

Are ultrafine ambient particles health hazards?

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1. Introduction

1.1 Epidemiological evidence

A growing body of epidemiological studies have shown consistent associations between the exposure to particulate air pollution in urban areas and acute increases in morbidity and mortality rates, especially for persons with obstructive lung and cardiovascular diseases (Pope et al., 1995, 1999, Pope, 2000; Samet et al. 2000). Interestingly, the relative risk is surprisingly similar in many of these studies although the studies have been performed at very different locations all over the world - with a predominance in North America and Western Europe. These data are currently collected and summarized by the US-EPA in a second external review draft of the Air Quality Criteria Document on Particulate Matter (2001).

At a first glance one would expect that particulate air pollution should vary widely between urban areas since sources of air pollution may considerably vary because of different industries, and other local sources. Indeed, in a recent article Green and coworkers (2002) posed the question "What is wrong with the National Ambient Air Quality Standard (NAAQS) for Fine Particulate Matter (PM_{2.5})?". They critically reviewed the epidemiologically and toxicologically available evidence and concluded: "*The central questions at issue now involve whether current, low-level, ambient concentrations of PM_{2.5} per se are fatal. If so, such harm must be due to some specific fractions of PM_{2.5}, since the thousands of forms of PM_{2.5} differ in myriad relevant ways. At present, no one knows what forms of ambient PM_{2.5}, if any, are fatal,*". So, PM_{2.5} (mass concentration of particles > 2.5 µm aerodynamic diameter) is more likely to be a surrogate parameter rather than a distinct cause-effective parameter for a well defined disease or for the initiation of a cascade of adverse health effects. It is much more likely that within the fine particulate mass noxious compounds may be hidden which, in addition, may be accumulating in given fractions and also specifically concentrating within the matrix or at the surface of the particles. Furthermore none of these single compounds are present at sufficiently high concentrations in the environmental aerosol such that they may be considered toxicologically relevant based on occupational hygiene expertise. Therefore, it appears plausible that research must aim for interactions of complex mixtures of compounds with biological systems. Although the risks from these mixtures of compounds may be low to an individual, the large number of persons at risk can make these compounds an important public health threat. Frequently, health effects only manifest in specific risk groups, i.e. persons predisposed by genetic susceptibility, age, and/or disease.

1.2 Carbonaceous aerosols released from incomplete combustion processes

Nevertheless, there is a common source contributing to air pollution in almost each of the epidemiological studies which, in addition, is not a distinctly located source but wide spread over the entire urban area: carbonaceous aerosols released from incomplete combustion processes. The latter include not only exhaust emissions from motor vehicles on the streets of urban areas but also domestic heating by fossil fuel burners situated in individual apartments and houses.

Due to modern motor and burner technologies today, these particles are below 200 nm in diameter and may be as small as a few nanometers. Many of them comprise of a carbon core onto which other compounds may condense during cooling of the exhaust after combustion in the burner chamber (Siegmann et al., 1997; Kittelson, 1998; Harrison et al., 2000). Compounds may be organic and inorganic. In particular, condensation and evaporation of compounds at the particle surface and homogeneous nucleation are dynamic and continuous processes which may change the particle surface depending on the thermodynamic conditions while the particle remains suspended in air and also during sampling.

Because the mass of particulate exhaust emission from Diesel engines is generally about a factor of 10 greater than that of gasoline engines, there has been more focus on the effects of Diesel exhaust emission than emission of the latter. (Sawyer et al., 1995) Yet the size distribution of particulate exhaust emission from gasoline engines is only slightly shifted towards smaller particles than that of Diesel exhaust and, accordingly, the total number concentration is lower by about one order of magnitude (Harrison et al., 2000). Fossil fuel burners used for domestic heating produce similar carbonaceous aerosols widely spread over urban areas.

In order to highlight the dynamics of these emission aerosols, the size distribution of Diesel exhaust number concentration has a median diameter of 80-100 nm with a geometric standard deviation of around 2 (Kittelson, 1998). This distribution changes rapidly in ambient air due to dilution and evaporation effects. Even several meters close to busy roads, number size distributions of ambient air show no longer a relative maximum at about 100 nm but the maximum is shifted towards 10-20 nm.

In summary the fact that numerous epidemiological studies find associations between adverse health effects and ambient particulate air pollution which have a dominant commonality: the diffusely spread entity of sources releasing carbonaceous aerosols from incomplete combustion processes strongly suggests to investigate the role of such aerosols. These aerosols are a fraction of PM_{2.5} comprising of particles 200-500 nm in size and they may dominate the fraction of ultrafine particles (UP, < 100nm). Due to the combustion process carbonaceous UP are mostly aggregates of primary particles which may be as small as a few nanometers. The fragile structure of these chain aggregates right after production may change rapidly during aging while being air borne. In addition, condensation and evaporation of gaseous compounds may grow or shrink and, in addition, reshape the particle towards more compact and isometric forms.

2. Toxicological Studies

In the beginning of the last decade toxicological studies started to seek biological plausibility for the epidemiological findings. Classical attempts were cho-

sen like lung function tests etc. This has changed substantially in recent years. An early key study demonstrated that ultrafine TiO₂ caused more inflammation in rat lungs than exposure to the same airborne mass concentration of fine TiO₂ (Ferin et al., 1992). So far TiO₂ had been considered as a non-toxic dust and indeed had served as a innocuous 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 could be toxic in the form of ultrafine particles.

In recent years research concentrates on the following hypotheses. Ultrafine particles:

- have a high specific surface area, which can catalyse reactions and which can adsorb high amounts of toxic substances (like PAH), making them a carrier into the deep lung during inhalation (Seaton et al., 1995)
- have a higher deposition probability particularly in the small airways and the alveolar region of the lungs (Bair et al., 1994)
- induce more oxidative stress than fine particles (Stone et al., 1998, 2001),
- are less well phagocytized by alveolar macrophages than larger particles and inhibit their phagocytic ability (Lundborg et al., 2001),
- to inhibit macrophage motility (Möller et al., 2002)
- are taken up by other cells of the respiratory epithelia such epithelial cells, dendritic cells (Ferin et al., 1992; Geiser et al., 2000),
- may form complexes with similar sized proteins and biomolecules which may result in functional changes of the latter (Kreyling, private communication),
- have greater access to interstitial spaces than larger particles (Stearns et al., 1994; Oberdörster et al., 2000),
- have access to systemic circulation (Nemmar et al., 2002; Oberdörster et al., 2002, Kreyling et al., 2002),
- cause more inflammatory effects than larger particles (Donaldson et al., 2001),
- adversely affect cardiac functions and vascular homeostasis (Stone & Godleski, 1999),
- affect immunity (Behrendt & Becker, 2001),
- the large surface area of ultrafine particles and its composition and structure play a pivotal role in the above mentioned interactions with biological target cells, body fluids and tissues (Donaldson et al., 2002).

For all of these hypotheses there exists a growing body of studies on a mechanistic level providing plausibility or evidence, however, on different levels of causality, which have recently been reviewed by the second external review draft of the Air Quality Criteria Document on Particulate Matter (2001). From many of these studies it became also clear that the hypotheses listed above may only be applicable to susceptible organisms and individuals predisposed either by disease or genetics or age while the healthy organism does not show such sensitive reactions. Yet, these toxicological studies are hampered by a number of short comes when compared with the long-term exposure of humans in urban environments with inherited and/or acquired susceptibility:

- mechanistic studies on biological systems (sub-cellular, cellular, organs, animal models) frequently use high doses which often are two and more

orders of magnitude higher than the dose resulting from ambient air exposure. Mechanisms and effects observed can usually not be proven at low concentrations in such studies. Therefore, extrapolation to low concentrations often remains speculative.

- So far most of toxicological studies are acute studies which may or may not result in adverse health effects. Unfortunately, there are virtually no long-term exposure studies looking for end points of adverse health effects as hypothesized above.
- Recent studies on air sampling quality (Wittmaack, 2002) indicate that toxicological studies based on ultrafine particle samples of the ambient aerosol collected on filters and other substrates may be hampered by artefacts occurring during extended sampling times on those substrates (blow-off, blow-on, chemical reactions, phase separation, etc.). Techniques using concentrated ultrafine air particles get complicated by the fact that particles first need to grow by a volatile liquid like water before aerodynamic separation and subsequent evaporation of the liquid which may lead to chemical reaction of the particle compounds with the liquid (Demokritou et al., 2002). In addition, a prerequisite of those studies is a very careful and hopefully complete characterisation of the aerosol used.
- Existing animal models are grossly inadequate for many susceptible population groups such as asthmatics, patients with chronic obstructive pulmonary disease (COPD), hypertensive and other high-risk patients for myocardial infarction or other cardiovascular diseases.

In summary toxicology has made considerable progress during recent years to provide plausibility and evidence for the adverse health effects associated with the exposure to ultrafine ambient particles as determined in epidemiology. New targets were identified like the cardiovascular and the immune system. Yet, much more research is required to better understand the underlying mechanisms at relevant doses of exposure which may lead to the gradual development from health to disease.

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