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REVIEW

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Pulmonary effects of inhaled ultrafine particles

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Abstract ***Introduction and Objectives***: Recent epidemiological studies have shown an association between increased particulate urban air pollution and adverse health effects on susceptible parts of the population, in particular the elderly with pre-existing respiratory and cardiovascular diseases. Urban particles consist of three modes: ultrafine particles, accumulation mode particles (which together form the fine particle mode) and coarse mode particles. Ultrafine particles (those of < 0.1 μm diameter) contribute very little to the overall mass, but are very high in number, which in episodic events can reach several hundred thousand/cm^3 in the urban air. The hypothesis that ultrafine particles are causally involved in adverse responses seen in sensitive humans is based on several studies summarized in this brief review. ***Methods and Results***: Studies on rodents demonstrate that ultrafine particles administered to the lung cause a greater inflammatory response than do larger particles, per given mass. Surface properties (surface chemistry) appear to play an important role in ultrafine particle toxicity. Contributing to the effects of ultrafine particles is their very high size-specific deposition when inhaled as singlet ultrafine particles rather than as aggregated particles. It appears also that ultrafine particles, after deposition in the lung, largely escape alveolar macrophage surveillance and gain access to the pulmonary interstitium. Inhaled low doses of carbonaceous ultrafine particles can cause mild pulmonary inflammation in rodents after exposure for 6 h. Old age and a compromised/sensitized respiratory tract in rodents can increase their susceptibility to the inflammatory effects of ultrafine particles significantly, and it appears that the aged organism is at a higher risk of oxidative stress induced lung injury from these particles, compared with the young organism. Results also show that ultrafine particle effects can be significantly enhanced by a gaseous co-pollutant such as ozone. ***Conclusions***: The studies performed so far support the ultrafine particle hypothesis. Additional studies are necessary to evaluate mechanistic pathways of responses.

Key words Ultrafine particles · Toxicity · Environment · Animal studies

Introduction

Exposures to ultrafine particles have increased over the years, and systematic studies on the toxicity of ultrafine particles have only recently been initiated. Earlier, such exposures were mostly a workplace phenomenon with workers' exposures to metal fumes consisting – at least initially – of ultrafine particles which could induce symptoms of metal fume fever. With increasing road traffic density and emissions from automotive combustion engines, environmental exposures have become more widespread in the general population. Workplace exposures to metal fumes can be very high, in the mg/m^3 range, which implies that the initially ultrafine particle size will quickly aggregate into larger particles. Environmental exposures from automotive exhaust, in contrast, is at much lower concentrations, and it is questionable as to whether airborne ambient concentrations will induce adverse effects. However, the sensitivity to even low concentrations may be different in a compromised organism, since results of a number of epidemiological studies have consistently shown an association of adverse effects on sensitive parts of the population, with slightly increased ambient particulate pollution. One sensitive subgroup that has been identified is the elderly with compromised respiratory and cardiovascular systems. Several hypotheses have been formulated to explain this increased sensitivity, and one

The investigators involved in these studies have reported their findings in a detailed report (Oberdörster et al. 2000)

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of these is that ultrafine particles could be responsible for the observed adverse effects (Oberdörster et al. 1995, Seaton et al. 1995). This suggestion is based on toxicological studies with ultrafine particles and is further supported by newer findings about the potential of singlet ultrafine carbon particles to cause pulmonary responses. These findings will be summarized in this paper.

Figure 1 shows a typical trimodal ambient particle size distribution found in cities.

Under normal background conditions, measured concentrations of ultrafine particles in terms of their mass are very low, ranging between 0.8 and 1.6 $\mu g/m^3$ (Tuch et al. 1997, Hughes et al. 1998), with particle numbers of between 1 and $5 \times 10^4/cm^3$. However, in episodic events, peak concentrations of up to 3×10^5 particles/cm^3, with approximately 50 $\mu g/m^3$ of mass concentration have been measured (Brand et al. 1992). Similarly, during traffic rush-hours in the city of Atlanta daily peaks of ultrafine particles reaching 4×10^5 particles/cm^3 have been determined (McMurry, personal communication). If atmospheric urban ultrafine particles, indeed, are more toxic than larger particles, one would expect to see adverse effects at very low mass concentrations, since ultrafines contribute very little to the overall ambient particle mass. An indication of such effects may be found in the old data of the London smog episodes in the 1950s through 1970s. Figure 2 summarizes those data in terms of daily mortality observed during these episodes (Schwartz and Marcus 1990), and it is obvious from the exposure-response curve that at lower concentrations the slope is steeper than at higher concentrations. One explanation for this would be consistent with the hypothesis of greater toxicity of ultrafine particles, namely, that at low ambient particle mass concentrations below ~100 $\mu g/m^3$, ultrafine particles are relatively persistent, whereas at higher concentrations

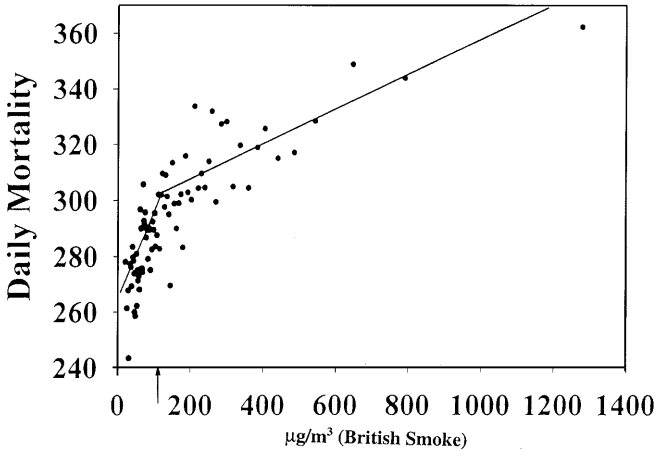

Fig. 2 Correlation between daily mortality rate and urban particle concentrations during the London smog episodes in the winters of 1958–1972 (data from Schwartz and Marcus 1990). Also shown are the regression lines for the steep slope and the shallow slope and the mathematically determined inflection point at ~125 $\mu g/m^3$

aggregation to accumulation mode particles (see Fig. 1) occurs much more rapidly. The resulting exposure to larger particles of the accumulation mode at higher concentrations would result in a flatter slope of the exposure-response, as is seen in Fig. 2, whereas persisting ultrafine particles at low concentrations cause a steeper slope. There may be other explanations for the curvilinear appearance of the data, and more studies are needed to confirm the ultrafine particle hypothesis.

However, there are a number of factors which suggest that ultrafine particles, indeed, may be more toxic than larger particles. One is related to dosimetric aspects of the deposition and disposition of particles, which are different for inhaled ultrafine particles compared with larger particles. Another relates to surface properties of

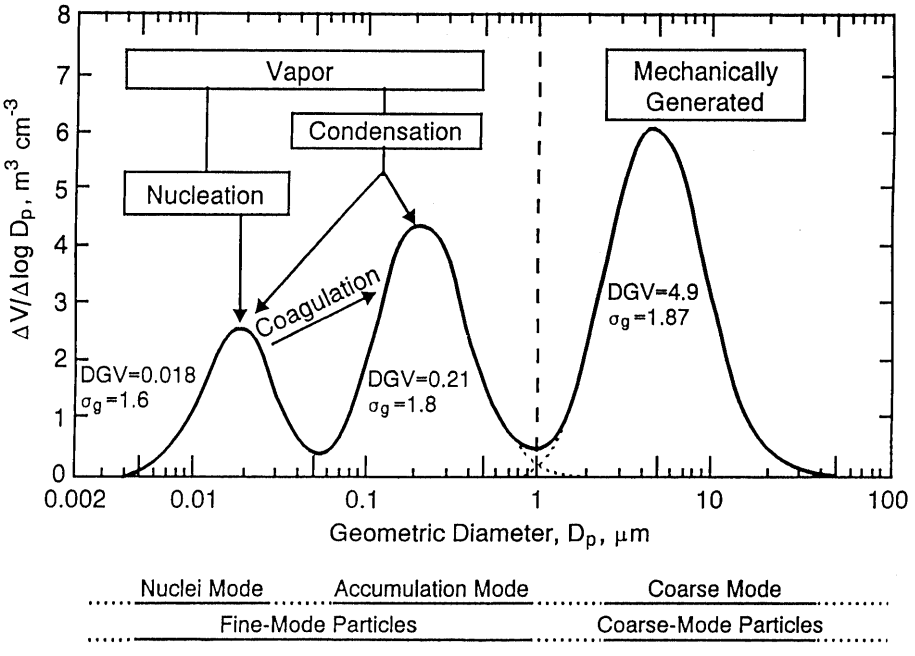

Fig. 1 Trimodal urban particle size distribution indicating particle sources and coagulation processes (EPA 1996)

ultrafine particles since these particles have a large surface area per given mass which may be able to act as a catalyst for specific reactions with cells. This increased surface area can also act as a carrier for co-pollutants such as gases and chemicals, specifically transition metals which could form a coat on the particle surfaces during their formation. Furthermore, there are host factors, such as a sensitized or compromised organism, and including age and respiratory and cardiovascular disorders, which have been identified in epidemiological studies. These factors could confer a predisposition to effects of inhaled particulate pollutants which in the healthy organism would not cause any effects.

Early studies with aggregated ultrafine particles

A number of studies have been reported which used inhalation of ultrafine particles by laboratory animals at very high concentrations. Obviously, these high concentrations, ranging up to many mg/m^3, resulted in the inhalation of aggregated ultrafine particles. The inhaled particles included carbon black or titanium dioxide (TiO_2) (Heinrich et al. 1995, Mauderly et al. 1994). These studies were performed to investigate effects caused by lung particle overload, i.e., induction of lung tumors in rats by high retained particulate lung burdens. Specifically, chronic inhalation studies with ultrafine and fine TiO_2 (average primary particle sizes ~20 nm and ~250 nm) have shown that more than ten times lower inhaled mass concentrations of the aggregated ultrafine particles, compared with the fine particles, are sufficient to produce the same amount of tumor-induction in rats in these long-term studies (Lee et al. 1985, Heinrich et al. 1995). In addition, studies have been performed with intratracheal instillations of aggregates of ultrafine and fine carbon black and TiO_2 in rats (Oberdörster et al. 1998, Li et al. 1996), and results demonstrated the significantly greater inflammatory potency of the ultrafine particles. When the instilled doses were expressed in terms of particle surface area, the responses of the ultrafine and fine TiO_2 particles fell on the same dose-response curve (Fig. 3), indicating that surface area is an important parameter in the toxicity of ultrafine particles.

Indeed, when the lung burdens in a number of long-term inhalation studies with different particles were expressed as retained particle surface area, the resulting lung tumor response showed a very good correlation with the particle surface area (Fig. 4). A further indication that surface area plays an important role was found in our most recent instillation studies with two different types of aggregated ultrafine TiO_2 (primary particle size ~20 nm). One type was coated with a silane compound, making the particle surface area hydrophobic, whereas the other was uncoated and hydrophilic. A significant difference in the pulmonary-inflammatory potency was observed between the two ultrafine particle types, i.e., the hydrophobic, coated particles induced a much lower pulmonary-inflammatory response 24 h after instillation than did the uncoated, hydrophilic TiO_2 particles (Fig. 5). This result appears to be somewhat in contrast to an earlier report by Pott et al. (1998), who showed that larger doses of 2 mg and more of the coated, hydrophobic ultrafine TiO_2 particles instilled into rats were acutely toxic and lethal. However, this increased toxicity may be because of some solubilization of the surface coating material which may not be effective at lower instilled doses. From these earlier investigations, which can be viewed as hypothesis-forming studies to derive the ultrafine particle hypothesis, it can be concluded that particle size plays a significant role in the pulmonary toxicity of inhaled particles, and that particle surface properties apparently are also important for the ensuing pulmonary response.

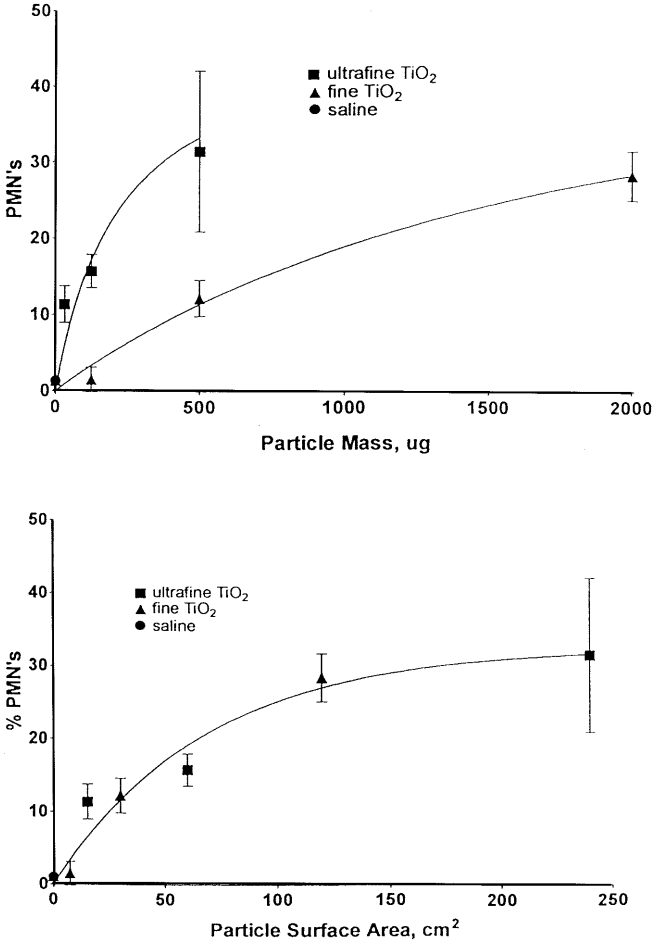

Fig. 3 Dose-response relationships for instilled ultrafine (20 nm primary particle size) and fine (250 nm primary particle size) titanium dioxide (TiO_2) 24 h after intratracheal instillation in rats. *Top* correlation between instilled particle mass and lavaged polymorphonuclear cells (PMNs) *Bottom* correlation between instilled particle surface area and lavaged PMNs

Studies with singlet ultrafine particles of high toxicity

Further studies with very low doses of inhaled singlet ultrafine particles were performed by exposing rats to

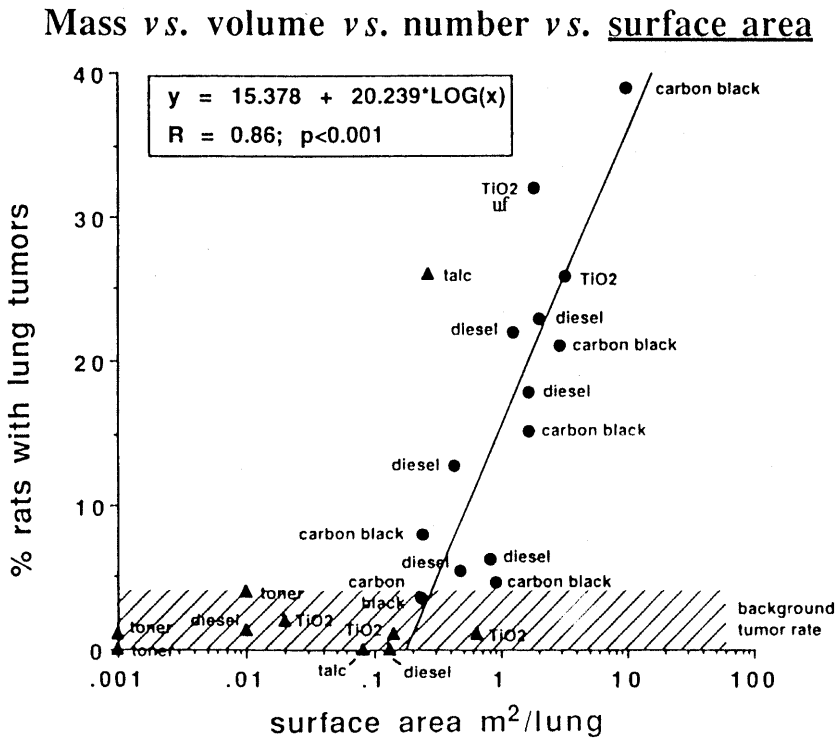

Fig. 4 Correlation between lung tumor incidence in rats in chronic inhalation studies with different particle types and retained particle surface area (summarized by Driscoll 1996)

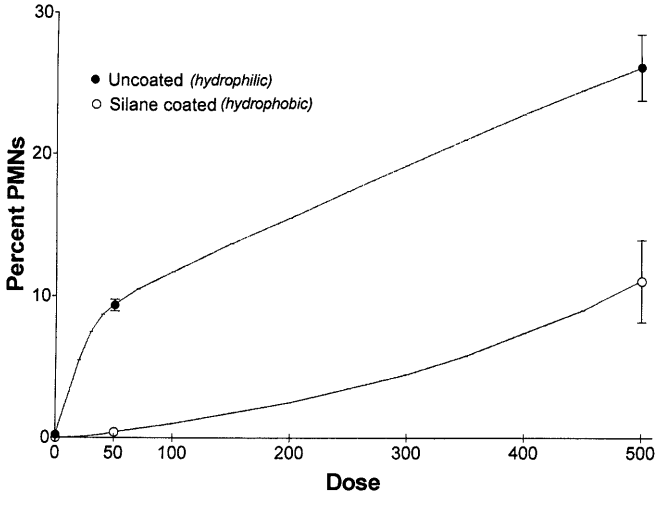

Fig. 5 Lavage polymorphonuclear cells (PMN) response in rats 24 h after intratracheal instillation of hydrophilic and hydrophobic ultrafine titanium dioxide (TiO_2)

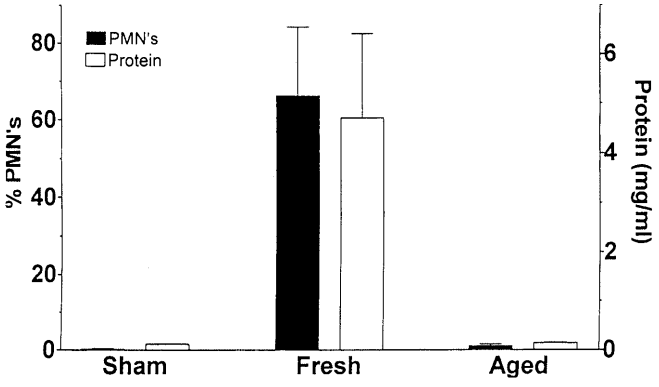

Fig. 6 Lavage polymorphonuclear cells (PMN) and protein 4 h after a 15-min exposure of rats to freshly generated (~50 μg/m^3, count median particle size 15 nm) and aged (~70 μg/m^3, count median particle size 110 nm) Teflon fumes

Teflon fumes generated by heating Teflon in a tube furnace. These fumes have been shown to be extremely toxic (Seidel et al. 1991, Warheit et al. 1990). Low inhaled mass concentrations of 50 μg/m^3 with a count median particle size of ~18 nm resulted in severe pulmonary edematous inflammation, hemorrhage and high mortality rate in rats, after 15–20 min of exposure (Oberdörster et al. 1995). Aging of the generated ultrafine Teflon particles for 3–4 min resulted in their aggregation to fine particles with resulting average median diameters slightly above 100 nm and loss of toxicity (Fig. 6). This result could either demonstrate the extreme high toxicity of freshly generated ultrafine Teflon particles and the loss of toxicity with larger particles of the same kind, or it could also indicate the existence of certain reactive surface groups on freshly generated Teflon fume particles that are lost with aging to large particles when they agglomerate. It appears that the high pulmonary toxicity of ultrafine Teflon fume particles is because of severe oxidative stress induced by the deposition and subsequent rapid translocation of these particles to interstitial sites in the lung.

Adaptation of pulmonary responses leading to tolerance towards oxidative stress has been reported after inhalation exposure to compounds such as ozone and cadmium. The development of tolerance could also be observed with ultrafine Teflon fume particles by

pre-exposing rats to freshly generated Teflon fumes for 5 min on 3 consecutive days, before exposing them for 15 min on day 4 at a concentration which induced severe toxicity. Figure 7 shows the result of this adaptation-experiment, demonstrating that 3 days pre-exposure made the animals tolerant to the highly toxic effects of the Teflon fumes, whereas non-adapted animals died within 4 h after the 15-min exposure. This result points out the importance of pre-exposure history for the induction of effects of ultrafine particles. Pre-exposures and subsequent adaptive events may also play a role in exposures to low toxicity ultrafine particles discussed further below. It should be kept in mind, however, that highly toxic ultrafine particles such as Teflon fumes are not representative of ultrafine carbonaceous particles in the environment.

Deposition and disposition of inhaled singlet ultrafine particles

As pointed out above, deposition and disposition of ultrafine particles play a significant role in inducing effects in the lung. Figure 8 shows the recent International Commission on Radiological Protection (ICRP) (1994) model for particle deposition in the human respiratory tract. As can be seen from this figure, the predicted alveolar deposition is highest for inhaled singlet ultrafine particles of ~20 nm diameter, higher than for any other particle size, coinciding with the particle peak of the ambient urban aerosol (Fig. 1). Thus, although inhaled mass concentrations of urban ultrafine particles may be very low, numbers of ultrafine particles depositing in the alveolar region of the lung are extremely high.

Even in the conducting airways the deposition efficiency is very high considering that the available surface area, compared with the alveolar region, is much lower.

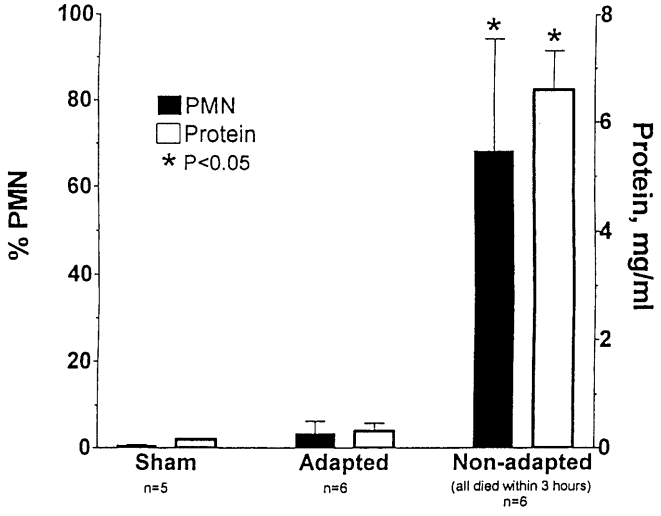

Fig. 7 Lavage polymorphonuclear cells (PMN) and protein response 4 h after a 15-min exposure to ultrafine Teflon fumes (~50 $\mu g/m^3$, count median particle size 18 nm) in fume-adapted and non-adapted rats

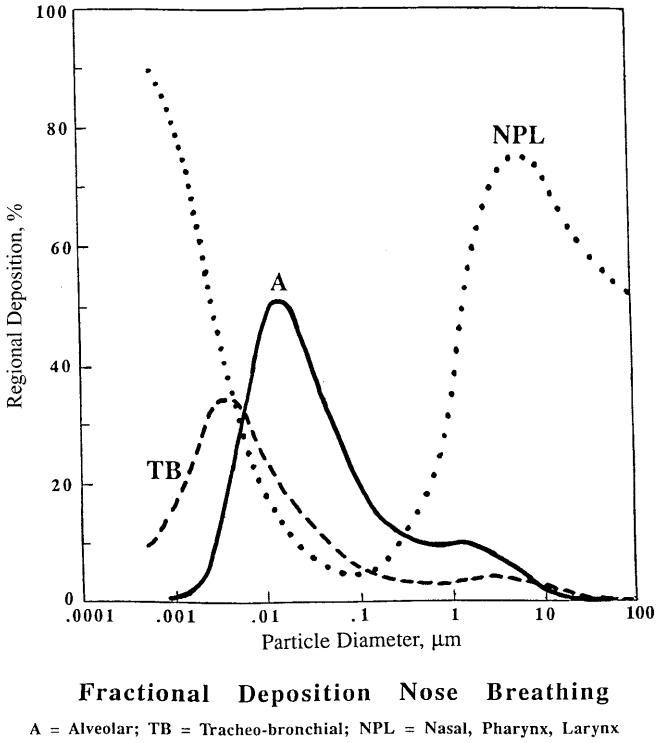

Fig. 8 Deposition of inhaled particle in the upper and lower human respiratory tract after inhalation of different particle sizes (International Commission on Radiological Protection (ICRP) model 1994)

Therefore, even a low deposition efficiency will result in a deposited dose, per unit of conducting airway surface area, which may be higher than in the alveolar region.

Furthermore, the fate of ultrafine particles after their deposition may be very different from that of larger particles. It appears that deposited ultrafine particles are not as readily phagocytized by alveolar macrophages as are larger particles, and that they consequently penetrate much more rapidly to interstitial sites, possibly including the endothelium. They may even enter the blood circulation which may result in their translocation to extrapulmonary tissues. Our preliminary studies have shown that after inhalation of particles, decreasing particle size, down to the ultrafine size, renders particles less lavageable within the alveolar macrophage pool, pointing to a decreased efficiency of phagocytosis by macrophages for ultrafine particles. Evidence that ultrafine particles after deposition in the lung may also be transported to other organs comes from a study with inhalation of ultrafine, poorly soluble, platinum particles. Figure 9 shows the result of retained platinum in lung lobes, trachea and liver as determined by inductively coupled plasma mass spectroscopy (ICPMS), showing that ~8% of the amount in the lung could be found in the liver after a 6-h exposure to a low concentration of ultrafine platinum particles in a rat. However, this result has to be interpreted with caution with respect to a direct extrapulmonary transport of ultrafine particles, since it cannot be excluded that some of the ultrafine platinum particles may have dissolved in the lung, which may account for

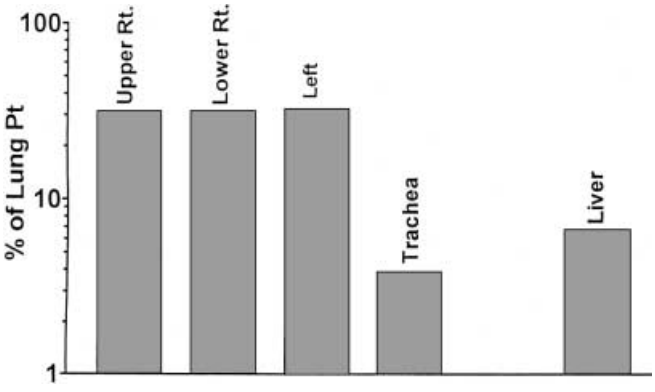

Fig. 9 Platinum content in different parts of the respiratory tract of the rat and in the liver after a 6-h exposure to ultrafine platinum particles (~110 μg/m^3, 18 nm count median particle size)

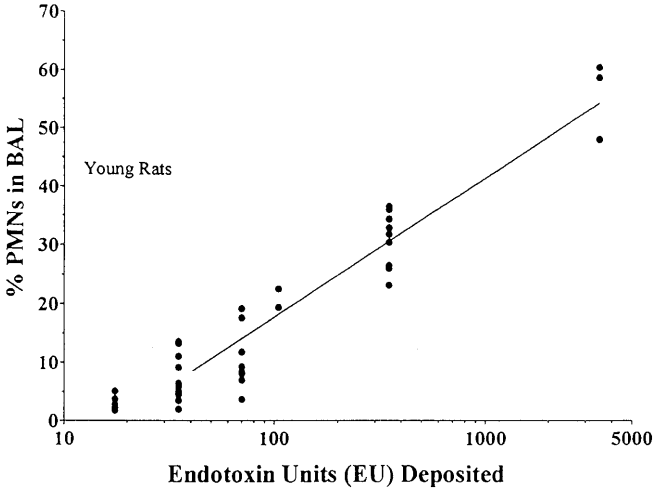

Fig. 10 Dose-response curve in 10-week old rats 24 h following a short-term endotoxin inhalation exposure. Dose is expressed as estimated endotoxin units in the alveolar region based on predictive lung deposition models

all or some of the platinum in the liver. Additional studies with insoluble particulate materials, such as carbon particles, are necessary to compellingly demonstrate such extrapulmonary transport.

Studies with singlet ultrafine particles of low toxicity

Further studies were performed using ultrafine carbon and platinum particles with count median diameters of ~15 and 25 nm. Experiments were performed in 18-month old mice, and compared with responses in 8-week old mice, with and without induction of pulmonary emphysema by intratracheal instillation of elastase. It was found that healthy animals of either age did not respond to ultrafine platinum or carbon particles at inhaled concentrations of ~110 μg/m^3 for 6 h, and that only the aged, emphysematous mice showed a very mild pulmonary-inflammatory response, as indicated by a slight increase in numbers of neutrophils in lung lavage, and by the appearance of significant lymphocytic infiltrations around the peribronchiolar spaces, determined by histological examination.

Since epidemiological studies on particulate air pollution showed adverse effects only in compromised persons, it is desirable to use respective animal models to mimic specific human disorders. One such model involves inhalation of low doses of endotoxin [lipopolysaccharide (LPS)] to induce and mimic early stages of respiratory tract infection with gram negative bacteria. Injection or inhalation of endotoxin is known to result in inflammation and oxidative stress with the induction of proinflammatory cytokines, chemokines, cell adhesion molecules, stress proteins, prostaglandins and activation of macrophages. LPS-exposure to the respiratory tract can occur from inhalation of road dust or infectious agents. In animal studies, the responses from inhaled endotoxin can range from low dose induced transient mild inflammation to severe respiratory stress symptoms at high concentrations. Figure 10 shows a dose-response curve of inhaled endotoxin expressed as the estimated deposited alveolar dose of endotoxin correlated with the response of neutrophils in the lung lavage fluid as a measure of the inflammatory response. At different timepoints after endotoxin exposure, either increased sensitivity of target cells (priming, very early after exposure) or development of tolerance (1 day or more after exposure) to a second stimulus can occur. In order to test the validity of the endotoxin-priming model, ultrafine and fine TiO_2 particles were instilled into rats 30 min after they were primed with a low dose of inhaled LPS. The result indeed confirmed that only the ultrafine TiO_2, not the fine TiO_2, induced a significant pulmonary inflammatory response which was greater than with LPS or with ultrafine TiO_2 alone (Fig. 11).

This model was further tested in an inhalation model of ultrafine carbon particles (~110 μg/m^3) in combination with a gaseous air-pollutant, ozone (Elder et al.

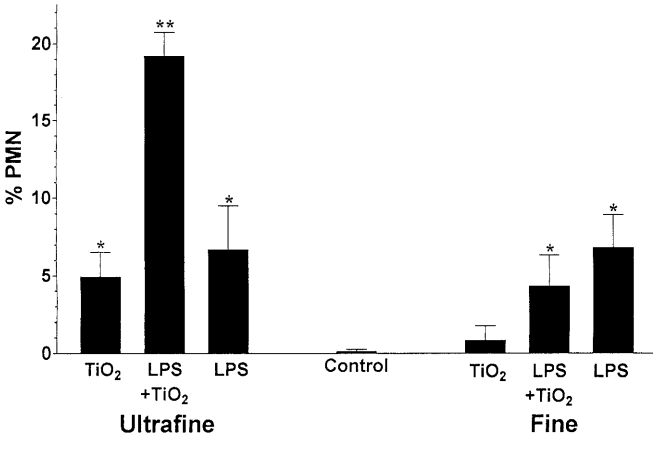

Fig. 11 Lavage polymorphonuclear cells (PMN) response 24 h following intratracheal instillation of 50 μg ultrafine or fine titanium dioxide (TiO_2) or of 70 endotoxin units of inhaled lipopolysaccharide (LPS) (estimated alveolar deposited dose) and the combination of both compounds

2000). The resulting response is shown in Fig. 12 with respect to the measured neutrophil response in lung lavage fluid in young rats. Statistical analysis of the results showed that ultrafine carbon particles have an inflammatory effect of their own, and that co-exposure to ozone and LPS increases the response even more. A similar study in aged rats showed that the aged organism may be at an even greater risk of induction of an oxidative stress response after such combined exposures following priming with inhaled endotoxin. This was determined by measurements of respiratory bursts of lavaged inflammatory cells (Elder et al. 2000). Thus, it appears that the endotoxin priming model is a sensitive tool for the examination of effects of low inhaled mass concentrations of carbonaceous ultrafine particles which are of ambient relevance for human exposures.

Summary

The studies summarized in this short review demonstrate that ultrafine particles cause a greater inflammatory response than do fine particles per given mass. Surface properties (surface chemistry) appear to play an important role in ultrafine particle toxicity. Contributing to the effects of ultrafine particles is their very high size-specific deposition when inhaled as singlet ultrafine particles rather than as aggregates. It appears also, that inhaled ultrafine particles deposited in the lung largely escape alveolar macrophage surveillance and gain access to the interstitium. Inhaled low doses of carbonaceous ultrafine particles can cause mild pulmonary inflammation in rodents. Age and a compromised/sensitized respiratory tract can increase the susceptibility to effects of ultrafine particles and it appears that the aged organism is at a higher risk of oxidative stress-induced lung injury. Furthermore, ultrafine particle effects can be significantly enhanced by a gaseous co-pollutant such as ozone.

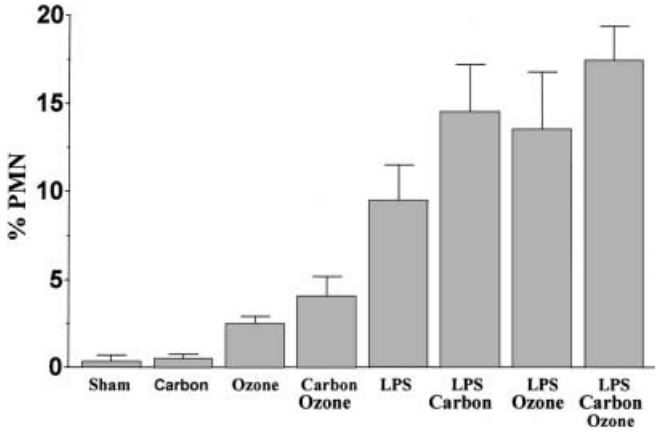

Fig. 12 Lavage polymorphonuclear cells (PMN) 18 h after a 6-h exposure to ultrafine carbon particles (~110 μg/m^3), ozone (1 ppm) or lipopolysaccharide (LPS) (70 endotoxin units estimated alveolar deposition) in young rats and the combination of these exposures (from Elder et al. 2000)

Outlook

Obviously, there are a number of open questions which still need to be answered with respect to the toxicity of ultrafine particles. One is related to the translocation of deposited ultrafine particles to extrapulmonary tissues, which has still not been shown convincingly at this point. Another is an elucidation of the mechanisms of effects of ultrafine particles at a cellular and molecular level. That relates both to local effects elicited in the lung as well as to systemic effects, for example, the cardiovascular system, since people with respective diseases have been found to be most susceptible to ambient particulate pollution. Furthermore, there is the question of the impact of co-pollutants, such as oxidant gases, transition metals, and organic chemicals, which may be adsorbed to, or condensed on, ultrafine particles. Most importantly, research has to be undertaken to investigate host susceptibility factors such as advanced age, specific disease states, and sensitization due to pre-exposures to sensitizing agents. Overall, in order to confirm the suggested increased toxicity of inhaled ultrafine particles, a rigorous comparison between ultrafine and fine particles in experimental as well as in controlled clinical and in epidemiological studies is needed.

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