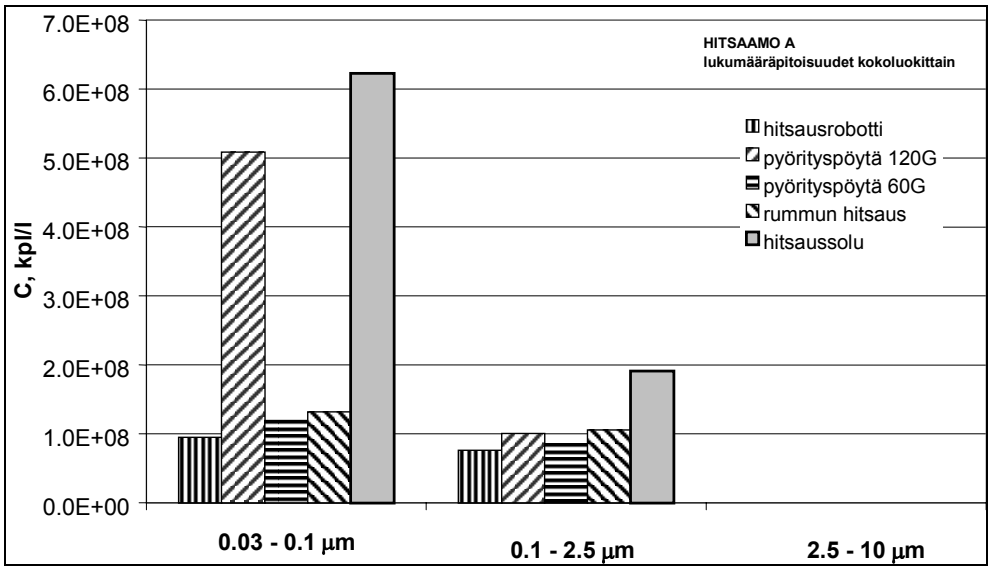


Figure 11:
Welding: relative mass concentration of the particles as a percentage in the different particle fractions (ultrafine, fine, large)



Key: see Figure 8

Figure 12:
Welding concentration of the particles as the number per litre of the different particle fractions (ultrafine, fine, large)



Key: see Figure 8

We felt it was important for us to use comparable methods so as to obtain information on the size of the particles in aerosols and so as to measure ultrafine and fine particles both in terms of the numbers and in terms of the mass. Collecting the mass fractions

gave us some insights into the chemical composition of the particles, and it supported the estimations we made about the health risks due to exposure to certain airborne pollutants at the workplace. Occupational hygiene experts need multifaceted tools for evaluating ultrafine particles at workplaces.

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Discussion

The techniques, technologies, and strategies for taking measurements at the workplace are very complex not only if we are to consider continuous and discontinuous sources, sources within and outside of the work area, but also if we want to determine the concentration, particle size distribution, and forms of the particles and agglomerations along with their chemical composition. Since toxicology does not as yet have guidelines here, toxicologists still need to receive quite thorough information on the aerosols in question from the field of measurement technology. There is a dire need for establishing a convention for getting this problem of diversity under control.

Pulmonary carcinogenicity of granular bio-durable particles without significant specific toxicity (GBP): relevance for occupational safety

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The pulmonary carcinogenicity of fine (i. e. respirable) **granular bio-durable particles without significant specific toxicity (GBP)**, such as talc, toner, TiO_2, and carbon, can be considered as proven by inhalation and intratracheal instillation experiment in rats under overload conditions. The effects of these dusts are apparently weaker than those of ultrafine GBP, such as carbon black and TiO_2. As a mechanism, it is not primary genotoxicity that is assumed, but rather a secondary genotoxicity (Figure 1, see page 182). This stems from an overloading of the lungs, which causes a diminution of alveolar clearance. The carcinogenicity is considered to be caused by particle accumulation: the chronic inflammatory reactions with a production of oxygen radicals and cell proliferation caused by particles. Generally, a threshold limit value has been postulated for this process, and observing the "general dust limit value" is intended to prevent exceeding this threshold limit value. Observations of the dose-frequency relationship in tumour generation and in mutagenicity related to inflammation reactions appear to confirm this hypothesis.

The recently published results of a 19-dust experiment by *Pott* and *Roller* [1; 2] calls this estimation into question. In this experiment, a relatively low, intratracheally applicated dose of not only ultrafine, but also fine, GBP caused a tumour rate > 10 %.

The authors thus asked whether – and contrary to the conventional interpretation – fine GBP could possibly produce carcinogenic effects even at the German "general dust limit value".

Figure 1:
Starting position

- The **carcinogenicity of** *granular bioresistant dusts without significant toxicity* **(GBD, fine and ultrafine)** can be considered as given in rats after inhalation and intratracheal instillation **„under overload conditions“**.

Mechnism under discussion:

- Lung overloading by clearance reduction.
- **„Secondary cancerogenity“** by particle accumulation, inflammation, formation of oxygen radicals und cell proliferation.

- An **effective limit value has** has been postulated, which is considered to be at or above the **German general dust limit value**.
- Studies of the **interrelationships** between the **dose and tumour frequency** and the **mutagenicity and the inflammatory reaction** sappear to confirm the existence of such a limit.

A joint working group of the commission for the investigation of health hazards of chemical compounds in the work area of the Deutsche Forschungsgemeinschaft DFG (so-called MAK Commission) and a working group on fibres at the advisory circle "Toxicology" at the committee for hazardous substances (Ausschuss für Gefahrstoffe – AGS) is currently working on answers to these important questions. The results of these consultations are still forthcoming. In the following, we can, however, provide an overview of the points of departure here. The three questions listed in Figure 2 (see page 183) are of particular importance.

As pertains to the search for suitable parameters for dust doses, we should first like to point out the example provided by *Timbrell*, et al. (1988) [5]. These authors correlated the local asbestos fibre deposits in lung tissue samples with the degree of fibrosis in the areas surrounding these deposits, and thus analysed the fibre mass and the fibre surface areas as dose parameters along with the number of fibres of all lengths. The best correlation was clearly found in the surface area of the retained fibres (Figure 3, see page 183).

Figure 2:
19-dust study of *Pott* and *Roller* [1; 3; 4] (16 GBPs, quartz, amorphous SiO_2, silanized TiO_2)

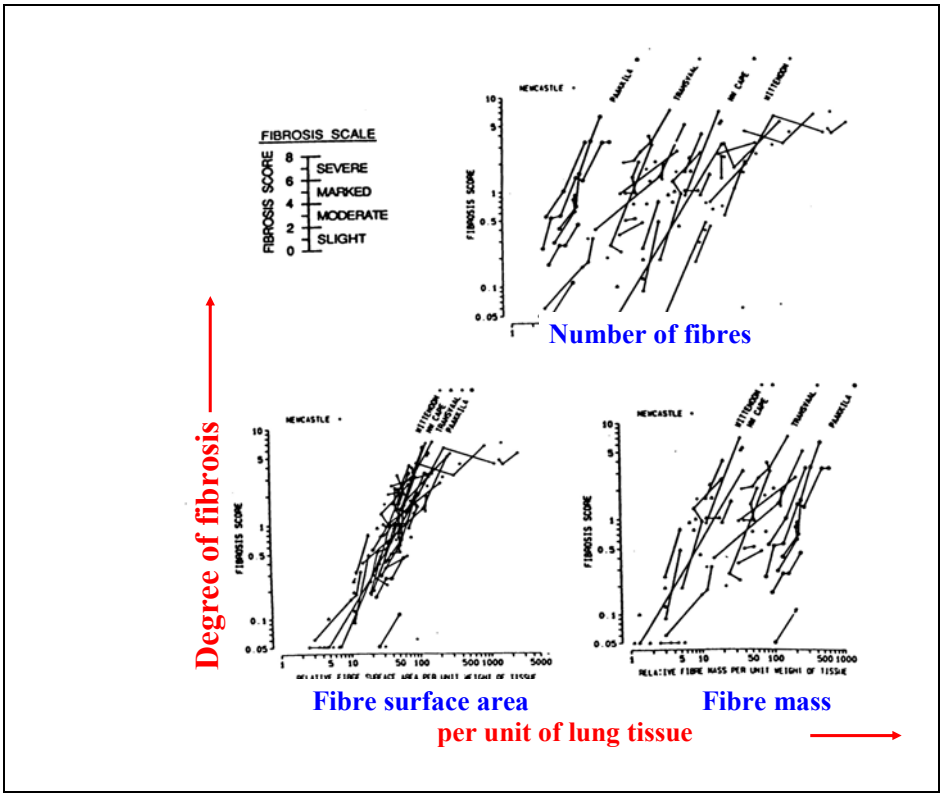
New finding

- Tumour rate > 10 % already for low intratracheally (IT) placed doses of not only ultrafine dusts, but also fine GBDs

Questions

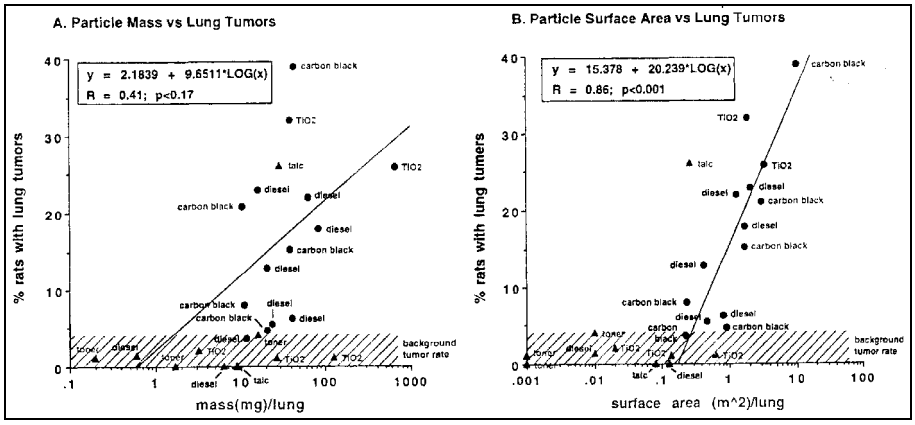
- **Does carcinogenicity habe to be anticipated for GBDs even at the German general dust limit value?**
- Which criteria for the dust dose in the lung describes best the impact of the carcinogenic effects? The **mass?** The **volume?** The **surface?** Or the **number of dust particles? A**nd **what is the shape of the dose-effect curve?**
- How do the results of the **IT** differ from those of the **inhalation test**?
- What **relevance** do these results obtained in rats have **for humans**?

Figure 3:
Local asbestos deposits in lung tissue samples and degrees of fibrosis, *Timbrell*, et al. (1988) [5]



Similarly, *Driscoll* (1996) [6] compared the frequency of lung tumours after inhalation and in part after instillation of granular and ultrafine dusts. In comparison to the particle mass, there was a better correlation with the surface of the particles deposited in the lungs in the range of > 0.2 m^2 to 10 m^2 per lung. The difference was, however, less impressive than in *Timbrell* (Figure 4).

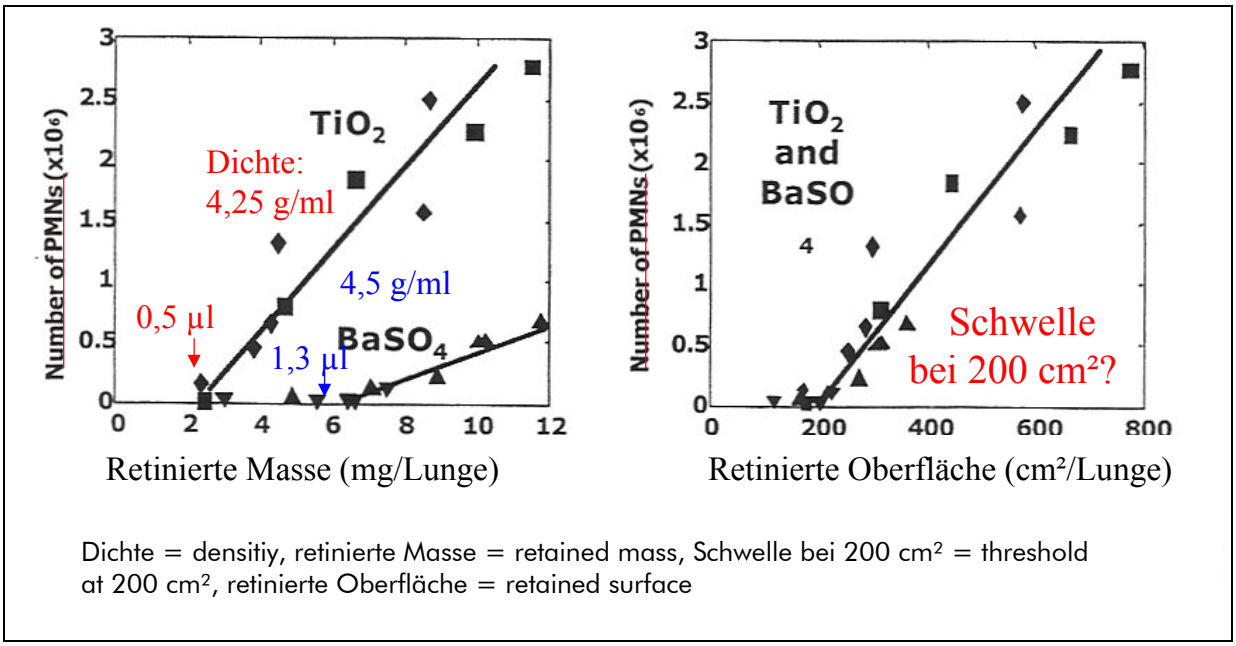
Figure 4:
Lung tumour frequency as dependent on the mass and surface of dust deposited in the lung, *Driscoll* (1996) [6]



Also in terms of the polymorphous neutrophilic cells (PMN) in the lavage fluid as a measure for the inflammatory reaction, *Tran*, et al. (2000) [7] found an initial indication that a better correlation with the deposited surface could exist for titanium dioxide and barium sulphate than there was with the deposited mass or the deposited volume of the particles. The increase in the PMN was already apparent at > 0.02 m^2/lung (Figure 5, see page 185).

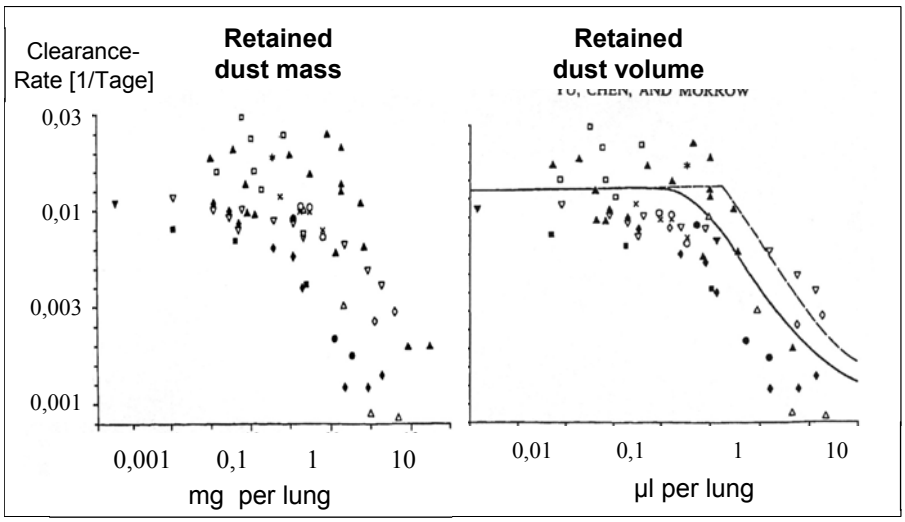
On the other hand, the obstruction of the alveolar clearance by deposited particles was found to be less related to the retained mass than to the retained volume (Figure 6, see page 185). At least in the comparison from 1989 presented here, this improvement is not too marked. Additional experiments are nonetheless now available that, however, were only representative of the retained volume.

Figure 5:
Cellular inflammation reactions, *Tran*, et al. (2000) [7]



Dichte = densitiy, retinierte Masse = retained mass, Schwelle bei 200 cm² = threshold at 200 cm², retinierte Oberfläche = retained surface

Figure 6:
Alveolar clearance: rate in rat lungs, *Yu*, *Chen*, and *Morrow* (1989) [8]



In 1997, the DFG provided the retained volume as the decisive causal parameter for slowing alveolar clearance and considered this delay as a reason for revising the "general dust limit value" [9]. The retained particle volume of fine GBP as laid down in this limit value under stationary conditions in a state of equilibrium in the rat may not

exceed 1 µl per gram of lung tissue – as related to the animals in the control group (Figure 7). In order to discuss the carcinogenic effects of GBP at the "general dust limit value", the dose thus refers to the per-gram retained particle volume in the following.

Figure 7:
German general dust limit value, Deutsche Forschungsgemeinschaft (DFG) 1997

DFG 1997:
German general dust limit value

- The **retained dust volume in the lung** is to be considered the critical parameter for reducing the alveolar clearanc.

Criteria for establishing the German general dust limit value:

- In rats, the retained volume of **fine GBP (GBP-F)** may not exceed an average of **1 µl dust per g of fresh lung weigth** of the controll lungs.
- The **GDLV** does not apply to **ultrafine GBP (GBP-UF)**.

Conclusion:

- For answering the question of whether there is a carcinogenic effect of GBP in rats even at the limit value, the **retained dust volume per gram of lung** is to be used as the standard.

The 19-dust carcinogenicity test was conducted by *Pott* and *Roller* on around 2,000 female Wistar rats (Figure 8, see page 187).

In contrast to the otherwise common categorisation, diesel soot and even lampblack were counted as fine GBPs, even though the DFG definition would group these as ultrafine particles due to the primary particle diameters of D < 100 nm, and even when they form larger aggregates. The results thus receive special markings below.

The elevated frequency of lung tumours in this experiment coincide with improvements in tumour diagnostics. The histological studies in the lungs of rats are thus based not on three, but instead on ten to 15 sections so as to record even smaller lung tumours

reliably but up to now they were only performed for some of the experiments. In addition, a defined macroscopic study was conducted beforehand.

Figure 8:
The 19-dust carcinogenicity test of *Pott* and *Roller*

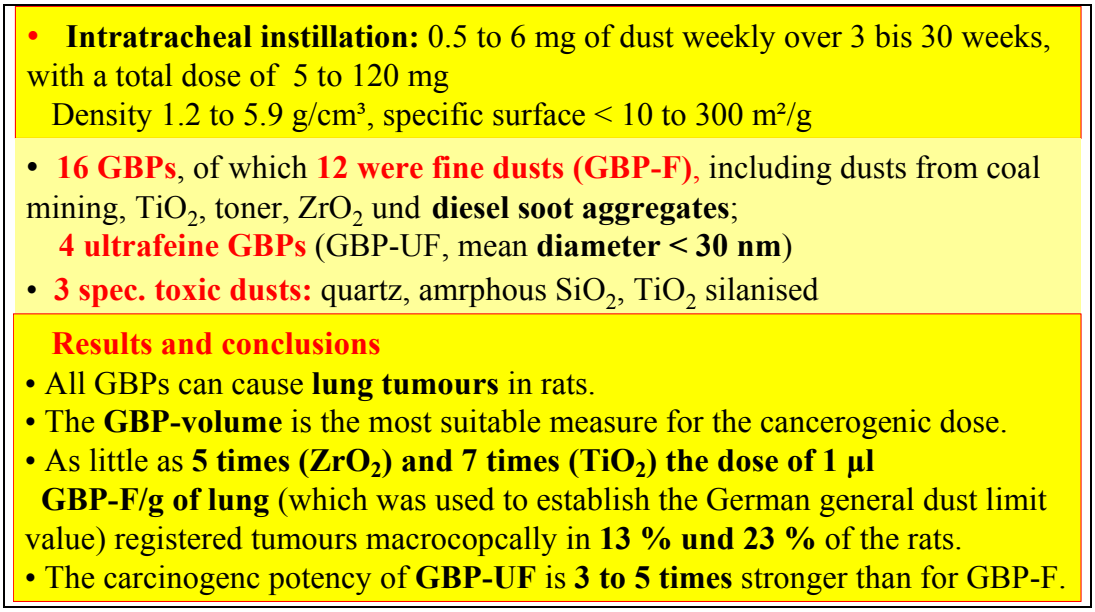
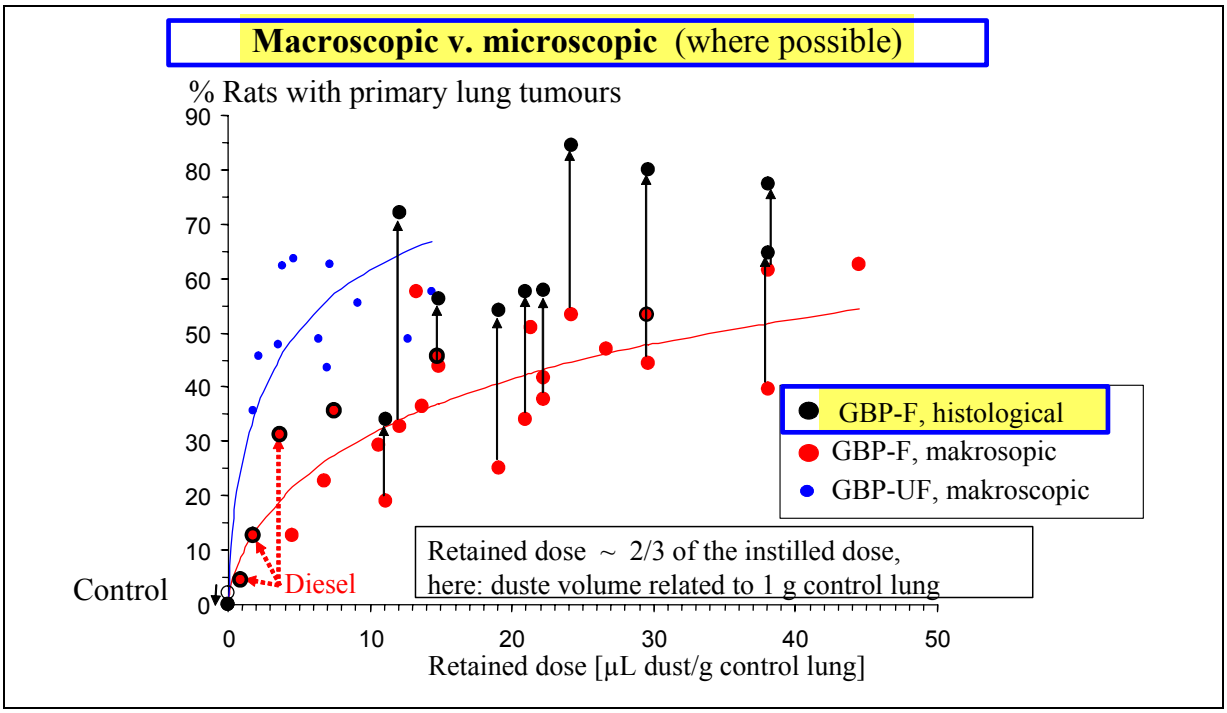


Figure 9 (see page 188) shows the tumour frequency as it relates to retained dust volume for fine GBPs as well as ultrafine GBPs under consideration of three experiments each with diesel soot and lampblack. The measuring points interpreted as fine GBPs for diesel soot and lampblack are outlined in black. The retained dust volume here is given as 2/3 of the instilled volume. A clear dose-frequency relationship was found to exist, without any suggestions of a threshold limit.

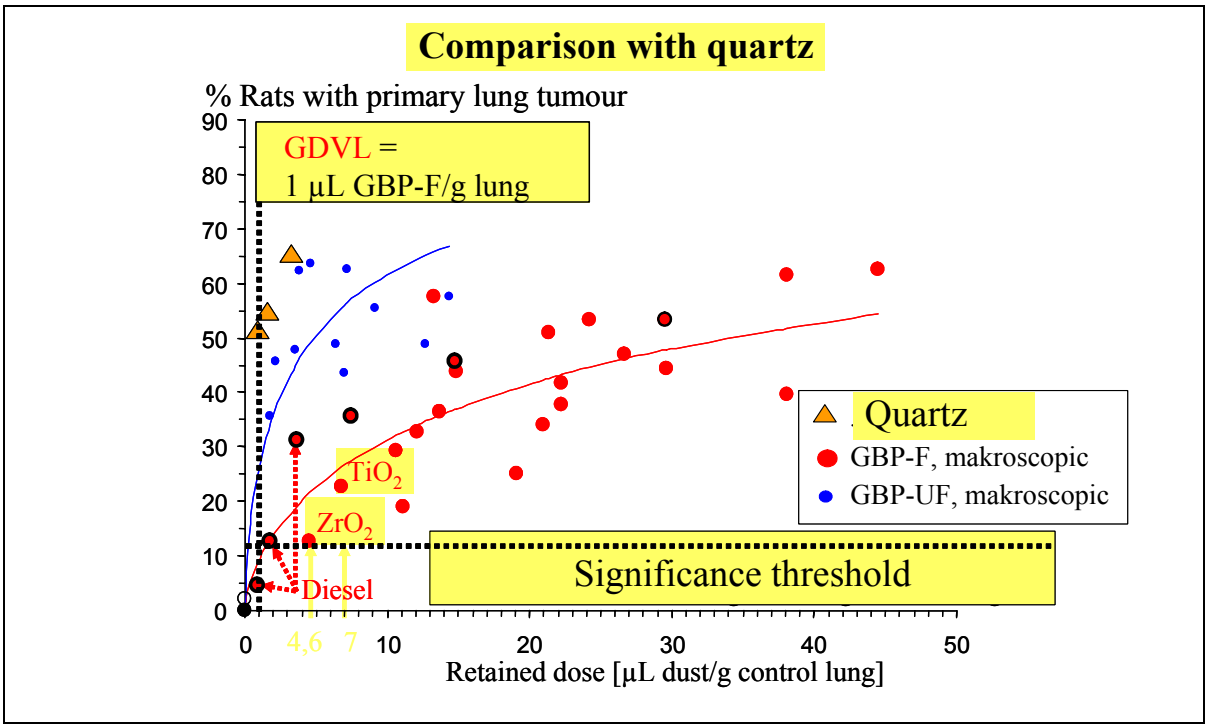
The histological corroboration of the tumour diagnoses is so far only available for the dusts from coal mining and for a dosage of titanium dioxide. These consistently result in an increase in the tumour rates to frequencies of up to 84 %. A decrease has only been observed in the control groups because a primary lung tumour was macroscopically diagnosed which histologically proved to be a metastasis.

Figure 9:
The 19-dust study by *Pott* and *Roller* on Wistar rats: lung tumour frequency with GBP-F and GBP-UF



The tumours macroscopically diagnosed can finally also be compared to the results for quartz (Figure 10, see page 189). As expected, the greatest effects are measured for quartz. Merely dosing 1 µl per gram resulted in an around 50 % tumour rate. For ultrafine particles, too, 50 % tumours are observed for dosages below 5 µl. The effectiveness of ultrafine particles apparently lies between those of quartz and fine GBPs. Ultrafine GBPs thus appear to have a three- to five-fold higher effectiveness than do fine GBPs. A retained volume of 1 µl/g of lung happens to correspond to the "general dust limit value". A quantity of around 45 animals each, both in the exposed group and in the control group that was only exposed to a suspension fluid, results in a significance threshold at a tumour frequency of 13 %. This value is achieved with zirconium dioxide already at a retained volume of 4.6 µl/g, and is markedly exceeded for TiO_2 at 7 µl/g. In fact, the macroscopically determined tumour frequency for all other dosages already markedly exceeds the significance limit with rates of up to 63 %.

Figure 10:
The 19-dust study of *Pott* and *Roller* on Wistar rats: lung tumour frequency with GBP-F and GBP-UF



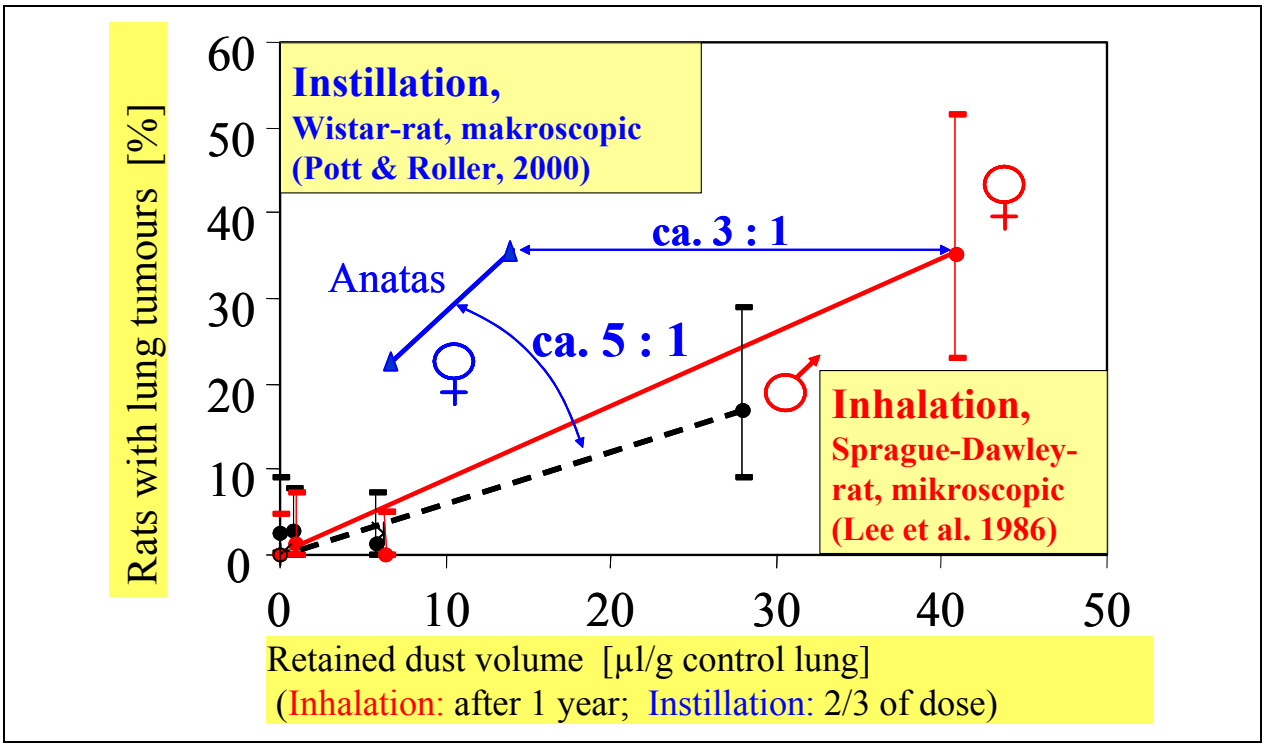
GDVL = general dust limit value

Yet only a few experiments were conducted using fine GBPs with dosages around the "general dust limit value" because such a high rate of tumours was at first not expected.

Both titanium dioxide (Figure 11, see page 190) and toner are available as GBPs tested in both inhalation and instillation experiments. For TiO_2 the inhalation experiments of *Lee*, et al. [10], on the Sprague-Dawley rat can be compared to the instillation experiments of *Pott*, et al. [1], on the Wistar rat. The retained dust volume is assumed to be the volume after one year in the inhalation experiment and for 2/3 of the dosed volume in the instillation experiment. The inhalation experiment produces significantly higher tumour rates only at the highest respective dosage. Yet in view of the large measurement uncertainty, this set of data is still consistent with a linear curve of the dose-frequency relationship even at low dosages.

In comparison to the instillation experiment of *Pott*, et al., there is an increase in the effectiveness of the retained dust volume of only a factor of around 5 between inhalation and instillation, or when comparing only the females, a factor of only around 3. Such an increase is already to be expected due to the different time dimensions of the exposures in the two experiments.

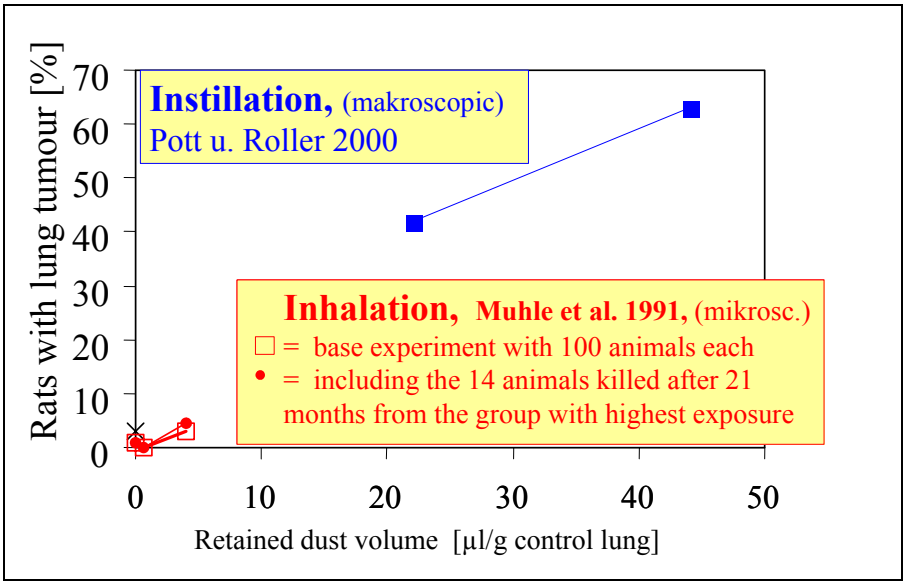
Figure 11:
Instillation and inhalation of TiO_2 "fine"



The inhalation experiment from *Muhle*, et al., [11] (using the Fisher rat) is compared to the instillation experiment from *Pott* and *Roller* (on the Wistar rat) correspondingly for toner dust (Figure 12, see page 191). The inhalation experiment, originally assessed as negative, does not contradict the instillation experiment due to the comparatively low dose. In fact, it must be added that the inhalation experiment can also be considered to be positive in terms of borderline significance. Now we are coming to the apparently problematic observation of threshold values in dose-effect relationships. Here, Figure 13 (see page 191) shows a comparison of the linear and half-logarithmic presentation of the relationship of identity. On superficial observation,

the latter presentation is obviously suitable for suggesting a threshold value even for the relationship of identity.

Figure 12:
Inhalation and instillation of toner dust (average diameter 3.5 µm; density 1.2 g/m²)



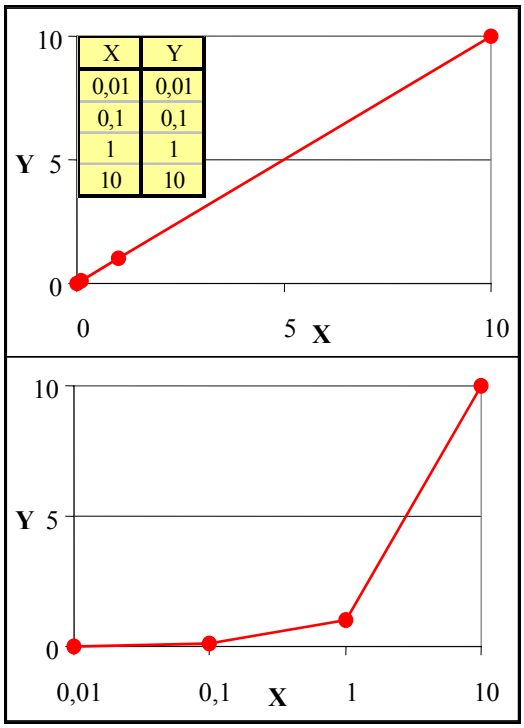
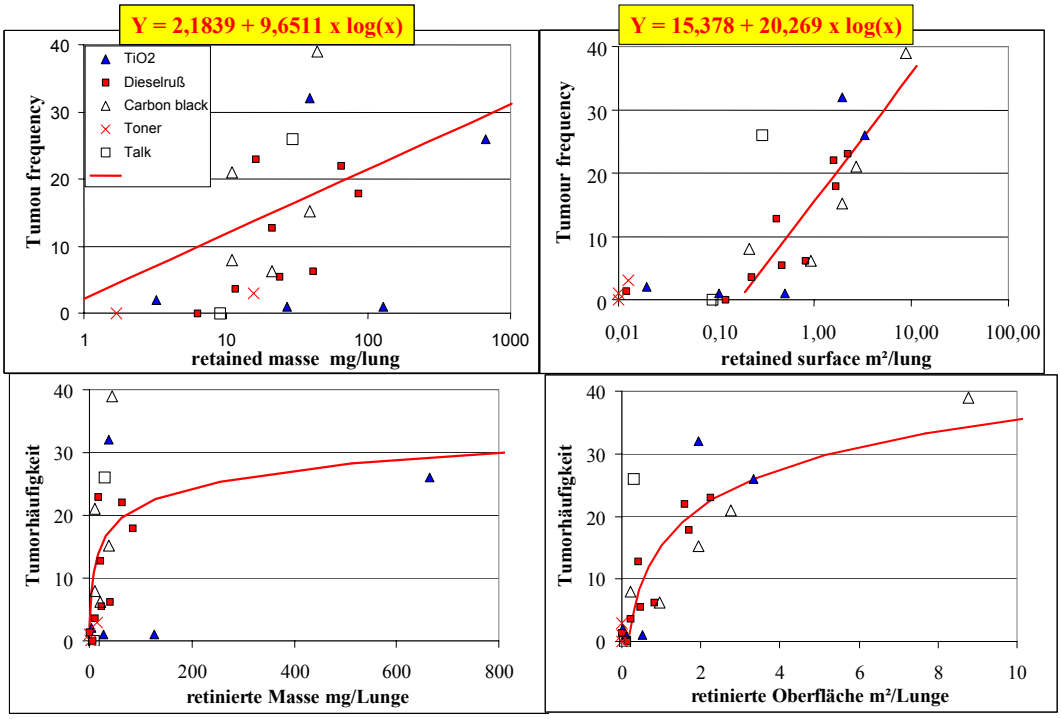


Figure 13:
Threshold value and half-log depiction of the dose-response relationship; presentation using linear y- and x-axes (top) and a linear y- but a logarithmic x-axis (bottom)

Indications of a threshold values in the dose-frequency relationship of the tumour generation were observed for tumour frequency as dependent both on the retained dust mass and on the retained surface (Figure 14), as *Driscoll* reports [6].

Figure 14:
Tumour frequency related to retained dust mass and retained surface area; comparison of the half-log (top) and the linear depiction (bottom)



Of the original half-log presentation (at the top,) which is here recreated using the authentic compensating curves, *Driscoll* writes, "The shape of the surface area dose - lung tumour response relationship appears consistent with a threshold for the rat lung tumour response". *Miller* [12], who uses a different regression function to describe the data gathered by *Driscoll*, concludes that "substantial lung overload is requisite for induction of lung tumours in rodents. A critical retained lung burden does exist for any given PSP ... for which there is essentially no carcinogenic risk".

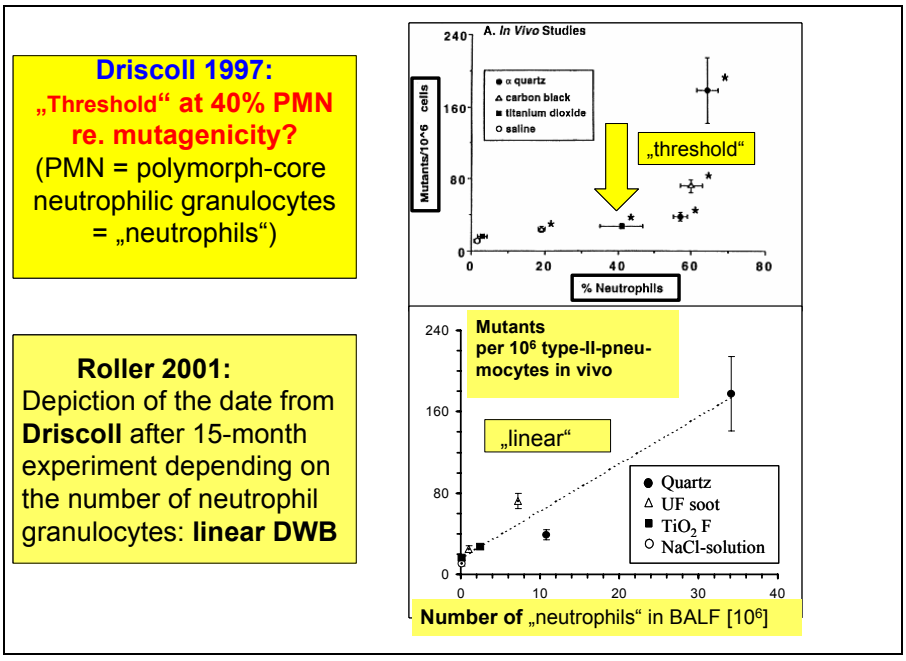
In fact, neither claim can be supported using the given data and curves. If a linear scaling of the x-axis is used (at the bottom) in place of the linear ordinates and

log abscissa, both the "lines" of *Driscoll* and of *Miller* take on a hyperlinear form. A threshold value cannot be thus concluded.

Driscoll (1997) [13] also postulates a highly noted threshold value at a proportion of 40 % of neutrophil cells in the lavage fluids for the relationship between the inflammatory reaction and the mutation rate as a partial step towards carcinogenesis.

Roller (2003) [2], on the other hand, used the data published in this study instead to show that a linear relationship was visible both for the intratracheally instilled dust mass and for the absolute number of neutrophils in the BAL fluids shown here instead of a threshold value (Figure 15). The hockey-stick curve for the mutation rate thus only resulted when the percentage proportion of neutrophils among all cells of the lavage fluid were depicted instead of the absolute number of neutrophils.

Figure 15:
Comparison of the dose-effect relationships of the studies by *Driscoll* and *Roller*



Indications of differences between the reactions of rats and humans to GBPs cannot be adequately discussed in this presentation. In the ILSI Consensus Report 2000 [14], it is noted that there are currently not enough data available to conclude that the carcino-

genicity observed with GBPs in the rat model would not be relevant for identifying a carcinogenic effect in humans (Figure 16). This is also true for the epidemiological studies, such as those from coal mining or those conducted with talc or diesel soot. On the other hand, a comparison of the carcinogenicity of quartz in rats and in humans could be helpful, as *Pott* and *Roller* suggest.

Figure 16:
Are the results obtained for rats relevant to humans?

ILSI workshop consensus report 2000:
There are insufficient data at present, to conclude, that the PSP tumour response in the rat model is not relevant for human hazard identification

According to Pott and Roller the **risk for GBP in humans** can be etsimated using the relationsship for carcinogenicity
- of GBP and quartz in rats
- and of quartz in rats and humans .

The course of the effects ove inflammation processes by GBP and quartz appear to differ only quantitatively, but not on principle, based on the current state of knowledge.

The following conclusions can be drawn based on what we have said so far:

- The carcinogenic potency of fine GBPs in rats, which has been considered to be very weak so far, was misinterpreted from the inhalation experiment of *Lee*, et al., [10] because of a rat strain rarely used in such experiments and because of the use of mass instead of volume as a standard.

- In contrast to the previously held view, the results of the 19-dust study give rise to the suspicion that, not only ultrafine, but also fine GBPs even at the “general dust limit value” may result in "appreciable" carcinogenicity.

- The volume retention for ZrO_2 and TiO_2 was macroscopically associated with tumour rates of 13 and 23 %, and was, with 5 and 7 µl GBP-F/g of lung, only 5 to 7 times higher than the volume retention permitted by the "general dust limit value".
- The inhalation experiments using toner, talc, and diesel soot do not contradict this interpretation.
- The differences between intratracheal and inhalation test of less than one order of magnitude are to be expected due to the differences in the exposure timeframe; they are not fundamental in nature.
- Scientific proof is lacking for the postulated effect thresholds.
- An analogy between humans and rats was proved for quartz dust with the corresponding effect patterns.
- There is a difference of a factor of 3 to 5 between the carcinogenicity observed for fine and ultrafine GBPs.

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Discussion

The question arises as to whether overload studies are suitable for estimating the effects and risks of inhaled ultrafine particles. It is also difficult to see that the volume concept (dependency of the effect on the retained particle volume) is generally applicable, as it was shown that the dose-effect curve is steeper for ultrafine particles than it is for fine particles. The difference between the dose-effect relationship between ultrafine and fine particles is nonetheless quite small at three to five.

If the statement made in the presentation is accurate that appreciable carcinogenicity is to be feared not only from ultrafine particles but also from fine granular bio-durable particles, this would have serious consequences on the limit value considerations for the workplace. In this case, there should not be a limit value as such, but rather a technical standard value without having to distinguish between fine and ultrafine particles, although it would still need to be determined whether the mass or volume concentrations, the surface concentration or number concentration within whatever particle size limits with whatever recording function would need to be used.

The effects of agglomerated ultrafine particles is as yet largely unknown and still requires further investigation. If ultrafine particles are inhaled as agglomerates, they are identified by the macrophages; if they are inhaled as individual primary particles, things are quite different. Ultrafine particles will thus have to be identified differently depending on their degree of agglomeration.

A large part of the discussion was concerned with the question essential for toxicology of what extent the results from the different test models of the animal experiments can be applied to humans and what conditions make them relevant to the workplace. It is currently beyond the scope of our science to provide an even partly reliable answer to this question.

Summary of the concluding discussion and outlook

People involved in occupational hygiene who are concerned with ultrafine aerosols are confronted with the following essential questions that naturally have an influence on the techniques and instruments chosen for measurement:

a) How should the fraction of ultrafine particles be defined? At what particle size do these sensibly begin, and what is the upper limit of their size? How does the course of the evaluation look in the meantime? That is, does a size-dependent recording function have to be taken into account?

b) What properties of ultrafine particles at the workplace should be recorded?

To a), even if ultrafine particles are defined as particles of less than 100 nm in size, it is insufficient to break off measurements abruptly at 100 nm. Due to their tendency to form aggregates and agglomerates that can break down into their primary particles after they are incorporated in tissue, the measurement range for small particles should extend to around 600nm. If we were only discussing the effects in the alveolar area, a limit of 15nm would fully suffice. Yet if other effects are also to be taken into consideration – which can be caused especially by deposits in the nose – the lower cut-off limit should be at around 5nm.

Due to their small size, ultrafine particles have unique chemical-physical properties, and they thus have special kinetics and reactivity within the organism. Because no dosage-effect curve is as yet available, the corresponding limit values or even a size-related evaluative function cannot at present be derived. It is thus preferable to determine the particle size distribution within the boundaries mentioned above.

To b), at a minimum of information, the size distribution (based on the mobility diameter) and the number concentration should be measured. Instruments introduced to do this include DMA or SMPS and CPC (differential mobility analyser or scanning mobility particle sizer and condensation particle counter). Information on the morphology of the particles is also important, especially with regard to aggregates

and agglomerates. Suitable sampling systems for this purpose are thermal precipitators and, as devices that provide images, electron microscopes. For a graphic illustration of the particle size distribution, the differential distribution over a logarithm of the particle diameter $\left(\frac{dN}{d\log D}\right)$ is suggested. If necessary, this information can also be used to calculate an estimate of the surface concentration.

Thermal precipitators and samples from low pressure impactors are also suitable for a later laboratory analysis of the chemical composition of the particles, where techniques such as mass spectroscopy (MS), total reflection x-ray fluorescence analysis (TRFA), particle induced x-ray emission (PIXE), or, with reservations, energy dispersive x-ray microanalysis (EDXA) can be used. One particular challenge in taking measurements is determining the in-vivo solubility of ultrafine particles, for which there are so far only partly satisfactory methods available. In any case, the complex and expensive analytic procedures for determining particle surface and chemical composition must be left to special problems, although prior knowledge of the work processes and the materials used at the workplace under study should also be used.

If it should become necessary to establish limit values for exposure to ultrafine aerosols at workplaces, a similarly reliable and acceptable measurement method should be developed and standardised. Doing so will require these general conditions:

- a definition of the recording function related to the mobility diameter of the ultrafine particles,
- description of the dimensions to be measured (number concentration, surface concentration, or volume concentration),
- the type of evaluation for aggregates and agglomerates,
- as needed, sufficient reference to the chemical components and properties to be analysed,
- description of the timeframe to be considered.

Satisfactory answers to all these questions will still require considerable scientific effort. In the end, what we are aiming for is the development of a personal measurement and sampling device suited to solving the problem.

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